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ZINC INTAKE AND THE RISK OF HYPERGLYCEMIA AMONG CHINESE ADULTS: THE PROSPECTIVE JIANGSU NUTRITION STUDY (JIN)

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Abstract: *Objective:* To prospectively examine the associations between zinc intake, the zinc to heme iron ratio and the incidence of hyperglycemia in Chinese. *Methods:* We followed 1056 healthy adults aged 20 and older from 2002 to 2007. Dietary data were collected using 3-day food record and food frequency questionnaire. Hyperglycemia was defined as fasting plasma glucose >5.6 mmol/l. *Results:* During the 5 years of follow-up, we documented 125 incident cases of hyperglycemia. Zinc intake alone was not associated with the risk of hyperglycemia. The zinc to heme iron ratio was inversely associated with the risk of hyperglycemia: odds ratios (OR, 95% CI) across increasing quartiles of the zinc to heme iron ratio were 1.00, 0.78(0.44-1.37), 0.40(0.19-0.83), and 0.21(0.08-0.54)(p for trend= 0.001). Adjustment for lifestyle covariates did not significantly change the associations. *Conclusions:* This cohort study suggests that the zinc to heme iron intake ratio was significantly associated with a decreased risk of hyperglycemia in Chinese adults.

Key words: Zinc intake, hyperglycemia, adults, China.

Zinc is a component of more than 300 enzymes (1). It has diverse biological functions in enzymatic catalysis, redox regulation, and the immune system (2). In animal studies, zinc has shown a beneficial effect on insulin sensitivity (3). Zinc deficiency activates stress pathways and may result in a loss of tyrosine phosphatase control, thereby causing insulin resistance (4). Zinc has an antioxidant effect and prevents the structural and functional properties of free radical treated-insulin (5, 6). Dietary Zn supplementation attenuates hyperglycemia and hyperinsulinemia in db/db mice (7).

In humans, it is found that zinc deficiency aggravates abnormal glucose metabolism (8). In a cross-sectional study, low consumption of dietary zinc and low serum zinc levels was associated with an increased prevalence of diabetes (9). Recently, a prospective study (i.e Nurses' Health Study (NHS)) investigated the dietary zinc intake and risk of diabetes. High zinc intake was associated with a decreased risk of type 2 diabetes in women (10).

Opposite to zinc, iron overload has been associated with diabetes in Western and Asian populations (11-13). Iron overload may stimulate oxidative stress and inflammation, thus promote the development of diabetes (14, 15). Competitive interaction of iron and zinc in the diet is observed (16). Zinc to heme iron ratio was recently found to be inversely associated with the risk of diabetes in US women (10). No study has examined the effects of zinc intake, especially in joint with iron intakes, on diabetes risk in Chinese.

Using Jiangsu Nutrition Study (JIN) prospective data, the objectives of the present study are: 1) to prospectively examine whether diet intake of zinc is related to risk of hyperglycemia in the Chinese population; and 2) to examine whether there is an interaction between zinc and heme iron in the development of hyperglycemia.

Research design and methods

Sample

The JIN cohort study of person aged 20 years or older and the methods of sampling have been described previously (17). In 2002, 2849 adults aged 20 and above living in two cities and six rural areas had fasting blood samples measured for glucose, and were obtained dietary information. In 2007, only 1682 participants can be identified, 1492 of them participated in the study, and 1175 of them had fasting blood samples measured. For current analysis, we included study participants with a fasting plasma glucose <5.6 mmol/l in 2002 and without known diabetes. The final sample in the study consists of 445 men and 611 women. The study was approved by institutional ethics committees of the Jiangsu Provincial Center for Disease Control and Prevention.

Biomedical Assessment

Medical assessment of participants included measurements of height, weight (in light clothing and without shoes). Body mass index (BMI) (kg/m^2) was calculated. Waist circumference (cm) was measured midway between the inferior margin of the last rib and the iliac crest in a horizontal plane. Hypertension was defined as systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg, or using antihypertensive drugs.

Overnight fasting blood samples were collected from all study participants. The blood samples were analyzed for fasting plasma glucose (FPG) in local Centres for Disease Control and Prevention according to standard procedures. We defined diabetes as FPG>7.0mmol/l, hyperglycemia as FPG>5.6 mmol/l.

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Dietary measurements

Nutrient intakes were measured by three day weighed food records. Participants were instructed to undertake this for 3 consecutive days including a weekend day. Food consumption data were analyzed using the Chinese Food Composition Table (18).

Four dietary patterns were identified by factor analysis based on food intake measured by Food Frequency Questionnaire, using standard principal component analysis. It has been described elsewhere (19).

Assessment of covariates

Questionnaire data were obtained on previous doctor diagnosis of diabetes, smoking history, physical activity and sedentary activity, family history of diabetes, and demographic details including work status (manual, non-manual), and income.

Statistical analyses

Chi square test was used to compare differences in categorical variables, and General Linear Models were used to compare mean values of quantitative traits between groups. The associations between zinc intake, the zinc to heme iron ratio and the risk of hyperglycemia were analyzed using logistic regression models. The multivariable logistic model controlled for age (continuous), energy intake, education, smoking, sedentary activity, family history of diabetes (yes/no) was applied. Household cluster was taken into consideration by using the xtmelogit procedure in STATA (version 10, Stata Corp, College Station, TX). We used restricted cubic spline regressions (20) to graphically model the associations between the zinc to heme iron intake ratio (continuous) and the risk of hyperglycemia. Statistical significance was considered when $p<0.05$ (two sided). All the analyses were performed by using STATA software.

Results

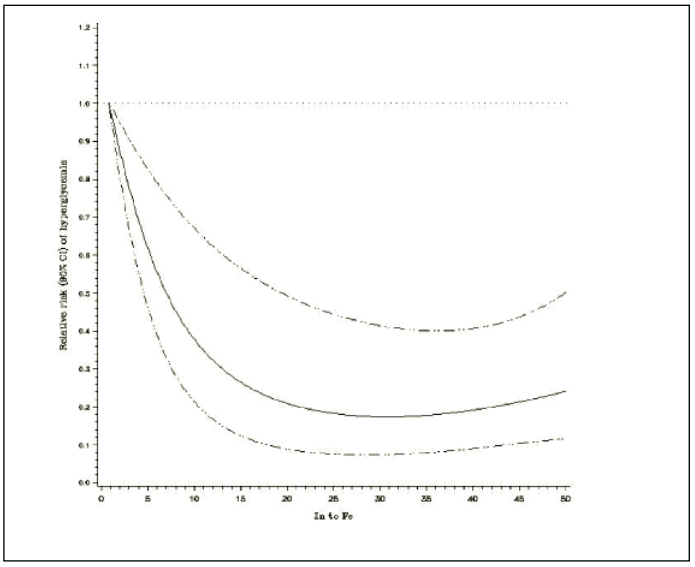
The mean intakes of zinc and heme iron were 12.2 and 2.4 mg/day, respectively. Zinc intake was positively associated with protein intake but negatively associated with carbohydrate intake at baseline (Table 1). During the 5-year follow-up, we identified 125 cases of hyperglycemia, among them 23 were cases of diabetes. 8 participants started taking diabetic medication during the follow up.

Intake of zinc was not associated with the risk of hyperglycemia in both crude and multivariate adjusted models. However, the zinc to heme iron ratio was significantly associated with a decreased risk of hyperglycemia. After adjustment for age and gender, the ORs for hyperglycemia across quartiles of zinc to heme iron intake ratio were 1.00, 0.83(0.48-1.43), 0.39(0.21-0.74), and 0.23(0.11-0.47) (p for trend<0.001).

In full model (model 3) adjusting for other known type 2 diabetes risk factors the ORs of hyperglycemia across quartiles of the zinc to heme iron intake ratio were 1.00, 0.78(0.44-1.37), 0.40(0.19-0.83), and 0.21(0.08-0.54)(p for trend= 0.001). Excluding those who took diabetic medication during follow up did not change the association (data not shown). The regression splines indicated a linear relation between the zinc to heme iron intake and hyperglycemia risk when the ratio was lower than 20 (Figure 1).

Figure 1

Association between the zinc to heme iron ratio and the risk of hyperglycemia among Chinese adults (OR adjusted variables cited in Table 1, model 3): Jiangsu Nutrition Study`



When we used diabetes as outcome, the inverse association between the zinc to heme iron ratio and risk of diabetes was statically significant although the confidence interval was wide due to the small number of cases (n=23). The ORs of diabetes across quartiles of the zinc to heme iron ratio were 1, 0.97(0.33-2.81), 0.60(0.18-1.98), 0.03(0.002-0.35) (p for trend 0.012).

Because the zinc to heme iron ratio was significantly correlated with heme iron intake (correlation coefficient = -0.27, $p<0.001$), it was possible that the association between the zinc to heme ratio and hyperglycemia was only a marker of the effect of heme iron. We therefore performed a further analysis by additionally adjusting for heme iron intake. The association remained significant: ORs across quartiles were 1, 0.82(0.45-1.52), 0.43(0.20-0.93), and 0.22(0.08-0.61) (p for trend <0.001).

Stratified analysis showed that the association between the zinc to heme iron intake and hyperglycemia was not modified by genders, smoking, drinking, central obesity, and dietary patterns (data now shown).

Table 1
Baseline sample characteristics of participants and odds ratio for hyperglycemia according to zinc intake and the zinc to heme iron intake ratio quartiles: Jiangsu Nutrition Study (n 1056)

	Zinc				p	Zinc/heme iron				p
	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
Median and range	8.4	10.8	12.9	16.1		3.1	5.5	9.2	83.4	
(zinc intake: mg/day)	(3.3-9.8)	(9.8-11.8)	(11.8-14.1)	(>14.1)		(0.3-4.3)	(4.3-6.8)	(6.8-14.8)	(>14.9)	
Nutrients intake (mean, SE)										
Energy (kcal/day)[1]	1748(27)	2172(26)	2477(26)	3022(27)	<0.001	2231(37)	2320(37)	2401(37)	2468(37)	<0.001
Fat, % energy[2]	31.7(0.7)	30.8(0.6)	32.1(0.6)	30.7(0.7)	0.015	35.9(0.5)	34.1(0.5)	31(0.5)	24.3(0.5)	<0.001
Protein, % energy[2]	11(0.2)	12.3(0.1)	14.1(0.1)	16.3(0.2)	<0.001	14.9(0.2)	14(0.1)	12.9(0.1)	11.9(0.2)	<0.001
Carbohydrate, % energy[2]	57.3(0.7)	56.9(0.6)	53.8(0.6)	53(0.8)	0.007	49.1(0.5)	51.9(0.5)	56.2(0.5)	63.8(0.5)	0.002
Heme iron	0.5(0.2)	1.7(0.2)	3.2(0.2)	4.2(0.2)	<0.001	5.8(0.1)	2.2(0.1)	1.3(0.1)	0.3(0.1)	<0.001
Magnesium (mg/day)[2]	280.5(6.7)	300.5(5.5)	319.4(5.4)	392.8(7)	<0.001	296.8(5.3)	297.3(5.3)	322.1(5.3)	376.9(5.3)	<0.001
Red meat (g/day)[2]	25.9(4.6)	52.4(3.8)	83.1(3.7)	109.3(4.8)	<0.001	126.3(2.9)	87.4(2.8)	49.7(2.8)	7.4(2.9)	<0.001
Dietary fiber (g/day)[2]	12.1(0.7)	11.3(0.5)	11(0.5)	13.2(0.7)	0.028	8.9(0.5)	9.4(0.5)	11.2(0.5)	18.2(0.5)	<0.001
Zinc (mg/day)[2]	8.9(0.1)	11.1(0.1)	12.8(0.1)	15.8(0.1)	<0.001	13(0.1)	12.2(0.1)	11.9(0.1)	11.5(0.1)	<0.001
Age (years)	52.4	48.0	47.7	46.6	<0.001	47.1	48.1	48.5	50.9	0.007
Women (%)	76.5	67.8	51.9	35.2	<0.001	51.5	54.6	60.2	65.2	0.008
BMI (mean, SE)[1]	23.1(0.2)	23.4(0.2)	23.1(0.2)	23.6(0.2)	0.267	23.3(0.2)	23.1(0.2)	23.0(0.2)	23.7(0.2)	0.084
Central obesity (%)[1]	23.0	28.7	27.8	36.6	0.008	24.0	26.9	26.5	38.8	<0.001
Anemia (%)[2]	28.9	28.8	32.7	24.7	0.251	36.6	35.1	29.3	14.1	<0.001
Smoker (%)	14.8	22.4	28.8	44.7	<0.001	34.5	26.1	24.6	25.4	0.040
Drinker (%)	9.9	20.8	28.4	43.2	<0.001	28.0	25.4	26.1	22.7	0.570
No. of new hyperglycemia cases	34	26	32	33		46	41	23	15	
OR (95%CI) for hyperglycemia										
Model 1[3]	1	0.73 (0.39-1.38)	0.89 (0.48-1.66)	0.85 (0.44-1.63)	0.772	1	0.83 (0.48-1.43)	0.39 (0.21-0.74)	0.23 (0.11-0.47)	<0.001
Model 2[4]	1	0.71 (0.38-1.34)	0.94 (0.50-1.75)	0.96 (0.50-1.87)	0.885	1	0.80 (0.47-1.38)	0.43 (0.23-0.82)	0.24 (0.11-0.52)	<0.001
Model 3[5]	1	0.70 (0.36-1.37)	0.87 (0.41-1.86)	0.93 (0.35-2.46)	0.981	1	0.78 (0.44-1.37)	0.40 (0.19-0.83)	0.21 (0.08-0.54)	0.001

1. Adjusted for age, sex; 2. Adjusted for age, sex and energy intake; 3. Model 1 Adjusted for age and gender; 4. Model 2 Additionally adjusted for BMI (continuous);central obesity(waist circumference: men≥90cm, women≥80cm); hypertension; family history of diabetes (yes or no); sedentary physical activity (<1, 1-2, 2-3, ≥3 hours/d); active commuting (no, 1-30, ≥30 min/d); cigarette smoking (never,1-19, ≥20 cigarettes/d); alcohol consumption (0, 1-2 times/week, 3-4 times/week, daily); education, income (low, medium, high), job (manual, non-manual); 5. Model 3 Additional adjusted for intakes of total energy, fat, fiber, and red meat.

Conclusions

In this prospective study we found an inverse linear association between dietary zinc to heme iron ratio and risk of hyperglycemia. The association remained significant after adjusting for known risk factors as well as intake of heme iron. Zinc intake alone was not associated with hyperglycemia.

Zinc is found to be protective to oxidative stress and can increase the level of insulin sensitivity (4). Opposite to zinc, both in Western and Asian populations, a positive relationship between iron store and diabetes has been found (15). In China, four studies have found a positive association between iron and diabetes (13, 21-23). Possible mechanisms by which body iron stores increases diabetes risk might be by promoting both insulin resistance and increased oxidative stress (14). Because there is a competitive relation between iron and zinc in relation to diabetes, a high ratio of the zinc to heme iron may lower the risk of diabetes. Our results support this hypothesis. In our study we found a linear relation between zinc to iron intake ratio and a reduced diabetes risk. The finding is consistent with results from the NHS (10). In NHS, the RR for diabetes comparing the extreme quintiles of the zinc to heme iron ratio is 0.72 (95% CI 0.66-0.80). The inverse association was much stronger in our study even though the value of the zinc to heme iron ratio in the reference group of our study was similar to NHS: comparing the extreme quartiles of the zinc to heme iron ratio, the OR for hyperglycemia was 0.21(0.08-0.54). The difference between the two studies may be due to disparities in the dietary compositions of US and Chinese populations. The iron intake was higher in our sample than that of the NHS. It might also be because different outcomes (hyperglycemia vs diabetes) were used in these studies. Furthermore, the difference in the levels of inflammation or infection between the two study populations could also be one of the explanations, e.g. the prevalence of hepatitis B infection is high in China (24). An inverse association between zinc and diabetes is also observed in NHS, but no such association was found in our study. It could be that in our study there was a significant difference of heme iron intake across zinc intake quartiles, while it was not so in NHS. Adjusting for heme iron intake may not adequately control the influence.

One strength of the study is that we used data from a

prospective study. Adding dietary pattern as a covariate strengthened the finding of the link between iron and abnormal blood glucose because it took the possible interactions between food components into consideration. Furthermore, nutrient intake was assessed by weighted food record that reduces the possible recall bias. A limitation of the study is the small number of incident cases of diabetes. However, we were able to show that the zinc to heme iron intake ratio could predict the risk of diabetes although the confidence interval was wide.

Overall, we found an inverse association between the zinc to heme iron ratio and hyperglycemia in Chinese people. Our results were consistent with the recent findings in a prospective cohort of US population and in line with the biological role of zinc in glucose metabolism.

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