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Associations between whole blood trace elements concentrations and HbA1c levels in patients with type 2 diabetes

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Abstract Previous researches have been conducted to study the associations of trace elements on Type 2 diabetes (T2D) risk. The present study focuses on the evaluation of potential associations between trace elements and Hemoglobin A1c (HbA1c) in patients with T2D, via the determination of their levels in human whole blood. 100 diabetes without complications, 75 prediabetes and 40 apparently healthy subjects were studied. The levels of eleven trace elements including lithium (Li), vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), cobalt (Co), copper (Cu), zinc (Zn), selenium (Se), strontium (Sr) and molybdenum (Mo) were measured using inductively coupled plasma mass spectrometry (ICP-MS). The levels of fasting glucose, HbA1c, Hemoglobin, lipid, liver function, kidney function, thyroid function and demographic data were obtained from the Laboratory Information System. Nonparametric correlation (Spearman) was used to analyze the relationship between trace elements and HbA1c. The contents of V, Cr, Mn, Fe, Co, Cu, Zn and Mo in diabetes increased comparing with the healthy subject while Li decreased. But the levels of Li, V, Cr, Mn, Co, Se and Mo negatively correlated with HbA1c in the diabetes subjects (r value: − 0.2189, − 0.2421, − 0.3260, − 0.2744, − 0.2812, − 0.2456, − 0.2240; 95% confidence interval − 0.4032 to − 0.0176, − 0.4235 to − 0.0420, − 0.4955 to − 0.1326, − 0.4515 to − 0.0765, − 0.4573 to − 0.0838, − 0.4266 to − 0.0458, − 0.4076 to − 0.0229; $p<0.05$, $p<0.05$, $p<0.001$, $p<0.01$, $p<0.01$, $p<0.05$, $p<0.05$). Accordingly, the contents of V, Cr, Mn and Se showed lower in HbA1c ≥ 7.0% group in contrast to HbA1c < 7.0% group. No correlation of HbA1c (or FBG) and trace elements was found in the healthy subjects. Trace element levels and metabolic abnormalities of blood glucose may be mutually affected. The extra supplement of trace elements needs to be cautious.

Keywords Type 2 diabetes · Hemoglobin A1c · Trace elements · Whole blood · Association

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Abbreviations

T2D	Type 2 diabetes
BMI	Body mass index
Fe	Iron
Cu	Copper
Zn	Zinc
Mn	Manganese
Se	Selenium
Sr	Strontium
Li	Lithium
V	Vanadium
Cr	Chromium
Mo	Molybdenum
Co	Cobalt
ICP-MS	Inductively coupled plasma mass spectrometry
FBG	Fasting blood-glucose
HbA1c	Hemoglobin A1

Introduction

Type 2 diabetes (T2D), representing > 90% of all cases of diabetes, is a complex disease caused by multiple genetic loci in interplay with lifestyle and environmental factors. Previous studies have identified a series of risk factors for T2D, age, body mass index (BMI), waist circumference, sex, ethnicity, low physical activity, smoking, diet including low amount of fiber and high amount of saturated fat, family history of diabetes, history of gestational diabetes mellitus, elevated blood pressure, dyslipidemia, and different drug treatments (diuretics, unselected β-blockers, statins) (Laakso 2019).

Trace elements are essential micronutrients required for physiological functions of the body. They can maintain the stabilization of the cellular structures, but their inadequacy and excess may both cause ailments (Nordberg and Nordberg 2016). There is a growing interest for studies aiming to clarify the role of trace elements in the etiopathogenesis and complications of diabetes mellitus. Many previous studies focus on the changes of single trace element in the serum of diabetic patients and the results are contradictory (Dubey et al. 2020; Chen et al. 2020; Zhang et al. 2017; Lian et al. 2021; Yary et al. 2016; Badran et al. 2016). Few studies have analyzed the correlation between the elements in whole blood and blood glucose levels. Glycated hemoglobin A1c (HbA1c) is a major component of glycated hemoglobin, which are the products of a non-enzymatic reaction between hemoglobin and glucose. The measurement of glycated forms of hemoglobin can reflect the average blood glucose from the previous 2 or 3 months (American Diabetes Association 2020; Chatterjee et al. 2017). So HbA1c is widely used for screening, diagnosis, and monitoring of hyperglycemia and is independent of factors such as fasting, insulin injections, and hypoglycemic drugs taken. Moreover, diabetics are often accompanied by thyroid diseases or other metabolic diseases such as dyslipidemia. It is reported that the balance of essential trace and toxic metals in patients significantly affect the pathogenesis of thyroid diseases and metabolic diseases (Hanif et al. 2018; Wu et al. 2021).

To provide the scientific evidence of the correlation of trace elements and HbA1c, we carried out a cross-sectional analysis of data from a population in east China. We examined the levels of trace elements including lithium (Li), vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), cobalt (Co), copper (Cu), zinc (Zn), selenium (Se), strontium (Sr) and molybdenum (Mo) in whole blood using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). The subjects were then divided into three groups according to HbA1c levels and the differences between groups were analyzed. In addition, we tested the associations between trace elements and HbA1c levels.

Methods

Study population

One Hundred diabetes without complications (74 men, 26 women), 75 prediabetes (55 men, 20 women) and 40 apparently healthy subjects (33 men, 7 women) were screened from the health examination centre of Shandong Provincial Hospital affiliated to Shandong First Medical University (the provincial medical union base) from March 2021 to November 2021. The diabetes inclusion criteria were as follows: (1) HbA1c ≥ 6.5%, (2) no concomitant disease apart from T2DM. Then the diabetes were furtherly divided into subgroups according to HbA1c level: HbA1c ≥ 7.0% and HbA1c < 7.0%, or subgroups according to FBG (fasting blood-glucose) concentration: ≥7.0 mmol/L and FBG < 7.0 mmol/L. The

prediabetes inclusion criteria were as follows: (1) HbA1c > 6.0% and HbA1c < 6.5%, (2) FBG < 7.0 mmol/L, (3) the diagnostic criteria for diabetes have not been met at the time of inclusion. The diagnosis of diabetes was based on fasting serum glucose level (≥ 7.0 mmol/L), 2-h serum glucose level (≥ 11.1 mmol/L), and hemoglobin A1c (HbA1c) value (≥ 6.5%). The common exclusion criteria for the diabetes and prediabetes subjects included other metabolic or nutritional diseases, such as thyroid disease, dyslipidemia, and anemia. The healthy subjects without any chronic disease were as control groups. None of the recruited subjects were supplemented with extra micronutrient. This study was approved by the Medical Ethics Committee of Shandong First Medical University in accordance with the Declaration of Helsinki (ethical approval number is NSFC: No. 2021-112).

Data collection

The diabetes, prediabetes and healthy subjects underwent thorough blood and urine tests on empty stomachs after admission. The remaining whole blood samples were collected at the same time and stored at -80℃ for trace elements determination using Agilent 7900 ICP-MS (Agilent, Tokyo, Japan) with whole blood element testing kit (LOT: WL2012011; Baichen, Hangzhou, China). We obtained the other medical reports of liver function, renal function, thyroid hormones, lipid, FBG, HbA1c, hemoglobin and urine protein of the participants from the Laboratory Information System.

Statistical analysis

Statistical analyses were performed using GraphPad Prism Software Version 5.0 (La Jolla, CA, USA). Shapiro-Wilk normality test was used for normality test. Because not all of the data were normally distributed, we present all data as median (Q1, Q3). The difference between > 2 groups were evaluated with the Kruskal Wallis one-way analysis of variance (ANOVA) and the difference between 2 groups were evaluated with the Mann-Whitney U test. Spearman coefficient values for correlation of two statistical variables were also determined. All p values were two-tailed and p values less than 0.05 were considered significant.

Results

The content of trace elements in diabetes, prediabetes and healthy groups

The demographic, clinical and biochemical characteristics of the diabetes, prediabetes and healthy subjects are shown in Table 1. The contents of Li, V, Cr, Mn, Fe, Co, Cu, Zn, Se, Sr and Mo expressed as 25th, 50th (median) and 75th percentiles in diabetes, prediabetes and healthy subjects' whole blood are shown in Table 2, while the average and SD values are presented in Fig. 1. There were statistically significiant differences of Li, V, Cr, Mn, Fe, Co, Cu, Zn, Se and Mo among the three groups ($p < 0.05$ for all). Higher contents of V, Cr, Mn, Fe, Co, Cu, Zn and Mo, but lower content of Li were detected in the diabetes subjects' whole blood in comparison to the healthy subjects (Fig. 1, $p < 0.05$ for all). However, in case of Se, there was no statistically significant difference between the diabetes and healthy subjects (Fig. 1, $p > 0.05$). And higher contents of V, Cr, Mn, Fe, Cu, Zn, Se and Mo were also detected in the prediabetes subjects' whole blood in comparison to the healthy subjects' (Fig. 1, $p < 0.05$ for all). As to diabetes subjects comparing with prediabetes subjects, higher contents of Mn, Fe, Cu and Se were detected (Fig. 1, $p < 0.05$ for all).

Association between trace elements in whole blood and HbA1c

As presented in Table 3, Spearman test revealed the correlations between trace elements concentrations and HbA1c levels in the prediabetes, diabetes, prediabetes and diabetes, healthy subjects. Positive correlations between HbA1c and Li (in the prediabetes subjects, $p < 0.0001$), HbA1c and Cu (in the prediabetes and diabetes subjects, $p < 0.05$) were observed. While negative correlations between HbA1c and Li, V, Cr, Mn, Co, Se or Mo (in the diabetes subjects, $p < 0.05$ for all), HbA1c and V, Cr, Mn or Se (in the prediabetes and diabetes subjects, $p < 0.05$ for all) were observed. As to FBG, negative correlation of Mn ($p < 0.05$) and positive correlation of Cu were found in the prediabetes and diabetes subjects ($p < 0.05$, supplement materials Table 1). For healthy subjects, no correlation of HbA1c (or FBG) and trace elements was found.

Table 1 Parameter of the subjects

	Age	HBA1c (%)	Fasting GLU (mmol/L)	ALT (U/L)	AIB (g/L)	TBIL (μmol/L)	DBIL (μmol/L)	TG (mmol/L)	CH (mmol/L)	LDL (mmol/L)	BUN (mmol/L)	CR (μmol/L)	FT3 (pmol/L)	FT4 (pmol/L)	TSH (μIU/mL)	HGB (g/L)	UTP
Diabetes (N = 100)																	–
Minimum	32	6.5	3.25	9	38.8	7.84	0.73	0.18	2.75	1.34	2.3	42.0	3.16	9.21	0.43	113	
25% Percentile	57	6.6	6.27	14	42.9	11.37	2.20	0.93	3.76	2.09	4.7	57.2	3.96	11.37	1.25	138	
Median	64	6.9	7.29	19	44.9	14.42	2.69	1.18	4.49	2.61	5.3	65.6	4.25	12.20	1.61	150	
75% Percentile	72	7.5	8.28	25	46.5	17.54	3.19	1.45	4.95	2.96	5.9	76.2	4.50	12.88	2.22	156	
Maximum	89	14.3	16.57	50	50.2	23.49	4.74	1.98	6.14	3.69	7.0	97.6	5.23	15.16	4.36	182	
Pre-diabetes (N = 75)																	–
Minimum	34	6.1	4.33	9	37.8	6.49	1.37	0.39	2.75	1.27	3.1	6.89	3.25	9.75	0.4456	117	
25% Percentile	57	6.1	5.3	14	42.6	11.73	2.19	0.88	4.06	2.28	4.5	56.4	4.01	11.48	1.172	138	
Median	62	6.2	5.72	20	44.3	13.7	2.53	1.09	4.52	2.66	5.2	66.4	4.35	11.94	1.683	146	
75% Percentile	69	6.3	6.21	26	45.5	16.32	3.07	1.37	5.13	3.18	6.2	75.5	4.75	13.11	2.474	154	
Maximum	85	6.4	6.79	42	51.7	41.1	8.87	1.68	5.85	3.37	9.6	108.5	5.22	15.18	3.99	175	
Control cohort (N = 40)																	–
Minimum	34	4.8	3.11	8	39.5	6.94	0.86	0.46	2.77	1.48	2.9	44.7	3.22	10.07	0.40	128	
25% Percentile	56	5.5	4.92	13	41.7	12.93	2.33	0.83	4.06	2.32	4.7	65.5	3.90	11.20	1.04	136	
Median	62	5.8	5.14	19	43.6	15.18	2.76	1.00	4.66	2.70	5.3	70.1	4.37	11.79	1.36	146	
75% Percentile	69	5.9	5.39	24	45.0	17.84	3.43	1.27	4.97	3.05	6.2	84.8	4.60	12.46	1.97	157	
Maximum	81	6.0	6.00	59	48.0	24.90	5.09	1.61	5.72	3.31	7.0	95.0	5.86	15.44	4.52	169	

Table 2 Comparison of various trace elements in diabetes, prediabetes and healthy subjects

	Li	V	Cr	Mn	Fe	Co	Cu	Zn	Se	Sr	Mo
Diabetes (N = 100)											
Minimum	0.00	0.00	2.52	5.74	334432	0.31	695.3	4516	147.5	13.05	1.16
25% Percentile	0.54	0.00	7.27	10.55	426104	0.52	849.2	6119	193.1	22.92	2.68
Median	1.00	0.10	11.05	12.54	455896	0.59	922.8	6673	219.9	28.54	3.49
75% Percentile	1.66	0.26	15.43	15.80	492520	0.67	1010.0	7323	250.8	33.14	4.54
Maximum	6.87	0.84	32.62	34.93	580384	1.40	1234.0	9013	401.5	87.60	26.41
Pre-diabetes (N = 75)											
Minimum	0.00	0.00	0.00	4.19	200984	0.33	561.9	3236	131.1	15.56	0.00
25% Percentile	0.48	0.01	8.36	11.70	435680	0.48	812.7	5686	200.4	23.46	2.51
Median	1.22	0.13	11.52	14.62	464688	0.58	876.1	6626	233.7	29.15	3.24
75% Percentile	1.98	0.28	17.44	17.43	502096	0.70	943.6	7248	261.3	35.93	4.50
Maximum	4.77	0.90	26.71	60.84	671384	0.96	1322	10,458	400.5	44.95	7.61
Control cohort (N = 40)											
Minimum	0.08	0.00	0.00	6.50	263368	0.19	412.7	2568	103.40	14.47	0.00
25% Percentile	1.26	0.00	0.00	8.65	377664	0.33	695.9	4976	181.90	22.27	0.00
Median	1.66	0.00	0.00	10.43	433272	0.52	772.0	5818	219.70	28.72	1.71
75% Percentile	2.07	0.00	10.54	12.71	460992	0.67	832.1	6783	236.00	36.27	2.41
Maximum	3.44	0.00	20.00	20.07	559888	1.19	1011.0	7899	436.80	45.55	3.12
Kruskal–Wallis test	6.54	50.46	37.52	28.62	15.55	6.45	42.22	18.72	9.56	1.20	61.79
p value	0.038*	< 0.0001****	< 0.0001****	< 0.0001****	0.0004**	0.040*	< 0.0001****	< 0.0001****	0.0084**	0.55	< 0.0001****

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$,****$p < 0.0001$

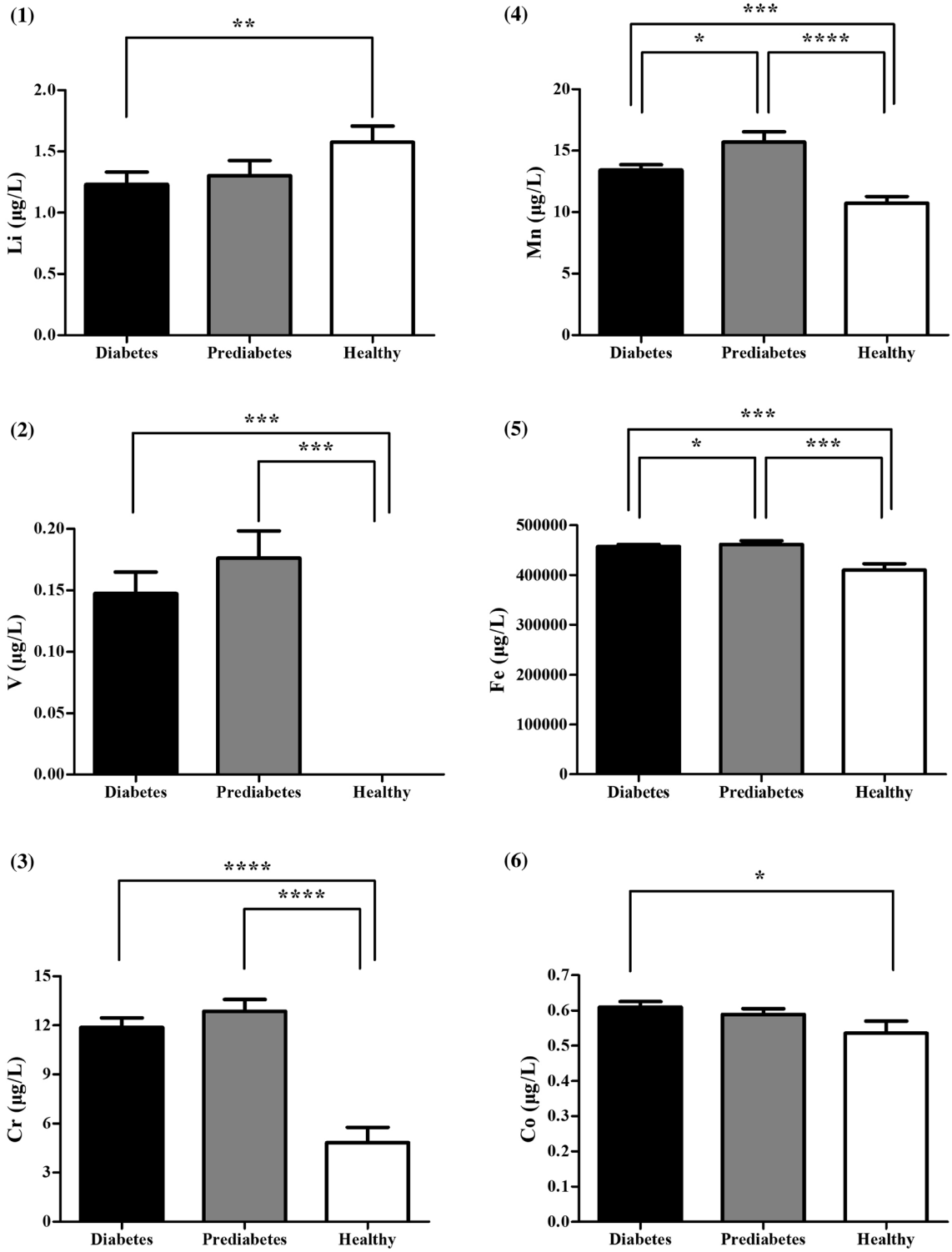

Fig. 1 Comparison of trace elements contents (µg/L) in the diabetes, prediabetes and healthy subjects. Bar graphs were used to visually display the changes in the peripheral whole blood and data were expressed as means ± standard deviation. Signifcant diferences between two groups were marked (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$,****$p < 0.0001$)

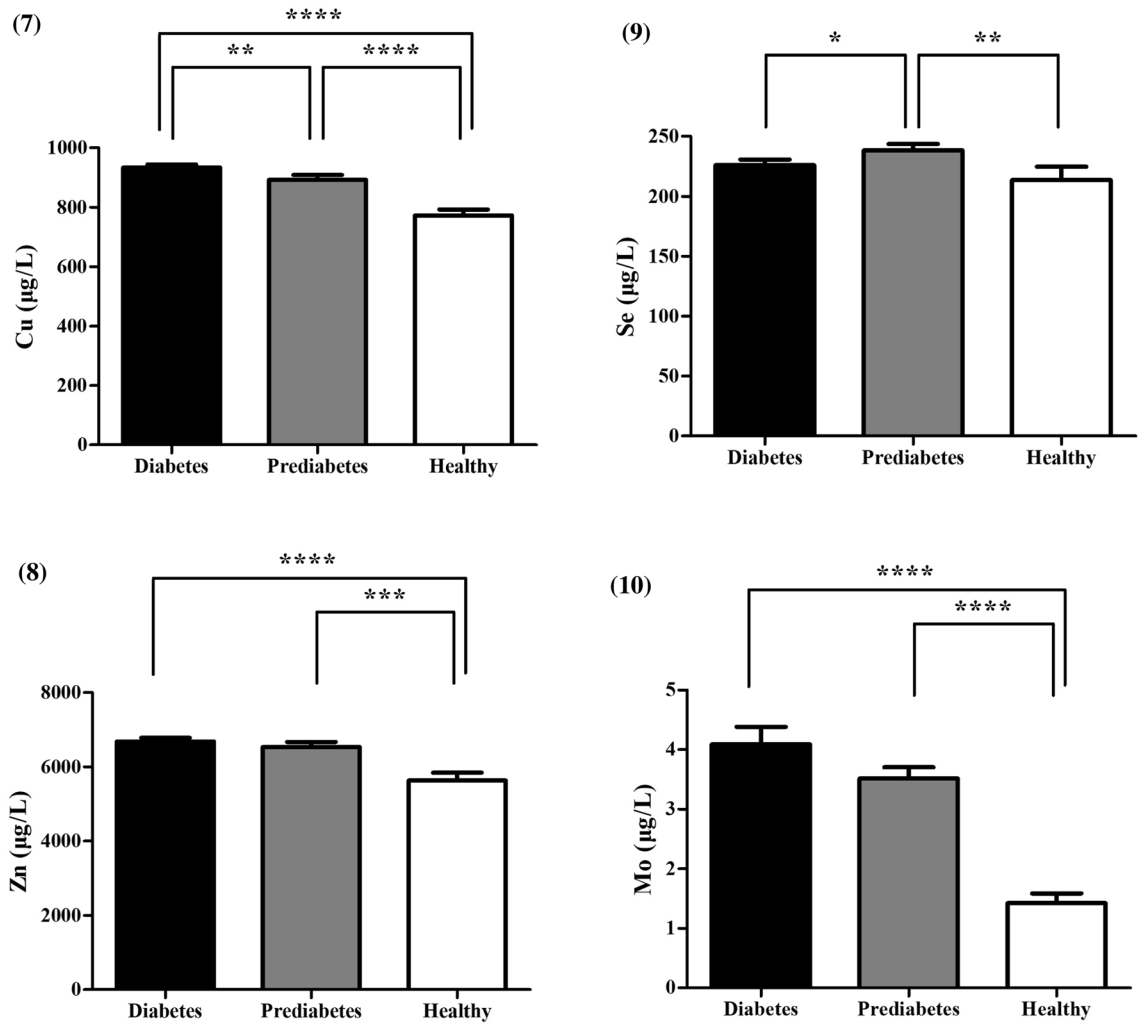

Fig. 1 (continued)

Subgroup analysis in patients with diabetes

Various elements (V, Cr, Mn and Se) which negatively correlated with HbA1c in diabetes also performed lower concentrations in HbA1c ≥ 7.0% group in contrast to HbA1c < 7.0% group ($p < 0.05$ for all) (Table 4). But all trace elements showed no obvious difference between FBG ≥ 7.0 mmol/L group and FBG < 7.0 mmol/L group ($p > 0.05$ for all) (supplement materials Table 2).

Discussion and conclusion

The importance of trace elements for diabetes has been increasingly recognized, but the conclusions reported controversially (Dubey et al. 2020; Chen et al. 2020; Zhang et al. 2017; Lian et al. 2021; Yary et al. 2016; Badran et al. 2016). In this study, the recruited patients newly diagnosed with diabetes and prediabetes on physical examination have not experienced dietary control or medication. The detection of eleven trace elements in peripheral whole blood using gold standard ICP-MS can better reflect the situation

Table 3 Associations between trace elements in whole blood and HbA1c

	Li	V	Cr	Mn	Fe	Co	Cu	Zn	Se	Mo
Pre-diabetes (N = 75)										
r value	0.5105	− 0.1694	− 0.0181	− 0.1138	− 0.1220	0.0489	0.1467	− 0.0944	0.0542	− 0.0264
95% Confidence interval	0.3145–0.6648	− 0.3876–0.0667	− 0.2505–0.2163	− 0.3383–0.1229	− 0.3456–0.1148	− 0.1867–0.2792	− 0.0899–0.3676	− 0.3208–0.1422	− 0.1816–0.2841	− 0.2583–0.2084
p value	< 0.0001****	0.1462	0.8777	0.3309	0.2972	0.6767	0.2093	0.4204	0.6444	0.8223
Diabetes (N = 100)										
r value	− 0.2189	− 0.2421	− 0.3260	− 0.2744	0.0043	− 0.2812	0.0972	0.0200	− 0.2456	− 0.2240
95% Confidence interval	− 0.4032 to − 0.0176	− 0.4235 to − 0.0420	− 0.4955 to − 0.1326	− 0.4515 to − 0.0765	− 0.1980–0.2063	− 0.4573 to − 0.0838	− 0.1070–0.2936	− 0.1828–0.2213	− 0.4266 to − 0.0458	− 0.4076 to − 0.0229
p value	0.0287*	0.0152*	0.0009***	0.0057**	0.9660	0.0046**	0.3360	0.8432	0.0138*	0.0251*
Pre-diabetes + diabetes (N = 175)										
r value	0.0096	− 0.2076	− 0.1920	− 0.2685	− 0.0955	− 0.0500	0.2283	0.0609	− 0.2019	− 0.0230
95% confidence interval	− 0.1433 ~ 0.1620	− 0.3492 to − 0.0567	− 0.3349 to − 0.0405	− 0.4046 to − 0.1208	− 0.2446 ~ 0.0581	− 0.2012–0.1035	0.0784 ~ 0.3682	− 0.0927 ~ 0.2116	− 0.3440 to − 0.0508	− 0.1751 ~ 0.1302
p value	0.8999	0.0058**	0.0109*	0.0003***	0.2088	0.5112	0.0024**	0.4234	0.0074*	0.7626
Control cohort (N = 40)										
r value	0.2710	–	− 0.1409	− 0.2037	− 0.1678	0.0039	0.1384	− 0.1598	− 0.2753	− 0.0137
95% Confidence interval	− 0.0539–0.5439	–	− 0.4412–0.1877	− 0.4918–0.1245	− 0.4631–0.1610	− 0.3167–0.3236	− 0.1902–0.4391	− 0.4566–0.1691	− 0.5472–0.0492	− 0.3324–0.3078
p value	0.0908	–	0.3858	0.2073	0.3006	0.9810	0.3943	0.3248	0.0855	0.9331

HbA1c Hemoglobin A1

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$,****$p < 0.0001$

Table 4 Comparison of various trace elements between HbA1c ≥ 7.0% group and HbA1c < 7.0% group in diabetes

	Li	V	Cr	Mn	Co	Se	Mo
HbA1c < 7.0% (N = 52)							
Minimum	0.00	0.00	3.61	6.44	0.32	158.1	1.16
25% Percentile	0.61	0.00	8.08	11.56	0.53	201.2	2.68
Median	1.13	0.19	12.28	13.53	0.62	226.2	3.76
75% Percentile	1.90	0.30	17.01	16.80	0.69	261.0	5.66
Maximum	3.93	0.84	32.62	34.93	1.40	338.0	26.41
HbA1c ≥ 7.0% (N = 48)							
Minimum	0.00	0.00	2.52	5.74	0.31	147.5	1.96
25% Percentile	0.42	0.00	6.48	10.22	0.50	180.9	2.64
Median	0.84	0.04	9.95	11.71	0.57	209.8	3.34
75% Percentile	1.64	0.18	13.84	13.97	0.65	240.3	4.18
Maximum	6.87	0.61	30.79	24.17	0.95	401.5	6.20
Mann–Whitney test							
U value	1068	969	867	897	978	890	1033
p value	0.2143	0.0452*	0.0087**	0.0156*	0.063	0.0136*	0.138

HbA1c Hemoglobin A1

*$p < 0.05$, **$p < 0.01$

of trace elements in vivo (Laur et al. 2020). The novel findings are as follows: First, the levels of Li, V, Cr, Mn, Fe, Co, Cu, Zn, Se and Mo differed among the diabetes, prediabetes and healthy subjects except for Sr. Second, the contents of various elements (V, Cr, Mn, Fe, Co, Cu, Zn, Se and Mo) in the diabetes subjects or in the prediabetes subjects did not decrease comparing with the healthy subjects except for Li. Third, the levels of various elements (Li, V, Cr, Mn, Co, Se and Mo) negatively correlated with HbA1c in the diabetes subjects. Moreover, the contents of V, Cr, Mn and Se also showed lower in HbA1c ≥ 7.0% group in contrast to HbA1c < 7.0% group.

Previous animal and cell studies of trace elements in T2D remains controversial with clinical studies. Similarly, our clinical study results also differed from previous results in certain elements, which are mostly due to the selection of specimen. In this study, we analyzed the levels of trace elements in peripheral whole blood, whereas previous studies used serum or urine (Dubey et al. 2020; Wu et al. 2021; Wang et al. 2016; Kohler et al. 2018; Siddiqi et al. 2020; Shan et al. 2016; Sun et al. 2020; Yin et al. 2019; Zhao et al. 2019; Fukunaka and Fujitani 2018). Authoritative assessments of trace elements levels in human body include trace elements intake and the intra-tissue content. However, trace elements intake is not a good indicator for the differences in absorption capacity of individuals. Due to uneven distribution, lower contents of trace elements or easily contaminated, the assessments of trace elements in serum, urine, nail or hair are also not good choices (Joda and Ward 2021; Luan et al. 2021). And it is difficult to extract and analyze trace elements of organ tissues from diabetic or healthy human. In comparison, the contents of trace elements in whole blood can more accurately reflect the nutritional status of body, especially for trace elements which are richer intracellularly. Moreover, previous studies mostly focused on single trace element in the development of diabetes (Dubey et al. 2020; Wu et al. 2021; Wang et al. 2016; Kohler et al. 2018; Siddiqi et al. 2020; Shan et al. 2016; Sun et al. 2020; Yin et al. 2019; Zhao et al. 2019; Fukunaka and Fujitani 2018). In fact, there are interactions between elements in the body (Luan et al. 2021; Zemrani and Bines 2020). Spearman test revealed a large number of correlations between trace elements in diabetic patients (supplement materials Table 3).

The results of this study showed that there are differences in whole blood trace elements levels among the diabetes, prediabetes and healthy subjects except for Sr. Sr level is relatively too low in whole blood due to 99.0% of Sr present in the bones (Zemrani and Bines 2020; Cannas et al. 2020). The results of

this study also showed that the majority of diabetic patients do not have micronutrient deficiencies except for Li. It has been reported that Li can enhance the synthesis and secretion of insuline (Zemrani and Bines 2020; Cannas et al. 2020; Calderón Guzmán et al. 2019; Jung et al. 2021). Li decreased in the diabetes comparing with healthy subjects, which is consistent with previous reports. The other elements excluding Se increased in different degree in the diabetes comparing with healthy subjects. Hence most trace elements are not deficient in diabetes, which is largely due to the excess nutrition that comes with the improvement of people's living standards (Weihrauch-Blüher et al. 2018). Both excesses and deficiencies of trace elements may cause oxidative stress and lead to imbalances in glucose homeostasis and insulin resistance (Dubey et al. 2020). Moreover, overdose metallic elements may be accumulated and deposited mainly in the liver, which is an important organ of glucose metabolism. Metallic elements overloading will increase the burden of liver, resulting in glucose dysregulation and diabetes mellitus (Shan et al. 2016; Sun et al. 2020; Yin et al. 2019; Zhao et al. 2019; Fukunaka and Fujitani 2018).

On one hand, our studies indicate that the excessive trace elements can be involved in the progression of diabetes mellitus. On the other hand, diabetes mellitus can also alter the concentrations of trace elements, which may further lead to changes in the micronutrients status of an individual (Dubey et al. 2020). The results of this study indeed showed negative relationships between the elements (Li, V, Cr, Mn, Co, Se or Mo) and HbA1c in the diabetes subjects. In accordingly, the levels of V, Cr, Mn and Se were lower in the diabetes with HbA1c $\geq$ 7.0% comparing with the diabetes with HbA1c $<$ 7.0%. There have been studies on the relationship between FBG and elements, but we did not find any correlation (supplement materials Table 1). And there was no difference of trace elements between the diabetes subgroups divided by FBG (supplement materials Table 2). However, in healthy subjects, we also have not found any trace elements concentrations associated with HbA1c or FBG. As is known that HbA1c can better reflect the average high blood glucose levels of the body (Ma et al. 2021). Obviously, hyperglycemia can affect gastrointestinal function of the body, and trace elements are mainly absorbed in the intestinal tract through active absorption and passive absorption (Chatterjee et al. 2017). Thus, the development of diabetes affects the absorption of trace elements and potentially alters the concentrations of trace elements. Our study also has some limitations. The absolute value of correlation coefficients were lower because of fewer patients with high HbA1c value ($>$ 10.0%).

The results of this study also showed that the change of Cu and Li with HbA1c in the body were different from other elements. Cu was elevated in the diabetes and positively correlated with HbA1c in the diabetes and prediabetes subjects, but there was no correlation in the diabetes subjects or in the prediabetes subjects. Our investigations indicate that excess of Cu is indeed not good for glucose regulation which is consistent with previous studies (Sun et al. 2020). Li was reduced in diabetes and positively correlated with HbA1c in the prediabetes subjects, but negatively correlated with HbA1c in the diabetes subjects. Although the change of Li appeared dramatically, it has protective effects on glucose regulation.

In this study, we evaluated eleven trace elements in whole blood for a population of diabetes and prediabetes. Although some elements are negatively correlated with HbA1c in the diabetes subjects, most of them are not significantly deficient and even higher comparing with the healthy subjects. The extra supplement of trace elements for diabetes and prediabetes needs consideration. Reasonable supplement and regular monitoring are essential. This study provides the most in-depth investigation of trace elements and HbA1c, and the obtained data is hoped to be helpful for clinical assessment for determining the appropriate level of nutritional intake and the need for supplements in diabetes and prediabetes.

Conclusions

In conclusion, by analyzing the contents of nutrient elements in whole blood of the diabetes without complications, prediabetes and apparently healthy subjects using ICP-MS, higher contents of various elements (V, Cr, Mn, Fe, Co, Cu, Zn, Se and Mo) were found in the diabetes subjects or in the prediabetes subjects comparing with the healthy subjects except for Li. However, the levels of various elements (Li, V, Cr, Mn, Co, Se and Mo) negatively correlated with HbA1c in the diabetes subjects. Moreover, the contents of V, Cr, Mn and Se showed lower in

HbA1c ≥ 7.0% subgroup in contrast to HbA1c < 7.0% subgroup of the diabetes. These data are hoped to be helpful for clinical assessment in the diagnosis and treatment of diabetes or health care.

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Author contributions FL and YW conceived and designed study. YC, YX, and XJ contributed to acquisition of data. FL, BL and YW analyzed the data and wrote the paper. All authors assisted in revising the text and approved the final manuscript.

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Data availability The datasets used and analyzed in this study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This study was approved by the Medical Ethics Committee of Shandong First Medical University in accordance with the Declaration of Helsinki (ethical approval number is NSFC: No. 2021-112).

Consent to participate Not applicable.

Consent for publication Participants were provided a study overview and verbal consent was attained.

References

American Diabetes Association (2020) 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. Diabetes Care 43(Suppl 1):S14–S31

Badran M, Morsy R, Soliman H, Elnimr T (2016) Assessment of trace elements levels in patients with type 2 diabetes using multivariate statistical analysis. J Trace Elem Med Biol 33:114–119

Calderón Guzmán D, Juárez Olguín H, Osnaya Brizuela N, Hernández Garcia E, Lindoro Silva M (2019) The use of trace and essential elements in common clinical disorders: roles in assessment of health and oxidative stress status. Nutr Cancer 71(1):13–20

Cannas D, Loi E, Serra M, Firinu D, Valera P, Zavattari P (2020) Relevance of essential trace elements in nutrition and drinking water for human health and autoimmune disease risk. Nutrients 12(7):2074

Chatterjee S, Khunti K, Davies MJ (2017) Type 2 diabetes. Lancet 389(10085):2239–2251

Chen S, Zhou L, Guo Q, Fang C, Wang M, Peng X, Yin J, Li S, Zhu Y, Yang W, Zhang Y, Shan Z, Chen X, Liu L (2020) Association of plasma chromium with metabolic syndrome among Chinese adults: a case-control study. Nutr J 19(1):107

Dubey P, Thakur V, Chattopadhyay M (2020) Role of minerals and trace elements in diabetes and insulin resistance. Nutrients 12(6):1864

Fukunaka A, Fujitani Y (2018) Role of zinc homeostasis in the pathogenesis of diabetes and obesity. Int J Mol Sci 19(2):476

Hanif S, Ilyas A, Shah MH (2018) Statistical evaluation of trace metals, TSH and T4 in blood serum of thyroid disease patients in comparison with controls. Biol Trace Elem Res 183(1):58–70

Joda BA, Ward NI (2021) Use of human teardrop fluid for the determination of trace elements in healthy individuals and diabetic patients. J Trace Elem Med Biol 65:126733

Jung SR, Park SY, Koh JH, Kim JY (2021) Lithium enhances exercise-induced glycogen breakdown and insulin-induced AKT activation to facilitate glucose uptake in rodent skeletal muscle. Pflugers Arch 473(4):673–682

Kohler LN, Foote J, Kelley CP, Florea A, Shelly C, Chow HS, Hsu P, Batai K, Ellis N, Saboda K, Lance P, Jacobs ET (2018) Selenium and type 2 diabetes. Syst Rev Nutr 10(12):1924

Laakso M (2019) Biomarkers for type 2 diabetes. Mol Metab 27S(Suppl):S139–S146

Laur N, Kinscherf R, Pomytkin K, Kaiser L, Knes O, Deigner HP (2020) ICP-MS trace element analysis in serum and whole blood. PLoS ONE 15(5):e0233357

Lian S, Zhang T, Yu Y, Zhang B (2021) Relationship of circulating copper level with gestational diabetes mellitus: a meta-analysis and systemic review. Biol Trace Elem Res 199(12):4396–4409

Luan F, Liu B, Sun S, Chen Y, Xu Y, Jiang X, Guo X, Cheng S, Wang Y (2022) Analysis of eight nutrient elements in whole blood of children and adolescents using inductively coupled plasma-mass spectrometry. Biol Trace Elem Res 200(7):3078–3087

Ma J, He H, Yang X, Chen D, Tan C, Zhong L, Du Q, Wu X, Gao Y, Liu G, Wang C, Ran X (2021) A new approach for investigating the relative contribution of basal glucose and postprandial glucose to HbA1C. Nutr Diabetes 11(1):14

Nordberg M, Nordberg GF (2016) Trace element research-historical and future aspects. J Trace Elem Med Biol 38:46–52

Shan Z, Chen S, Sun T, Luo C, Guo Y, Yu X, Yang W, Hu FB, Liu L (2016) U-shaped association between plasma manganese levels and type 2 diabetes. Environ Health Perspect 124(12):1876–1881

Siddiqi SM, Sun C, Wu X, Shah I, Mehmood A (2020) The Correlation between dietary selenium intake and type 2 diabetes: a cross-sectional population-based study on North Chinese adults. Biomed Res Int 2020:8058463

Sun C, Wu QJ, Gao SY, Ma ZM, Liu YS, Zhang JY, Zhao YH (2020) Association between the ferritin level and risk of gestational diabetes mellitus: a meta-analysis of observational studies. J Diabetes Investig 11(3):707–718

Wang XL, Yang TB, Wei J, Lei GH, Zeng C (2016) Association between serum selenium level and type 2 diabetes mellitus: a non-linear dose-response meta-analysis of observational studies. Nutr J 15(1):48

Weihrauch-Blüher S, Richter M, Staege MS (2018) Body weight regulation, socioeconomic status and epigenetic alterations. Metabolism 85:109–115

Wu Q, Sun X, Chen Q, Zhang X, Zhu Y (2021) Genetically predicted selenium is negatively associated with serum TC, LDL-C and positively associated with HbA1C levels. J Trace Elem Med Biol 67:126785

Yary T, Virtanen JK, Ruusunen A, Tuomainen TP, Voutilainen S (2016) Serum zinc and risk of type 2 diabetes incidence in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. J Trace Elem Med Biol 33:120–124

Yin J, Wang X, Li S, Zhu Y, Chen S, Li P, Luo C, Huang Y, Li X, Hu X, Yang W, Bao W, Shan Z, Liu L (2019) Interactions between plasma copper concentrations and SOD1 gene polymorphism for impaired glucose regulation and type 2 diabetes. Redox Biol 24:101172

Zemrani B, Bines JE (2020) Recent insights into trace element deficiencies: causes, recognition and correction. Curr Opin Gastroenterol 36(2):110–117

Zhang H, Yan C, Yang Z, Zhang W, Niu Y, Li X, Qin L, Su Q (2017) Alterations of serum trace elements in patients with type 2 diabetes. J Trace Elem Med Biol 40:91–96

Zhao T, Huang Q, Su Y, Sun W, Huang Q, Wei W (2019) Zinc and its regulators in pancreas. Inflammopharmacology 27(3):453–464