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The Study on the Correlation Between Six Kinds of Mineral Elements and Diabetes

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Abstract The study aimed to explore the relationship of six kinds of mineral elements and diabetes among adults in northeast China. A cross-sectional survey was conducted in Jilin Province, northeast China. A total of 366 males and 204 females aged 18 ~ 77 years from Jingyu town, Dongliao town, and Changling town were included using a multistage stratified random cluster sampling design. Data was obtained from face to face interview, physical examination, and laboratory measurement. We defined the normal people (3.9 ~ 6.0 mmol/L), impaired fasting glucose (IFG) individuals (6.1 ~ 6.9 mmol/L), and diabetes mellitus (DM) (> 7.0 mmol/L) according to the WHO diagnostic criteria. Kruskal-Wallis test, Spearman rank correlation, as well as binary logistic regression were used to analyze influencing factors. lg(Cu/Zn)was correlated with DM (OR 8.390; 95% CI of OR 1.272–55.347). The specific mineral elements such as Zn, Ca, as well as Cu/Zn ratio may be the potential risk factors for diabetes. So, the supplement or reduction of these elements is supposed to be told to IFG to prevent or delay the occurrence of diabetes or DM to avoid its complication.

Keywords Mineral elements · Diabetes · Cross-sectional study · North China

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Background

International Diabetes Federation (IDF) points out that diabetes mellitus (DM) affects 415 million adults worldwide; what's more, this number will increase to 642 million people by 2040, which means one adult in ten and one birth in seven will suffer from diabetes and gestational diabetes, respectively, and every 6 s a person will die from diabetes [1]. Within China, the prevalence of DM is 9.7% in people over 20 years old, and the number reaches to 92.4 million, making up of one fourth of all DM all over the world [2]. Besides, the diabetes prevalence was 11% in the American population aged 20 to 79 years [1] and will keep rising with the population increasing and life spans lengthening. In other developed countries such as Singapore, Malta, Portugal, and Cyprus, the prevalence is 10.5, 10, 10, and 9.5%, respectively [1]. In contrast, the countries with the lowest diabetes prevalence are all in Africa, in part due to their higher prevalence of other diseases and lower life expectancy.

Besides serious outcomes of DM, numerous complications [3], for example, coronary atherosclerosis and microvascular lesion, diabetic nephropathy, retinopathy, periodontal diseases, nervous system disease, and diabetic foot, lead to severe health damage too. In addition, the socioeconomic burden of DM is heavy [4]. The health care cost of DM amounted to $673 billion in 2015, and according to IDF, this number would increase to $ 8020 billion by 2040 [1]. Back in China, the situation did not get better that the related expenditure amounted to 26.0 billion USD in 2007 and were predicted to increase to 47.2 billion USD in 2030 [5].

A lot of studies have showed that DM is influenced by the combined action of genetic factors including race and individual difference [6] and environmental factors such as built environment [7], residential noise [8], climate [9, 10], and dietary structure [11]. Influenced by the differences of region and diet, the content of mineral elements in bodies varies from person to person. While individual and lifestyle determinants relating to DM have been explored, there have been few studies on potential risk factors such as mineral elements in northeast China.

Impaired fasting glucose (IFG) is a significant status leading to DM, indicating the inordinate glucose metabolism and insulin homeostasis. A growing body of evidence showed that lifestyle adjustment in this stage could prevent the onset of diabetes, at least delayed the occurrence of overt symptom [12, 13].

The goal of this study was to explore whether hair mineral element contents as well as demographic factors were associated with DM in Jilin Province, northeast China.

Methods

Study Setting and Design

We recruited subjects aged 18 to 79 years old from typical regions of Jilin Province, northeast China. The attention focused on many variables, including age, sex, area, ethnic, education, occupation, marriage, BMI, and the concentrations of various mineral elements in hair.

Demographic and clinical information was gathered via a population-based, cross-sectional survey of chronic diseases and related risk factors accomplished in Jilin Province (22,855,797 subjects in total, including 12,355,852 and 10,499,945 subjects in urban and rural areas of northeast China, respectively [14]). Some characteristics of this survey were reported previously [15]. The inclusion criteria were (1) adults (18 to 79 years old) and (2) fasting serum glucose level no less than 3.9 mmol/L. Participants affected with endocrine, nutritional, and metabolic diseases or had no data on the content of hair metallic elements were excluded. Ultimately, 570 participants were included in this study. Among subjects, one hundred and forty-three individuals had IFG/DM (92 with IFG and 51 with DM), and four hundred and twenty-seven control subjects had normal fasting serum glucose levels.

Ethical Standards

The Ethics Committee of Jilin University School of Public Health approved this study (Reference Number: 2012-R-011). Written informed consent was obtained from each participant.

Data Collection

Questionnaire Investigation

Information on the demographic characteristics was collected from consenting participants using the well-structured questionnaires, which included questions about age, sex, areas, etc. There was at least one well-trained investigator for assistance while the subjects filled in the questionnaires in case some entries were misunderstood.

Anthropometry Measurements

Trained survey personnel performed measurements of height and weight. The height and weight of subjects were measured with bare feet, and body mass index (BMI) was calculated as the weight (kg) divided by the squared height (m^2).

Laboratory Measurements

After fasting for at least 8 h, a whole blood sample was collected from the antecubital vein into vacuum EDTA contained tubes in the morning. Plasma blood glucose was determined within 2 h of collection using a Bayer Contour TS blood glucose meter and test strips.

Mineral elements in hair were also measured in laboratory. Firstly, we collected hair roots and washed three times (15 min per wash) using a cleanser and deionized water successively. Secondly, the hair was put into dry clean test tubes, which contained 1 mL of 70% HNO_3 after cut (1–2 mm) and weighed (0.100 ± 0.003 g) precisely. Then, the tubes were capped and digested at 140 °C in electric digestion. Finally, after the samples cooled down to indoor temperature, the content of mineral elements was measured via the inductively coupled plasma mass spectrometry (ICP-MS) after diluting with deionized water to volume of 20 mL.

Definitions

According to WHO diagnostic criteria, normoglycemia, IFG, and DM were defined as the fasting serum glucose level ranging from 3.9 to 6.0 mmol/L, 6.1 to 6.9 mmol/L, and above 7.0 mmol/L, respectively. BMI was classified into four groups, such as thin (< 18.5), normal (18.5~), overweight (24.0~), and obesity (28.0~) according to Chinese standard.

Statistical Analysis

Descriptive data analysis was conducted. The Kruskal-Wallis test was used to analyze the difference of elements between the IFG, DM, and normoglycemic individuals. Eight covariates were included in log-binomial regression model to study the association between sociodemographic characteristics and diabetes and find potential confounding factors. Then, we explored the adjusted association between the element level and the diabetes using log-binomial regression analysis. All procedures above conducted in SPSS 20.0 and $p < 0.05$ were considered to be statistically significant.

Results

After strict exclusion, 570 subjects aged 18 years and over remained in the final analysis (Table 1). In the study, the mean age was 48.36 ± 12.56 years, and the majority were middle age, 64.2% were male, 43.2% were from Jingyu county, and 94.9% were Han. 28.5% studied in senior school or above, 66.8% were manual worker, 89.3% were married, and the majority had the normal BMI.

Table 2 suggested the comparison of element levels between IFG/DM and normoglycemia group. Cu/Zn ratio was significantly higher in IFG subjects or DM patients than that in normoglycemic individuals ($p = 0.006$ (IFG) and $p = 0.001$ (DM)). The content of Fe and Ca in IFG subjects or the content of Zn in DM patients was significantly lower than that in normoglycemic individuals (Fe $p = 0.013$ (IFG); Ca $p = 0.017$ (IFG); Zn $p < 0.001$ (DM)).

Table 3 showed the correlation of blood glucose levels and hair element contents. Contents of hair Zn and Ca were negatively correlated with blood glucose levels (Zn $r = -0.161$, $p < 0.001$, 95% CI (− 0.241, − 0.080); Ca $r = -0.110$, $p = 0.008$, 95% CI (− 0.194, − 0.022)). Contents of hair Cu/Zn ratios were positively correlated with blood glucose levels (Cu/Zn $r = 0.171$, $p < 0.001$, 95% CI (0.086, 0.254)).

Table 4 showed the effect of sociodemographic factors on susceptibility to DM compared with normoglycemic individuals and age, sex, region, ethnic, educational level, occupation, marriage, and BMI as covariates. The result showed that age was a risk factor for DM (45 ~ 60: OR = 3.673, OR 95% CI = 1.288–10.476; 60~: OR = 6.324, OR 95% CI = 1.865), and the old subjects had a significantly higher incidence of high blood glucose levels.

Table 5 showed the significant result of binary logistic regression between DM and mineral elements, such as Mg, Fe, Cu, Zn, Ca, V, Cu/Zn, and Ca/Mg. After adjusting for age and gender, our study suggested that higher Cu/Zn was a risk factor for DM to some extent, for the value of lg(Cu/Zn) was higher in DM group (OR = 8.390, OR 95% CI = 1.272–55.347).

Table 1 Sociodemographic characteristics among adults aged 18 and over in Jilin Province, China

Characteristics	*n*	%
Age		
Young	205	40.0
Middle	254	44.6
Old	111	19.4
Sex		
Male	366	64.2
Female	204	35.8
Area		
Jingyu county	246	43.2
Dongliao county	172	30.2
Changling county	152	26.6
Ethnic		
Han	541	94.9
Minorities	29	5.1
Education		
Primary school and below	230	40.4
Junior middle school	177	31.1
Senior middle school	104	18.2
Undergraduate and above	59	10.3
Occupation		
Manual worker	380	66.8
Mental worker	93	16.3
Retired	55	9.7
Unemployed or others	41	7.2
Marriage		
Unmarried	30	5.3
Married	509	89.3
Separated/divorced/widowed	31	54.4
BMI		
< 18.5	19	3.3
18.5~	264	46.3
24.0~	204	35.8
28.0~	83	14.6

Discussion

In this study, we explored the association between six kinds of mineral elements and diabetes among adults in Jilin Province, northeast China. The data was collected from the questionnaire, anthropometry measurements, and laboratory. Epidemiological investigations showed that age, overweight, obesity, drinking, and smoking contributed to both IFG and DM [7, 16–19], which were roughly consistent with our findings. The individuals with age more than 45 years old and higher BMI were more susceptible to DM. Also, people living in Changling town had a significantly lower prevalence of DM under the condition of no adjustment for region, educational level, BMI, etc. However, the results about the educational level which university level and middle school level had lower incidence of DM without adjustment was not consistent with our understanding, so further research needs to be done.

Besides all mentioned above, the content of hair metallic elements measured in laboratory varied in various groups. Understanding whether or not the content of mineral elements in hair is associated with DM can provide a new perspective for diabetes prevention: mineral element supplement or reduction. The content of Fe or Ca in IFG subjects and Zn in DM patients was significantly lower than that in normal individuals, whereas the content of Cu/Zn in IFG/DM patients was

Table 2 The content of hair mineral elements in normal/IFG/DM groups

Variables	Normoglycemia	IFG	DM	*H*	*p*
V	0.117 (0.075, 0.192)	0.107 (0.069, 0.166)	0.136 (0.094, 0.199)	4.61	0.10
Cu	9.725 (8.167, 11.921)	10.525 (8.505, 13.108)	9.821 (8.110, 12.415)	3.41	0.18
Fe	69.007 (42.069, 116.109)	58.098 (37.783, 85.113)[a]	73.049 (48.457, 106.783)	6.49	0.04
Zn	145.751 (122.790, 184.925)	137.634 (105.318, 172.924)	124.890 (106.686, 147.740)[b]	15.32	< 0.001
Ca	819.600 (585.800, 1299.200)	692.300 (522.300, 1143.650)	687.000 (520.400, 1126.600)	7.12	0.03
Mg	105.800 (71.400, 169.000)	103.500 (64.400, 150.850)	96.000 (62.000, 141.200)	3.55	0.17
Cu/Zn	0.065 (0.051, 0.086)	0.075 (0.057, 0.098)[a]	0.085 (0.062, 0.109)[b]	17.17	< 0.001
Ca/Mg	8.003 (6.200, 10.356)	6.979 (5.422, 9.600)	8.245 (6.588, 10.151)	5.43	0.07

[a] $p < 0.017$, comparison between IFG and normoglycemia

[b] $p < 0.017$, comparison between DM and normoglycemia

[c] $p < 0.017$,comparison between DM and normoglycemia

significantly higher when compared to that of normal individuals.

Huth's study showed that iron was inversely associated with T2DM (OR = 0.61 (95% CI 0.38–0.97)) [20]. However, Zafar came to the inverse conclusion that serum iron was positively associated with insulin resistance in non-diabetic offspring of type 2 diabetics [21] ($p = 0.027$). What's more, Ponikowska's study suggested that both low and high serum ferritin along with high serum sTfR identified patients with type 2 diabetes [22]. Derived from his meta-analysis, Bao confirmed that increased heme iron intake and body iron stores were positively associated with T2DM while dietary total iron, non-heme iron, or supplemental iron intakes were not [23]. As a matter of fact, there were several markers of iron metabolism in our bodies. The high serum ferritin was a universally acknowledged risk factor for DM [20] for that iron overload would increase lipid oxidation, influenced the synthesis and secretion of insulin, and decreased ingestion of insulin by liver and muscle tissue. Except for ferritin, evidence was sparse for other markers of iron metabolism. Our results suggested that tissue iron was inversely associated with T2DM. Considering that the content of tissue iron could better reflect the true level of iron in body than other markers of iron, our results might offer more credible guidance compared with others. Also, we thought that Zafar's conclusion might be due to the special subjects. Non-diabetic offspring of type 2 diabetics had more chance to bring the diabetes genes than ordinary people, so we could not attribute the insulin resistance to serum iron wildly.

Table 3 Correlation between blood glucose levels and hair element contents

Blood glucose			
	r	95% CI	*p*
Mg	− 0.076	− 0.160,0.004	0.069
Fe	− 0.074	− 0.154,0.007	0.078
Cu	0.069	− 0.016,0.150	0.102
Zn	− 0.161	− 0.241,-0.080	0.000*
Ca	− 0.110	− 0.194,-0.022	0.008*
V	− 0.003	− 0.082,0.080	0.952
Ca/Mg	− 0.044	− 0.122,0.035	0.293
Cu/Zn	0.171	0.086,0.254	0.000*

* The correlation was considered to be significant if p is less than 0.05 (two-tailed)

When it came to Ca element, the situation seemed complicated as well. Zaccardi suggested that there was a positive association between serum calcium (total calcium or an indirect estimate of active, ionized calcium) and incidence of T2DM in his previous study while an association between direct measurement of active calcium and risk of T2DM was not found in his serial study recently [24]. Nonetheless, Lorenzo's and Becerra-Tomás's studies showed that elevated serum calcium was associated with increased risk of developing type 2 diabetes independently of other factors like measured glucose and insulin secretion [25, 26]. We all knew that calcium played an important role in insulin secretion for that extracellular calcium was indispensable for glucose to increase insulin secretion and intracellular calcium initiated exocytosis of insulin granules [25]. When the intracellular calcium is excessive, the insulin will continue to secrete but with low activity. This is why the content of insulin in T2DM is not in deficiency, sometimes even in excess. We found no significant differences between DM and the control group in calcium content, but we observed that the content of calcium was significantly lower in IFG than that in normal group. Except for involving in the synthesis and secretion of insulin, calcium increased the sensitivity of insulin as well. IFG, a sign of prediabetes, was not surprising to have calcium deficiency. As for DM, maybe there was an extra calcium supplement

Table 4 Association between DM and sociodemographic factors among adults in Jilin Province, China

Variables	DM		
	OR	95% CI	*p*
Age			
~ 45	1.000		
45 ~ 60	3.673	1.288, 10.476	0.015
60~	6.324	1.865, 21.451	0.003
Sex			
Male	1.000		
Female	0.609	0.300, 1.237	0.170
Area			
Jingyu county	1.000		
Dongliao county	0.831	0.348, 1.986	0.678
Changling county	0.795	0.369, 1.711	0.557
Ethnic			
Han	1.000		
Minorities	0.417	0.052, 3.352	0.411
Education			
Primary school and below	1.000		
Junior middle school	0.609	0.268, 1.387	0.238
Senior middle school	0.644	0.238, 1.741	0.386
Undergraduate and above	0.131	0.013, 1.331	0.086
Occupation			
Manual worker	1.000		
Mental worker	1.766	0.480, 6.502	0.392
Retired	1.905	0.693, 5.237	0.212
Unemployed or others	0.844	0.213, 3.343	0.809
Marriage			
Unmarried	1.000		
Married	0.450	0.080, 2.518	0.363
Separated/divorced/widowed	0.278	0.032, 2.449	0.249
BMI			
< 18.5	1.000		
18.5~	0.436	0.079, 2.401	0.340
24.0~	0.759	0.139, 4.151	0.751
28.0~	1.696	0.293, 9.806	0.555

to escape from calcium-related complication such as osteoporosis.

Table 5 Adjusted association between mineral elements and DM among adults in Jilin Province, China

Variables	DM		
	OR	95% CI	*p*
lg(Cu/Zn)[a]	8.390	1.272, 55.347	0.027

[a] Adjusted for age and gender and only significant result was presented

In Zargar's findings, plasma zinc level was significantly higher in type 1 DM patients [27], whereas Valera's and Afridi's studies found that there lied a negative correlation between Zn and DM [28, 29], which were consistent with our results. In fact, the deficiency of Zn might lead to DM can be understood. Zn existed in islet cells and could promote crystallization of insulin. Therefore, Zn deficiency will decrease the serum insulin level to cause obstruction of glucose utilization [30, 31]. Partida-Hernandez's and Xu's studies suggested the serum copper and the Cu/Zn ratio rose with the decline of serum zinc level in DM [32, 33]. Also, the serum Cu level was positively associated with HbA1c in T2DM subjects [33, 34]. These findings were consistent with ours. In binary regression analysis, lg(Cu/Zn) was a prominent risk factor for DM (OR 12.76; 95% CI of OR 2.02–80.73). The reduction of Zn in diabetes could explain the increase of Cu/Zn ratio. The mechanism of elevated serum Cu/Zn ratio in diabetics has not been figured out yet. Most investigators tended to think that there was mutual interaction between Zn and Cu to keep their appropriate proportion, and when the proportional relationship was destroyed, people were likely to suffer from IFG or DM [35, 36]. This viewpoint was based on the similar atomic structure of copper and zinc so that they were both capable of going into the cells via the anion channels on the cell membrane to attain antagonism. The characteristics of this have been applied to clinical treatment [37–39].

However, we found no significantly differences between IFG/DM and normal subjects in the content of Mg, which was not consistent with studies from Del Gobbo, Barbagallo [40, 41]. In most studies, the deficiency of Mg caused DM by decreasing the synthesis of hepatic glycogen, increasing the enzyme activity of gluconeogenesis, and suppressing the insulin response to glucose [42–46].

All in all, the balance of mineral elements in human body contributes a lot to the sugar metabolism and stability of insulin secretion so that it can influence the occurrence of IFG/DM or not. The IFGs are supposed to apply these findings to regulate lives with increasing or reducing the intake of relevant mineral elements appropriately to delay or prevent the occurrence of the chronic killers while DM should do the same to improve their ill condition.

Conclusion

Besides lifestyle improvement such as weight control and supplements of specific metal elements, such as iron, zinc, and calcium, should be told to the large proportion of subjects, especially the IFG as well. In addition, the ratio of copper and zinc is supposed to be paid attention to. We believe that an individual at risk for DM can prevent the onset of the disease or at least delay its progress by proper weight loss, appropriate metal element supplements, and frequent blood glucose monitoring.

Limitations and Strengths

Firstly, the binary logistic regression analysis in our study showed that “male” is a strong risk factor for IFG and DM (IFG p = 0.045, OR = 0.99, 95% CI = 0.98–1.00; DM p = 0.046, OR = 0.99, 95% CI = 0.98–1.00) without adjustment. The ORs did not reach a statistical significance after adjusting for age, region, educational level, as well as BMI. The instability of results may be due to the small number of cases. Hence, larger populations are supposed to study on to reach a consistent conclusion. Secondly, some studies showed that dietary therapy aimed at supplementing mineral elements may be an emerging way for diabetic patients. However, our study did not elaborate a specific dietary composition so that our findings cannot apply to diabetic therapies directly. With the expectation that our findings can benefit more diabetics and people who are at risk, we will keep on exploring in this field in the near future. Thirdly, when taking the numerous forms and status of the trace elements into consideration, I hold the view that the trace elements in our study should be divided into more forms to find their relationship with IFG/DM. The different conclusions derived from the same kind of mineral elements are mostly due to the various status of the elements they studied on. Finally, according to the totally different pathogenesis, clinical manifestation, diagnosis, therapies, and outcomes towards type 1 diabetes and type 2 diabetes, I think the findings will be more specific and scientific to benefit more people. Till now, quite few published papers have studied the correlation between mineral elements and diabetes, though it has been put forward that trace elements may be related with diabetes for a long time. Therefore, the findings from our study could help deepen our understanding about the effects of mineral elements on diabetes and make proper guidance towards supplements of mineral elements for individuals who are in risk of IFG/DM.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that there is no conflict of interest.

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