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Association of Serum Concentrations of Magnesium and Some Trace Elements with Cardiometabolic Risk Factors and Liver Enzymes in Adolescents: the CASPIAN-III Study

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Abstract This study aims to investigate the association of serum concentrations of magnesium (Mg), selenium (Se), chromium (Cr), and copper (Cu) with cardiometabolic risk factors and liver functions in Iranian children and adolescents. This case-control study was conducted under a national surveillance program. It comprised 320 students, aged 10–18 years, in two groups of equal number with or without metabolic syndrome (MetS). Serum concentrations of Mg and abovementioned trace elements were measured by atomic absorption spectrophotometry. Median regression analysis and different models of logistic regression were used to determine the associations of these elements with cardiometabolic risk factors. In the MetS group, the median of Mg, Se, Cr, and Cu was lower or equal to controls. Mg had significant inverse association with some MetS components; however, the corresponding figure was stronger for the simultaneous association of Mg, Se, Cr, and Cu with MetS components. The binary logistic regression revealed that Mg was a significant protective factor against MetS (P=0.0001). Likewise, by considering the simultaneous association of Mg, Se, Cr, and Cu with MetS, Se was a significant protective factor against MetS. The corresponding figures were not significant for Cr and Cu. Se and Cu had significant inverse association with liver enzymes. The protective role of Mg and Se against MetS and liver enzymes, as well as the associations of these elements with some cardiometabolic risk factors and liver enzymes in the pediatric age group should be considered in future preventive and interventional studies.

Keywords Trace elements · Metabolic syndrome · Cardiometabolic risk factors · Adolescents · Prevention

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Introduction

The escalating trend of obesity and related metabolic disorders is becoming a universal health problem. Metabolic syndrome (MetS) is the most important problem of this category with late-onset complications. It has different definitions, but in general, it consists of the co-existence of three of following components: obesity, elevated blood pressure, increased serum glucose, and dyslipidemia including increased triglycerides (TG) and depressed high-density lipoprotein cholesterol (HDL-C) levels [1–4].

A growing body of evidence exists on the emergence of Mets in the pediatric age group both in developed and developing countries [1, 5–9]. Some studies proposed the association of some major minerals and trace elements with MetS components [2, 4, 10]. Liver enzymes have strong association with cardiometabolic risk factors including the MetS components [11]. Major minerals and trace elements play key roles in

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diverse organs and several reactions; they might be correlated with some chronic diseases [12–14]. The role of magnesium (Mg), copper (Cu), selenium (Se), and chromium is underscored in this regard [13, 15, 16]. Mg, as second most plentiful intracellular-positive ion in living cells, plays a key role as a cofactor in enzymatic reactions and also in adjusting insulin action, glucose metabolism, and vascular tone, and its concentration possibly can be connected to cardiometabolic disorders [11, 16]. Cu is an essential element for human growth and development, and its deficiency may result in cardiac hypertrophy, poor neuronal myelination, blood vessel disorders, and improper immune responses. Moreover, it affects liver function and lipid and iron metabolism [17–19]. Se is a main constituent of various selenoproteins involved in essential enzymatic functions, an important material related to immune and reproductive system efficiency. Regarding these effects, scientists pay attention to its possible relationship with prevention of chronic diseases [15, 20, 21]. Cr is a trace element in the human body with integral impact on glucose homeostasis, insulin signaling, and development of insulin sensitivity. Consequently, these effects appear to be useful in prevention and management of cardiometabolic disorders [22, 23].

Given the origins of cardiometabolic disorders from early life, this study aims to investigate the association of serum concentrations of Mg, Se, Cr, and Cu with cardiometabolic risk factors and liver enzymes in Iranian children and adolescents.

Materials and Methods

This case-control study was conducted under the third survey of the countrywide school-based surveillance system entitled Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable disease (CASPIAN-III) study. This case-control study comprised 320 adolescents in two groups of equal number with or without MetS.

The institutional review and ethical boards approved the main study at national and provincial levels. Written consent and oral assent were obtained from students and their parents, respectively. The current substudy was conducted from May to September 2013 on frozen sera collected in the main study; it was approved by the Ethics Committee of Isfahan University of Medical Sciences and was conducted in accordance with the ethical standards of the Helsinki Declaration.

The main study was conducted as a school-based nationwide health survey among 5570 students aged 10–18 years, who were recruited by multistage random cluster sampling from urban and rural areas of 27 provincial counties in Iran. Those students with history of any acute or chronic diseases and any medication use were not included to the study [24]. For recruiting a nationally representative sample in the current substudy, individuals were randomly selected by using random number table from among those students who fulfilled the criteria of MetS for the case group and those without MetS as controls. Both groups were selected from various parts of the country, where the main study was conducted. We matched the case and control groups for gender, age group, and the living area.

A trained team of health professionals conducted the physical examination under standard protocols by using calibrated instruments. Weight, height, and waist circumference (WC) were measured. Body mass index (BMI) was calculated as weight (Kg) divided by height squared (m^2). Blood pressure (BP) was measured under standard protocol [25].

For blood sampling, students were invited to the nearest health center to the school. Fasting venous blood samples were centrifuged, and fresh sera were analyzed for fasting blood glucose (FBG), lipid profile, and liver functions, i.e., alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST), by using Pars Azmoon reagent kits (Tehran, Iran).

For measuring Mg and trace elements, frozen sera (−70 °C) of participants with MetS and an equal number of healthy controls were used. Serum Mg, Cu, Cr, and Se levels were determined with atomic absorption spectrophotometer by using hollow cathode lamps of each element. Similar to the first survey of the CASPIAN study [26], we used the MetS definition provided by Cook et al. [27]. This definition is based on criteria analogous to that of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III (ATP III) [28]. It characterizes an adolescent with MetS who met at least three of the following criteria: WC≥the age- and gender-specific 90th percentile value; systolic and diastolic BP (SBP and DBP)≥the 90th percentile for age, sex, and height; and HDL-C≤40 mg/dL, TG≥110 mg/dL [26, 27], and FBG≥100 mg/dL [29].

Statistical Analysis All statistical analyses were done in R (available on CRAN at www.r-project.org.softwares) and SPSS statistical package (SPSS, Chicago, IL; version 18:0) for Windows. Data that were described with descriptive statistics included mean, standard deviation (SD), and median. MetS components were considered as dependent variables, and their normality was evaluated with Q-Q plot. In most cases, the dependent variables had skewed distributions and deviated from normal distribution. Therefore, for examining the associations of trace elements with MetS components, median regression was used. This analysis is a robust analysis against parametric regression approaches as mean regression. In the median regression analysis, independent variables (i.e., trace elements) linked with distribution median of dependent variables (i.e., MetS components). The crude and simultaneous associations of trace elements with MetS

components were evaluated in different models. Model 1 denotes the single association of elements, and model 2 denotes the association of elements when other elements existed in the model. Both models were adjusted for gender and age. Results are reported as regression coefficient, standard error (SE), and significance level. Moreover, the relationship of trace elements with existence of MetS was evaluated by binary logistic regression; obtained results are reported as coefficients regression and odds ratio (OR). It was assessed by three models: model 1 presents the crude relationship, model 2 for the association of each trace element with MetS in existence of other elements, and model 3 included only trace elements that had significant association with MetS. Model 3 was obtained by backward stepwise selection variable.

Results

The study population consisted of 320 adolescents (160 with MetS and 160 healthy controls). The mean age of the case and control groups was not significantly different (15.3± 2.6 vs. 14.96± 2.51 years, respectively, $P>0.05$). Table 1 presents the characteristics of variables studied including the trace elements, MetS components, and liver enzymes. As most variables had asymmetric distribution, median index was reported. In the MetS group, the median of trace elements was lower or equal to controls. As expected, mean and median of most MetS components were greater in the MetS group than in controls.

Table 2 shows the results of fitting regression models for each MetS component considered as a separate dependent variable. Cr had no significant association with the MetS components whether in the presence or non-existence of other elements. Se has a statistical inverse association with ALT in model 2 ($P=0.03$). In both models, Cu had statistical inverse association with AST ($P=0.04$). In both models, Mg had significant inverse association with some MetS components; this association was stronger in existence of other trace elements. In model 2, Mg had significant association with most MetS components including SBP and DBP ($P=0.0001$), TG ($P=0.001$), FBG ($P=0.009$), AST ($P=0.007$), ALT ($P=0.001$), and BMI ($P=0.01$).

Results of the three aforementioned models used for binary logistic regression of trace elements and existence of MetS are presented in Table 3. Based on the results of all three models, Mg was a significant protective factor against MetS ($P=0.0001$ in all models). In the presence of other elements, the inverse association of Mg with MetS was stronger (model 2).

In the presence of other trace elements, Se was a significant protective factor against MetS ($P=0.03$), but the crude association (model 1) was not significant.

The corresponding figures were not significant for Cu and Cr.

Table 1 Trace elements and cardiometabolic risk factors in adolescents with or without metabolic syndrome: the CASPIAN-III Study

	Metabolic syndrome					
	Negative			Positive		
	Mean	Standard deviation	Median	Mean	Standard deviation	Median
Cr (μg/mL)	0.17	0.07	0.17	0.17	0.07	0.17
Se (ng/mL)	84.24	16.19	84.32	81.82	16.51	81.92
Cu (mg/L)	0.82	0.27	0.80	0.81	0.26	0.80
Mg (mg/dL)	1.65	0.08	1.65	1.54	0.09	1.54
SBP (mmHg)	101.74	14.51	100.00	121.89	10.93	120.00
DBP (mmHg)	64.55	11.06	61.00	79.32	6.85	80.00
TC (mg/dL)	147.28	24.28	145.50	162.95	38.75	160.00
HDL-C (mg/dL)	41.45	9.83	38.00	41.56	15.66	40.00
LDL-C (mg/dL)	90.47	20.28	88.50	91.56	24.15	94.00
TG (mg/dL)	79.81	20.63	80.00	132.28	66.70	120.50
FBG (mg/dL)	81.34	6.29	83.00	97.43	16.90	100.50
AST (U/L)	22.54	7.29	21.00	25.25	9.89	24.00
ALT (U/L)	16.84	5.88	16.00	22.70	11.23	20.00
WHtR	0.42	0.09	0.41	0.51	0.13	0.50
BMI (Kg/m^2)	18.49	3.86	17.64	23.31	5.15	22.88

Cr chromium, *Se* selenium, *Cu* copper, *Mg* magnesium, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *FBG* fasting blood glucose, *AST* aspartate aminotransaminase, *ALT* alanine aminotransaminase, *WHtR* waist-to-height ratio, *BMI* body mass index

Table 2 Association of trace elements with cardiometabolic risk factors: the CASPIAN-III study

		SBP	DBP	Total cholesterol	HDL-C	LDL-C	TG	FBG	AST	ALT	Abdominal obesity	BMI
Model 1	Cr	0.00 (6.07)	−14.08 (12.24)	5.41 (33.94)	−17.39 (13.64)	19.05 (22.05)	−36.76 (27.41)	−2.76 (9.94)	7.02 (7.40)	3.13 (5.57)	−0.02 (0.10)	−5.91 (4.37)
	Se	−0.05 (0.04)	0.05 (0.06)	−0.08 (0.12)	0.00 (0.06)	0.03 (0.10)	−0.18 (0.19)	−0.04 (0.04)	0.04 (0.03)	−0.01 (0.03)	0.00 (0.00)	0.00 (0.02)
	Cu	0.00 (3.44)	−4.00 (3.80)	1.94 (8.71)	−3.33 (4.21)	−2.14 (6.98)	−0.91 (9.71)	1.54 (2.19)	−3.93 (2.04) *	0.00 (1.39)	0.00 (0.03)	0.59 (1.16)
	Mg	−58.82 (11.69) ***	−39.68 (4.91) ***	−20.00 (20.42)	−4.30 (11.73)	−1.41 (16.61)	−71.03 (24.80) **	−35.67 (9.81) ***	−14.77 (4.79)	−11.11 (4.39)**	−0.11 (0.07) *	−7.46 (3.17) **
Model 2	Cr	2.07 (13.68)	−6.54 (9.21)	24.81 (29.82)	−12.74 (16.24)	16.48 (27.32)	−25.67 (30.72)	8.90 (14.43)	4.96 (5.84)	5.40 (4.95)	0.01 (0.08)	−3.54 (4.28)
	Se	−0.09 (0.06)	−0.03 (0.04)	−0.05 (0.13)	0.02 (0.07)	0.04 (0.12)	−0.15 (0.13)	−0.06 (0.06)	0.01 (0.03)	−0.04 (0.02) *	0.00 (0.00)	−0.01 (0.02)
	Cu	1.42 (3.71)	−1.93 (2.49)	0.23 (7.93)	−0.23 (11.57)	−2.46 (7.38)	−4.32 (8.35)	1.37 (3.89)	−3.15 (1.59) **	1.30 (1.33)	−0.01 (0.02)	0.85 (1.16)
	Mg	−60.09 (9.75)***	−40.13 (6.51) ***	−24.35 (21.35)	−3.41 (4.39)*	−12.72 (19.53)	−76.79 (21.91) ***	−27.47 (10.39) ***	−11.50 (4.20) ***	−12.16 (3.48) ***	−0.10 (0.06) *	−7.75 (3.09) **

Model 1 is the result of median regression denoting single effect of elements on MetS components; model 2 denotes effect of each trace element in existence of others. Results are reported in term of coefficient (SE)

Cr chromium, *Se* selenium, *Cu* copper, *Mg* magnesium, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *FBG* fasting blood glucose, *AST* aspartate aminotransaminase, *ALT* alanine aminotransaminase, *BMI* body mass index

*P=0.1; **P=0.05; ***P=0.01 (significance level)

Table 3 Association of magnesium and trace elements on the existence of metabolic syndrome based on binary logistic regression: the CASPIAN-III study

		Coefficient regression	Standard error	OR	95 % C.I. for OR		
					Lower	Upper	*P* value
Model 1	Cr	−1.14	1.60	0.32	0.01	7.36	0.47
	Se	−0.01	0.01	0.99	0.98	1.00	0.19
	Cu	−0.04	0.43	0.96	0.41	2.21	0.91
	Mg	−15.02	1.78				
Model 2	Cr	−0.52	1.95	0.59	0.01	27.02	0.79
	Se	−0.02	0.01	0.98	0.97	1.00	0.03
	Cu	−0.10	0.53	0.90	0.32	2.56	0.84
	Mg	−15.42	1.83				
Model 3	Cr						
	Se	−0.02	0.01	0.98	0.97	1.00	0.03
	Cu						
	Mg	−15.22	1.80				

Model 1 is the result of logistic regression denoting single association of trace elements on metabolic syndrome (MetS); model 2 denotes simultaneous association of trace elements on MetS; model 3 is the result of backward logistic regression including only statistically significant elements in the model. All models are adjusted for age and sex

Cr chromium, *Se* selenium, *Cu* copper, *Mg* magnesium

Discussion

In this nationwide study, which to the best of our knowledge is the first study of its kind, we investigated the individual and cumulative associations of Mg, Se, Cu, and Cr with cardiometabolic risk factors and liver function tests in a pediatric population. According to the results of different applied statistical analysis models, among these trace elements, Mg showed significant inverse associations with cardiometabolic risk factors and liver enzymes and was a protective factor against MetS. In the presence of other trace elements, the inverse association of Mg with MetS and its components was stronger than its individual association.

The evidence on the association of Mg concentrations with cardiometabolic risk factors is mainly limited to studies conducted in the adult population. A recent study revealed that low serum Mg levels increases the risk of poor glycemic control in children and adolescents with type 1 diabetes [30]. Our findings on the protective role of Mg against pediatric MetS and its components are consistent with this study conducted among diabetic children and adolescents. A study that analyzed the role of Mg deficiency on insulin resistance in American obese children found significantly lower serum Mg concentration in obese children [31]. Our cross-sectional findings on the inverse association of Mg with MetS and its components are in line with a longitudinal study conducted among American young adults, which showed higher Mg

intake decreased the risk of development of MetS and also Mg concentration was inversely related to individual MetS components and fasting insulin levels [32]. Likewise, another study in adults revealed significant inverse association of Mg concentration with SBP, DBP, and insulin resistance. However, our finding on the association of serum Mg with liver enzymes is not consistent with this study in adults [33]. We found that in the presence of other trace elements, Se had a significant protective role against MetS, but the crude association was not significant. Moreover, Se had significant inverse association with AST. Some previous studies have evaluated such associations in adults, but similar data are scarce in the pediatric population. A study among adult patients with chronic liver diseases and found that serum Se concentration was lower in patients with normal ALT than in those with higher ALT levels [34]. A study in Turkey examined the association of Se and liver function in cirrhotic children and found that Se concentration had significant relationship with AST [35].

In our study, serum Cu concentration was associated with ALT, but not with other variables studied. Controversial findings are reported by different studies. A clinical trial among adults found that while Se had significant positive association with all MetS components, Cu correlated with total, LDL-C, and HDL-C [36]. However, in a cross-sectional study among 100 elderly individuals, serum Se and Cu concentrations had no significant association with MetS and its components [37]. In a study that analyzed the relationship of Cu with inflammation, oxidative stress, and metabolic variables, serum Cu level had significant inverse association with total cholesterol and HDL-C [38]. Some trials conducted among adults did not document significant effect of Cr on improvement of the key features of MetS, insulin resistance, and weight loss that reported no significant development in those parameters [23, 39, 40].

Our study demonstrated some association of serum Mg, Se, Cu, and Cr levels with cardiometabolic risk factors and liver enzymes among children and adolescents. Trace elements play important roles in the human body, and further studies are necessary to be conducted about their relationships to cardiometabolic risk factors in the pediatric age group.

Study Limitations and Strengths

The main limitation of this study is its cross-sectional nature, so the associations of diverse variables should be considered with caution. The study strengths are the novelty of studying the association of different trace elements with liver enzymes and cardiometabolic risk factors in the pediatric age group and using data of a nationally representative group of adolescents, which would increase the generalizability of the study findings.

Conclusion

The protective role of Mg and Se against MetS and liver enzymes, as well as the associations of these elements with some cardiometabolic risk factors and liver enzymes should be considered in future preventive and interventional studies in the pediatric age group.

Conflict of Interest None to declare.

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