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Association Between Serum Calcium and Metabolic Syndrome Indicators among Women in Mazandaran, Northern Province of Iran

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ABSTRACT

Introduction: Metabolic syndrome (MetS) is defined by indicators of hypertension, abdominal obesity, abnormal lipid profile, and hyperglycaemia. Few studies have investigated the association between serum calcium and MetS. Thus, this study examined prospectively the association between serum calcium in Iranian women with onset of MetS, and key components of MetS. **Methods:** A total of 460 subjects were recruited, comprising 232 with MetS and 228 as a control group. Waist circumference (WC) and blood pressure (BP) were measured and fasting blood samples were obtained for determination of glucose, insulin, total triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum calcium. **Results:** Compared to the control group, women with MetS had significantly higher WC, BP, TG, glucose, and LDL-C levels but lower HDL-C levels with 97.1±8.4 cm, 123.2±16 mmHg, 219.9±88.7 mg/dl, 119.2±38.8 mg/dl, 121.3±201 mg/dl, and 38.8±4.9 mg/dl, respectively. Serum concentrations of calcium were significantly higher in women with MetS (9.9±0.3 mg/dl) compared to the control group (9.1±0.7 mg/dl). Serum concentrations of calcium and phosphorus are predictors of MetS. Serum calcium level had a positive association with the risk of having high levels of glucose, TG, BP and WC. **Conclusion:** Serum calcium level showed a positive association with the risk of having high levels of parameters associated with MetS in the Iranian women studied. More studies on MetS are suggested to include measuring serum calcium as well to verify the present findings.

Key words: Calcium, Iranian women, metabolic syndrome

INTRODUCTION

Metabolic syndrome (MetS) is defined by some symptoms including hypertension, abdominal obesity, abnormal lipid profiles, and hyperglycaemia. The special importance of MetS is its role as a powerful independent contributor to the onset of metabolic diseases such as cardiovascular disease (CVD), and type 2 diabetes. In most countries, the prevalence of MetS is

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about 12 to 41% among adult populations, and appears to correlate with the increase in the incidence of metabolic diseases (Ramachandran *et al.*, 2003).

Prevalence of MetS is increasing in developing countries (Lameira, Lejeune & Mourad, 2008; Pan, Yeh & Weng, 2008). The prevalence of MetS in different provinces in Iran has been assessed to be between 21.9% and 31.1% (Gharipour, Bagheri & Boshtam, 2006; Sadrbafoghi, Salar & Rafiee, 2007). Therefore, identification of nutritional and environmental risk factors of MetS in the Iranian people is urgently needed to prevent development of MetS.

The precise mechanism linking the high serum calcium concentration to MetS is not well known, but it is hypothesised that high serum calcium might be a correlation factor or contributory predictor for MetS. The novelty of this study is that it focused on a new factor, serum calcium, as a predictor of MetS, for the first time, unlike previous studies. Moreover, nothing in the literature has investigated the link between high serum calcium and MetS in the Middle East, which is among the areas with a high prevalence of MetS.

Minerals, especially calcium, can influence obesity and obesity-related inflammatory reactions (Shi, Dirienzo & Zemel, 2001). Some studies have shown that obesity plays the most important role in the development of MetS, and it contributes to metabolic diseases (de Koning *et al.*, 2007). Thus, it is thought that controlling and monitoring obesity, and the reactions induced by obesity (*e.g.*, MetS) due to calcium should be considered.

Dietary calcium plays an effective role in the regulation of energy metabolism. High calcium diets attenuate adipocyte lipid accretion. These diets increase lipolysis and preserve thermogenesis during caloric restriction (Shi *et al.*, 2001). The direct effect of intracellular calcium on adipocytes regulates lipid metabolism, storage, and insulin-stimulated glucose uptake (Yamaguchi *et al.*, 2011).

Some studies have shown that dietary calcium intake may have beneficial effects on hypertension and cardiovascular disease (Ramachandran *et al.*, 2003; Wang *et al.*, 2008). However, some studies indicate that there is an association between increased serum calcium concentration and impaired glucose tolerance, high blood pressure (BP), and dyslipidaemia (Ahlstrom *et al.*, 2009; Yamaguchi *et al.*, 2011).

The effect of calcium consumption on decreasing risk of developing MetS by affecting one or several of its components including weight gain, high BP, glucose uptake, lipid levels, and insulin sensitivity, has been shown by numerous observational and interventional studies (Fumeron *et al.*, 2011; Major *et al.*, 2008; Tremblay & Gilbert, 2009. Azadbakht *et al.* (2005) showed that consumption of dairy products is inversely associated with the risk of having MetS, and suggests that the relation is somewhat attributed to calcium. Another study reports that calcium intake is inversely associated with the risk of having MetS in post-menopausal women, and concluded that prospective or longitudinal studies concerning sex are necessary to evaluate an association between calcium intake and MetS (Cho *et al.*, 2009). However, according to a review by Major *et al.* (2008), insufficient conclusive data have been gathered from prospective and interventional trials to decisively assume that increasing the consumption of products rich in calcium, or altered levels of serum calcium, result in a decrease of fat mass and related factors.

It is thought that serum calcium may be related to metabolic disorders such as obesity and MetS. A study showed that increased serum calcium concentration has been associated with some abnormalities related to impaired glucose tolerance, high BP, and dyslipidaemia (Ahlstrom *et al.*, 2009; Yamaguchi *et al.*, 2011). However, there have been few studies investigating the association between serum calcium and MetS in female adults, especially in Middle Eastern populations. As different

results have been found between men and women, which are probably due to lifestyle differences (Shin *et al.*, 2015), we focused on the female population. This study aimed to prospectively examine the associations of serum calcium in Iranian women with the onset of MetS, and all components of MetS.

METHODS

This cross-sectional study entitled Mazandaran Metabolic Diseases Study involved 460 women (232 with MetS and 228 in the control group) and was carried out between 1 January 2011 and 31 December 2014. Profiles of all households of the Sari district are maintained at the Mazandaran district health centres; the sampling unit was the household. Subjects were invited by phone to participate in this study. After the study was explained, women who agreed to participate gave written consent. Overall, 1431 subjects aged between 20 and 60-years were selected by multistage cluster random sampling methods from residents of the district of Mazandaran because of their similar socio-economic status. The study was approved by, and performed under the guidelines of the Research Ethics Committee of Mazandaran University of Medical Sciences, Iran.

Participants were asked to complete a self-administered questionnaire that included questions on social and demographic information (including marital status, educational attainment, and occupational status) as shown in Table 1. Two practitioners recorded medical history, family history, medication, and performed physical examinations on all subjects. Waist circumference (WC), weight, height, and body mass index (BMI) were measured. All blood samples were obtained after a 12-hour fast. BP was measured using a standard mercury sphygmomanometer on subjects who had been at rest for at least 10 min. Blood levels of glucose, insulin, triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured for all subjects in the same laboratory. Oral glucose tolerance test (OGTT) by 75 g glucose was performed on subjects without previous diagnosis of diabetes.

Calcium (assayed by the ortho cresolphthalein complexone method) was measured using an auto-analyser. MetS was defined according to the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) criteria, if at least three of the following conditions were met: abdominal obesity (WC>102 cm in men and >88 cm in women, high glucose with fasting plasma glucose (FPG)≥100 mg/dl (includes diabetes)), TGs>150 mg/dl, HDL-C< 40 mg/dl in men and <50 mg/dl in women, high BP (systolic blood pressure>130 mmHg or diastolic blood pressure>85 mmHg21). In total, 232 subjects with MetS were selected, and 228 subjects without MetS were matched for age, marital status, education level, and occupation as the control group. Subjects with a previous or current history of disease including cancer, hepatic and renal disease, hypothyroidism or hyperthyroidism, cardiovascular disease, taking medications such as hormones for bone disorders, hypertension, hyper-lipidemia, and diabetes were excluded.

The coefficient of variation for calcium was 2.17%. A 168-item semi-quantitative food frequency questionnaire (FFQ) was used to calculate dietary intake. Validity and reliability of this FFQ were confirmed previously (Hosseini Esfahani *et al.*, 2010). A list of foods had been developed in this FFQ with standard serving sizes. Food consumption frequency was self-reported by study subjects on a daily, weekly or monthly basis. Food intake was analysed using Nutrition 4 version 3.5.2.

The normality of variables was examined with the Kolmogorov Smirnov test. Categorical variables were described as number (percentage). Quantitative

variables were described as mean±standard deviation (SD). An independent sample *t*-test was used to compare quantitative parameters with normal and abnormal distribution between the two groups. Chi-square test was used to compare qualitative variables. The Pearson correlation test was used to evaluate associations between serum calcium and components of MetS. Multiple logistic regression analysis was performed to investigate the independent association of MetS, calcium and other potential risk factors. SPSS version 16.0 was used for statistical analysis. P-values less than 0.05 were considered significant.

RESULTS

Overall, 232 subjects with MetS, and 228 subjects without MetS were evaluated. The two groups had no statistically significant differences in their demographic characteristics as shown in Table 1. The mean age was 49.6±8.8-years in subjects with MetS and 47.9±9.3-years for the non-MetS group. BMI was significantly different between the groups : 23.9± 3.5 kg/m^2 for subjects without MetS and 29.1±4.1 kg/m2 for MetS subjects.

The clinical and dietary intake results of the subjects according to the presence or absence of MetS are shown in Table 2. Women with MetS had significantly higher mean WC, BP, TG, glucose, and LDL-C levels, but lower HDL-C levels, compared to women without MetS. The mean serum calcium concentrations was significantly higher in women with MetS (9.9±0.3 mg/dl) compared to that of the control group (9.1±0.7 mg/dl). The mean dietary intake of calcium, phosphorus and dairy products was not significantly different between the two groups. Distribution of calcium in subjects with and without MetS is shown in Figure 1.

Pearson's partial correlations between serum calcium and diagnostic components of MetS are shown in Table 3. There were positive correlations of serum calcium with diastolic BP, glucose, TC, HDL-C, LDL-C, and TG concentrations, but the correlation between serum calcium and systolic blood pressure was insignificant.

DISCUSSION

In this study on Iranian women from the district of Mazandaran, mean serum calcium concentration was notably higher in subjects with MetS compared to subjects without MetS. Several studies have reported that calcium intake is inversely

Table 1. Demographic characteristics of the study subjects

Variables		*Cases (MetS participants) (n= 232)* *Number*	*Percent*	*Controls (n= 228)* *Number*	*Percent*	*P value*
Marital status						0.211
	Single	21	9.1	17	7.5	
	Married	208	89.7	210	92.1	
	Divorced	3	1.3	1	0.4	
Educational attainment						0.424
	Lower than high school	18	7.8	25	11.0	
	High school	170	73.3	164	71.9	
	College	44	19.0	39	17.1	
Occupational status						0.331
	Employed	54	23.3	60	26.3	
	Unemployed	137	59.1	130	57.0	
	Retired	41	17.7	38	16.7	

Table 2. Characteristics of subjects with and without MetS: demographic data, clinical and dietary intake

	Cases with MetS (n= 232		*Controls without MetS (n= 228)*		
Variables	*Mean*	*SD*	*Mean*	*SD*	*P value*
Age (yr)	49.6	8.8	47.9	9.3	0.561
BMI (kg/m2)	29.1	4.1	23.9	3.5	0.033
WC (cm)	97.1	8.4	87.3	9.7	0.022
Systolic blood pressure (mmHg)	123.2	16	113.9	13.1	0.001
Diastolic blood pressure (mmHg)	78.1	11.1	68.9	11.2	0.035
Fasting plasma glucose (mg/dL)	119.2	38.8	91.2	17.9	0.001
Triglycerides (mg/dL)	219.9	88.7	110.2	39.6	0.001
LDL-C (mg/dL)	121.3	20.1	109.1	25.1	0.031
HDL-C (mg/dL), female	38.8	4.9	48.8	8.8	0.021
Serum calcium (mg/dL)	9.9	0.3	9.1	0.5	0.032
Serum phosphorus (mg/dL)	3.1	0.3	3.8	0.2	0.046
Calcium intake (mg/day)	701.6	231.4	773.2	271.9	0.056
Phosphorus intake (mg/day)	1351.2	335.1	1412.6	372.2	0.052
Dairy intake (servings/day)	1.2	0.8	1.6	0.8	0.059

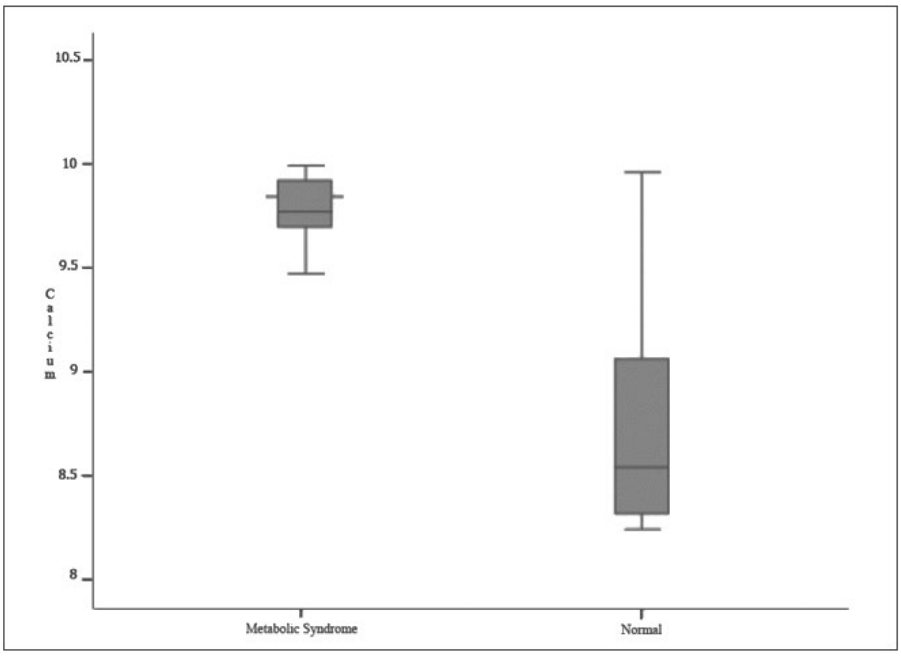

Figure 1. Distribution of serum calcium levels in subjects with and without metabolic syndrome

associated with the risk of having MetS in women (Cho *et al.*, 2011; Shin *et al.*, 2015). So, there is a discrepancy between the association of serum calcium level with MetS and the association of dietary calcium intake with MetS. Recent studies have demonstrated a converse association with calcium intake especially from dairy products and body weight, hypertension, glucose homeostasis and type 2 diabetes,

Table 3. Correlation* between serum calcium level and the diagnostic component of MetS

MetS Components	*r**	*p value*
WC cm	0.113	0.027
Serum glucose mg/dl	0.117	0.001
Serum TG mg/dl	0.213	0.001
SBP mm Hg	0.006	0.62
DBP mmHg	0.074	0.041
Serum HDL cholesterol mg/dl l	0.068	0.021
Serum LDL cholesterol mg/dl	0.048	0.008
Total cholesterol mg/dl	0.128	0.003

* r : Pearson's correlation coefficient.

which are risk factors for MetS (Shin *et al.*, 2015; Moore-Schiltz *et al.*, 2015). Delavar *et al.* (2009) showed an inverse favourable association of total calcium intake with MetS. Using the data from the Korean National Health and Nutrition Survey between 2001 and 2005, Cho *et al.* (2009) reported an inverse association with the risk of having MetS and serum calcium in post-menopausal women. Meanwhile in other studies, the inverse relationship between MetS and its components and calcium intake has been reported giving credence to the discrepancy noted above (Cho *et al.*, 2009; Moore-Schiltz *et al.*, 2015).

Going forward, the issue of elevated serum calcium levels seen in subjects with MetS needs to be addressed. A notable point in the study population is that it seems that the dietary intake of calcium did not differ between subjects with MetS and the control group. Therefore, dietary intake of calcium alone cannot account for the difference in serum calcium of the two study groups. It was assumed that there are multiple reasons for increased serum calcium levels in subjects with MetS. The reasons seem to be related somehow to the parathyroid hormone (PTH) levels. The reasons could be elevated renal and intestinal absorption, increased skeletal resorption, or a combination of these factors (Ahlstrom *et al.*, 2009). It is possible that hyper-insulinemia and/or insulin resistance are the key determinants in disturbed PTH-regulation (Saltevo *et al.*, 2011). There is an association between serum calcium concentration and MetS indicators. For example, the regulation of energy metabolism is somehow influenced by dietary calcium. Intracellular calcium plays an important role in regulating lipid metabolism by directly acting on adiposities. Also, it can regulate uptake and storage of insulin-stimulated glucose by modulating insulin secretion and glucose metabolism partly through stimulating calcium-sensing receptors in pancreatic β-cells (Yamaguchi *et al.*, 2011).

Studies suggest that disturbed calcium metabolism may play an important role in the pathophysiology of hypertension as one of the risk factors for MetS by stimulating the mineralisation of smooth muscle cells in humans resulting in their tightening (Yao *et al.*, 2013; He *et al.*, 2014). A Swedish survey with a large population of participants carried out from 1969 to 1970 showed that changes in calcium metabolism were related to impaired glucose tolerance, hypertension, and hyperlipidaemia. These changes were significant even within the physiological range (Yamaguchi *et al.*, 2011). Another survey in Canada reported that altered calcium homeostasis correlated with some results such as disruption of β-cell function, impaired fasting serum glucose, and insulin resistance (Sun *et al.*, 2005). In this study, the association between serum calcium concentration and MetS indicators has been shown. Higher serum calcium

levels have been seen in subjects with high BP. Significantly, Schutte *et al.* (2010) state that serum calcium is positively associated with a risk of having high BP.

Aoki & Miyagawa (1990) reported that an increased serum calcium level is linked to an influx of calcium into the arterial muscle, increasing cytosolic calcium after intravenous calcium infusion, which will induce vasoconstriction and elevation of blood pressure in normotensive men. Some other studies have shown that the increased serum calcium will increase the levels of systolic and/or diastolic blood pressure (Yao *et al.*, 2013; Schutte *et al.*, 2010).

In this study, the subjects with high levels of TG had significantly higher levels of serum calcium compared to those without TG. Thus, TG level was positively correlated with serum calcium level. These findings agree with those of other studies (Cho *et al.*, 2011; Yao *et al.*, 2013; Samara *et al.*, 2013). Some studies have reported that calcium supplementation increases endogenous serum TG via decreasing hepatic cholesterol catabolism in oestrogen deficiency and found it to be a key target in mediating calcium induced triglyceride increase. Oestrogen is involved in the regulation of the influx of calcium ions in many cells via the transient receptor potential cation channel subfamily V member 5 (TRPV5) channel (He *et al.*, 2014; Li *et al.*, 2013). In this study, the older participants, might have had oestrogen deficiency, which increased their serum calcium level.

Increased calcium intakes attenuate post-prandial lipidaemia (most probably because of calcium binding to fatty acids and bile acids in the gut and interfering with intestinal absorption of fat), bile acids, and cholesterol (Reid *et al.*, 2002). This may justify the association between dietary calcium intake and MetS (Cho *et al.*, 2009). In turn, this could be a possible explanation for the different results, and the clear discrepancy that is found between the association of dietary calcium level with MetS and the association of serum calcium intake with MetS. Further studies are needed to better understand the reasons for this discrepancy. In this study, different levels of serum calcium were positively associated with glucose levels, and a risk of having high glucose. These findings are in line with the results of other studies (Yamaguchi *et al.*, 2011; Sun *et al.*, 2005).

It has been reported that low levels of serum calcium are related to an increase in the calcium content of soft tissues, which is a paradoxical phenomenon (Major *et al.*, 2008). Stimulating fatty acid synthase and inhibiting lipolysis by increasing the expression of fatty acid synthase enzyme promotes energy storage in human adipocyte, and this process is achieved by an increase in intracellular calcium levels (Yamaguchi *et al.*, 2011). However, in this study, serum calcium was positively associated with WC in contrast to previous studies. The reason is unclear and needs further investigation. It could be due to participants' older age and their hormonal situation. High WC and abdominal obesity, which have been seen in women nearing menopause, have positive relation with visceral adipose tissue, which promotes insulin resistance and dyslipidaemia (de Koning *et al.*, 2007). Thus, it is hypothesised that serum calcium is positively correlated with WC.

The strength of this study was the optimum size of the population of a specific province in Iran.

The limitation of the study is that analysing serum concentration of vitamin D and PTH levels were not feasible because of budget limitations. These factors are tightly regulated by serum calcium levels and some studies report a relationship between these factors and MetS indicators. For example, one study showed that PTH is associated with metabolic syndrome (Reis, von Muhlen & Miller, 2008), and vitamin D, as pivotal for calcium homeostasis, is also known to be associated with metabolic

syndrome (Reis *et al.*, 2008). Therefore, future research may need to consider PTH and vitamin D levels to confirm the association between serum calcium and metabolic syndrome.

One other limitation of the study was that the target population was women and men were excluded. Another limitation of this study was its cross-sectional nature. Thus, it was not possible to establish a cause-effect relationship between serum calcium and MetS. Thus, because of the practical or clinical importance of the association between serum calcium and MetS indicators, other longitudinal or prospective studies are necessary to determine if there is any association between them, and therefore, allow MetS to be taken into consideration when interpreting serum calcium levels.

CONCLUSIONS

Serum calcium level had a positive association with the risk of having high levels of glucose, TG, BP, and WC. Serum calcium concentration was a proper predictor of MetS. More studies are needed to provide a better understanding of the reasons for this discrepancy. Therefore, the levels of serum calcium may have associations with MetS and MetS indicators in adult Iranian women.

Conflict of Interest

The authors declare no conflict of interest in carrying out and reporting this research.

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