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# Association of serum S100B, S100A1 and Zinc-α2-Glycoprotein levels with anthropometric, metabolic and clinical indices in men and women

*Sorayya Kheirouri[1], Mohammad Alizadeh[1], Elham Ebrahimi[2], Masoumeh Jabbari[2]*

[1]Associate Professor, Department of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran - Email: kheirouris@tbzmed.ac.ir, mdalizadeh@tbzmed.ac.ir; [2]MSc. student, Department of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran

**Summary.** *Objectives:* We aimed to investigate serum levels of S100B, S100A1, and Zinc-α2- glycoprotein (ZAG) in men and women and to find association of these proteins with anthropometric, metabolic and clinical indices. *Methods:* Eighty-eight apparently healthy adults, 43 men and 45 women, participated in the study. The participants' body mass index (BMI), waist circumference (WC), systolic and diastolic blood pressure (SBP and DBP) were measured. Serum levels of total cholesterol (TC), triglyceride (TG), low and high density lipoprotein cholesterol (LDL-C and HDL-C), fasting blood sugar (FBS), insulin, S100B, S100A1 and ZAG protein were examined by enzymatic and ELISA laboratory methods. Homeostatic model assessment-insulin resistance (HOMA-IR) index was calculated. *Results:* Serum levels of S100B, S100A1 and ZAG were comparable between men and women groups. S100B protein was positively associated with TG (r= 0.41, p= 0.006), SBP (r= 0.46, p= 0.002), and DBP (r= 0.37, p= 0.02), but negatively with HDL-c in men. Serum levels of S100A1 were significantly and negatively correlated with WC (r= -0.33, p= 0.03), TG (r= -0.37, p= 0.01), insulin (r= -0.31, p= 0.04) and HOMA-IR (r= -0.32, p= 0.03), in women. There was strong positive correlation between serum ZAG and S100A1 levels in both men (r= 0.86, p< 0.0001) and women (r= 0.67, p< 0.0001) groups. *Conclusion:* The findings suggest that S100B and S100A1 proteins might have gender-specific activity or regulation. Visceral obesity attenuates S100A1 protein in serum, while enhancement of S100A1 leads to improved metabolic status in women. In contrary, S100B increases with visceral obesity and increment of this protein aggravates metabolic status and blood pressure in men. Positive correlation between S100A1 and ZAG indicates that these two proteins may act in a same biological pathway.

**Keywords:** Gender; S100B, S100A1; Zinc-α2-glycoprotein; Anthropometry, Blood Pressure, Metabolic Indices

## Introduction

S100 calcium -binding protein B (S100B) and A1 (S100A1) belong to a multigenic EF-hand family of small proteins (25 members, 9–13 kDa). S100B is predominantly produced by astrocytes(1) and additionally from many cell types including adipocytes, chondrocytes, cardiomyocytes and lymphocytes (2-4). S100B, in low amounts, acts as a neurotrophic factor and regulates proliferation and differentiation of neurons and glia. While, increased levels of S100B leads to neuronal dysfunction and apoptosis. Findings suggest that S100B is increased in neurodegenerative diseases such as schizophrenia, parkinson and that this augmentation is associated with metabolic syndrome, overweight, visceral obesity, gender, body mass index (BMI), and insulin resistance (2-4). Alterations in S100B levels have also been associated with changes in glucose metabolism and it has been shown that insulin modulates glucose metabolism and stimulates S100B

secretion (5). There is also evidence that S100B serum levels are enhanced in schizophrenia female patients, but not male patients, compared to controls (6).

S100A1 is greatly expressed in cardiac myocytes and has a major role in cardiovascular performance (7) and has also been shown to be expressed in vascular smooth muscle cells (8) and has been known as important regulator of cardiac performance and vascular biology. Previous animal studies have determined that lack of S100A1 is associated with hypertensive phenotype in mice. Further, S100A1 has a gender specific contribution in regulation of blood pressure (9). Besides, S100 A1 influences resting energy expenditure and has been recognized as possible susceptibility gene for obesity based on its altered expression in adipose tissue from obese individuals (10). However, evidence about the link between S100A1 and anthropometry, clinical and metabolic factors is remarkably scarce.

Zinc-α2-glycoprotein (ZAG), a novel adipokine, initially regarded as a tumor product, since its levels are raised in cancer patients with cachexia (11). Evidences also indicate that ZAG is expressed in adipose tissue (12, 13) and inversely associated to adiposity, being increased in cachexia while decreased in obesity. Animal researches demonstrated that ZAG is an important modulator of lipid metabolism including both mobilization and utilization and participate in systemic lipid homeostasis. Treatment of mice with purified ZAG can decrease body fat (14) and stimulates overall fatty acid oxidation (15). Therefore, according to above mentioned findings, it was speculated that circulating ZAG level might be in connection to lipid profile. Furthermore, in adipose tissue ZAG mRNA level is negatively correlated with body fat mass (16). Since, body fat mass is greater in women than men, we hypothesized that circulating ZAG content may vary by gender.

However, it remains to be recognized whether serum S100B, 100A1 and ZAG levels are influenced by gender in healthy individuals and are these factors associated with metabolic, clinical and anthropometric measurements. Therefore, this study was designed to compare serum levels of these proteins in women and men and to find their association with metabolic, clinical and anthropometric measurements.

## Materials and Methods

### *Participants*

This cross sectional study was carried out from January to June, 2014. Eighty eight adult volunteers (43 men and 45 women) participated in the study. Participants were recruited from those who underwent routine medical check-ups. Convenience sampling method was used for employment of the participants. A written informed consent was obtained from each subject. The study was approved by the Ethical Committee of Tabriz University of Medical Sciences, Tabriz, Iran.

Inclusion criteria were men and women aged 30–50 years, apparently healthy with no obvious symptoms of any disease and under any kind of medications when the study was performed. Exclusion criteria were BMI ≥ 40 kg/m$^2$, infectious and chronic inflammatory diseases, history of psychiatric diseases, receiving anti-obesity, anti-inflammatory, anti-hypertensive, corticosteroid and estrogen drugs and contraceptives during the study period, thyroid disorders, endocrine diseases, irregular menstrual periods, previous stomach surgery, smoking, excessive consumption of alcohol, pregnancy and breast-feeding, menopause and diet therapy during the 3 months prior to the study.

### *Assessments of Anthropometric and Clinical Parameters*

Body weight was measured while participant just covered light underwear with no shoes, by the SECA scale with 100 gram accuracy in measurement. Height was measured with 0.5 centimeter bias while person stood upright normal and feet were beside to the other. We calculated BMI using metric units (kg/m$^2$). Waist circumference was measured at the midpoint between the lower costal margin and iliac crest to the nearest 0.5 cm by a flexible tape without making any pressure on body surface while person was at the end of normal expiration phase. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. Systolic and diastolic blood pressure were measured two times for each participant with at least 15 minutes rest before first measurement and 15 minutes interval for the next one, as clinical

parameters using a mercury manometer. Mean of these two findings was regarded as personal blood pressure including SBP and DBP.

*Biochemical Assessment*

After an overnight fasting, 5 ml of venous blood was collected. The serum samples were separated from whole blood by centrifugation at 3500 rpm for15 min at 4°C. Aliquots were stored at -70 °C until analysis.

The serum levels of total cholesterol (TC), HDL-C and TG were measured by enzymatic colorimetric methods with a commercially available kit (Pars Azmone, Tehran, Iran) on an automatic analyzer (Abbott, model Alcyon 300, USA). Serum LDL-C was calculated by Friedewald equation (17). Fasting blood sugar were determined by the glucose oxidase method. Insulin levels were determined by insulin ELISA kit (MonobindInc, lake forest, CA 92630, USA). To investigate insulin sensitivity the homeostasis model assessment (HOMA-IR) was calculated.

*Determination of S100β, S100A1 and ZAG Levels in Serum*

S100B, S100A1and ZAG levels were quantified using commercially ELISA kits (Hangzhou Eastbiopharm CO., LTD) and following the manufacturer's protocol. 50 μL of streptavidin-HRP was added to all wells of the pre-coated plates, except for blank wells. Then, 50 μL of related standards and 40 μL of samples together with the related secondary antibody labeled with biotin were added to the appropriate wells and the plate incubated for 1 hour at 37°C. The wells were washed five times with wash buffer, added chromogen solutions, and incubated for 10 minutes at 37°C. Color development was stopped and the optical densit of the wells was measured at 450 nm wavelength.

*Statistical Analyses*

Normally distributed data were presented as mean ± standard deviation (SD) and non-normally distributed data were expressed as median (percentile 25, 75). Differences between two groups were assessed by independent sample t-test for normally distributed data and Mann-Whitney U test for nonparametric variables. Spearman's and Pearson's coefficient tests were used to evaluate the correlation between S100B, S100A1 and ZAG proteins with together and also with Mets components. Data analysis was performed by SPSS 16 Software (IBMSPSS statistics, IL, Chicago, USA) and P- values less than 0.05 were considered statistically significant.

## Results

*Characteristics of the Participants*

As shown in Table 1, average age of men and women were 43.16 ± 5.95 and 37.00 ± 5.71 years, respectively ($P< 0.0001$). Systolic and diastolic blood pressure of men was significantly higher (both, $P< 0.0001$) in comparison with women. There was no statistical significant difference in anthropometric measurements between the two groups ($P> 0.05$) (Table 1).

*Laboratory Parameters*

As shown in Table 2, serum levels of TC, TG, LDL-c and HDL-c did not differ statistically between the two groups ($P> 0.05$). There were no also statistically significant difference in serum levels of FBS, insulin, HOMA-IR, S100B, S100A1 and ZAG between men and women (Table 2).

**Table 1:** Characteristic of the studied groups

| | **Men** (N= 43) | **Women** (N= 45) | **P** |
|---|---|---|---|
| **Age** (year) | 43.16 ± 5.95 | 37.00 ± 5.71 | <0.0001 |
| **WC** (cm) | 101.09 ± 14.61 | 96.92 ± 16.28 | 0.21 |
| **WHR** | 0.89 ± 0.07 | 0.90 ± 0.08 | 0.53 |
| **BMI** (kg/m$^2$) | 28.76 ± 4.43 | 30.35 ± 5.79 | 0.15 |
| **SBP** (mmHg) | 129.16 ± 13.57 | 113.11 ± 15.05 | <0.0001 |
| **DBP** (mmHg) | 83.72 ± 9.26 | 75.71 ± 11.33 | <0.0001 |

*Data were expressed as mean ± SD.*
*WC, waist circumference; WHR, waist hip ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.*
*p-values were reported based on independent samples t-test.*

**Table 2.** Laboratory data of the studied groups

| | **Men** (N= 43) | **Women** (N= 45) | P |
|---|---|---|---|
| **TC**[a] (mg/dl) | 188.35 ± 41.12 | 190.44 ± 41.51 | 0.81* |
| **TG**[a] (mg/dl) | 192.86 ± 106.29 | 169.02 ± 88.31 | 0.26* |
| **LDL-C**[a] (mg/dl) | 109.23 ± 37.21 | 113.36 ± 32.24 | 0.58* |
| **HDL-C**[a] (mg/dl) | 40.49 ± 8.85 | 43.33 ± 10.61 | 0.17* |
| **FBS**[a] (mg/dl) | 99.14 ± 27.27 | 100.40 ± 19.32 | 0.80* |
| **Insulin**[b] (mU/mL) | 0.77 (0.70, 0.85) | 0.77 (0.70, 0.83) | 0.92† |
| **HOMA-IR**[b] | 22.00 (20.00, 25.00) | 22.00 (20.00, 24.00) | 0.83† |
| **ZAG**[b] (µg/ml) | 403.50 (314.12, 746.00) | 343.50 (289.44, 512.56) | 0.11† |
| **S100A1**[b] (µg/ml) | 1148.00 (925.50, 2825.50) | 995.50 (843.00, 1501.80) | 0.11† |
| **S100B**[a] (pg/ml) | 49.93 ± 4.97 | 47.64 ± 4.58 | 0.82* |

*[a]Data were expressed as mean ± SD. [b]Data were expressed as median (percentile 25, 75).*
*FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol*
** p-values were reported based on independent samples t-test. † p-values were reported based on mann- whitney U test.*
*ZAG, zinc-α2-glycoprotein*

*Association of S100B, S100A1 and ZAG with Age and Anthropometric Measurements*

As shown in Table 3, in men, serum levels of S100B was positively correlated with WC and WHR (both, r= 0.29, *P*= 0.06), but the correlations did not reach to statistically significant level. In women, a significant negative correlation was observed between serum levels of S100A1 and WC (r= -0.33, *P*= 0.03). Serum levels of S100A1 and ZAG were not correlated with age, BMI and WHR both in men and women group.

*Association of Serum Levels of S100B, S100A1 and ZAG with Metabolic and Clinical Parameters in Men and Women*

As shown in Table 4, in men, serum levels of S100B significantly and positively correlated with serum levels of TG (r= 0.41, *P*= 0.006), and with SBP (r= 0.46, *P*= 0.002) and DBP (r= 0.37, *P*= 0.02). In men, a significant negative correlation was observed betweenS100B and HDL-c (r= -0.39, *P*= 0.01). Metabolic (TC, TG, LDL-c, HDL-c, FBS, insulin, HOMA-IR) and clinical (SBP and DBP) parameters did

**Table 3.** Correlation of serum levels of S100B, S100A1 and ZAG with age and anthropometric measurements in the studied groups

| | **S100B**[a] | | | | **S100A1**[b] | | | | **ZAG**[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | | Men | | Women | |
| | r | *p* | r | *p* | r | *p* | r | *p* | r | *p* | r | *p* |
| **Age** | 0.00 | 0.99 | -0.20 | 0.18 | 0.02 | 0.92 | 0.04 | 0.79 | -0.04 | 0.78 | 0.15 | 0.31 |
| **BMI** | 0.20 | 0.20 | -0.01 | 0.97 | 0.01 | 0.96 | -0.21 | 0.17 | 0.13 | 0.42 | -0.10 | 0.53 |
| **WC** | 0.29 | 0.06 | 0.01 | 0.96 | -0.09 | 0.57 | -0.33 | 0.03 | 0.06 | 0.72 | -0.18 | 0.24 |
| **WHR** | 0.29 | 0.06 | 0.10 | 0.51 | 0.09 | 0.57 | -0.23 | 0.13 | 0.16 | 0.32 | -0.04 | 0.81 |

*BMI, body mass index; WC, waist circumference; WHR, waist hip ratio*
*[a] Pearson correlation test, [b] Spearman correlation test*

**Table 4.** Correlation of serum levels of S100 B, S100A1 and ZAG with metabolic and clinical parameters in men

| | S100B[a] | | S100A1[b] | | ZAG[b] | |
|---|---|---|---|---|---|---|
| | r | *p* | r | *p* | r | *p* |
| **TC** | 0.13 | 0.41 | 0.12 | 0.44 | 0.13 | 0.39 |
| **TG** | 0.41 | 0.006 | -0.11 | 0.47 | -0.03 | 0.84 |
| **HDL-c** | -0.39 | 0.01 | 0.12 | 0.43 | 0.01 | 0.95 |
| **LDL-c** | 0.00 | 1.00 | 0.11 | 0.47 | 0.11 | 0.47 |
| **FBS** | 0.13 | 0.41 | 0.004 | 0.98 | 0.08 | 0.59 |
| **Insulin** | -0.11 | 0.49 | -0.02 | 0.88 | -0.01 | 0.96 |
| **HOMA-IR** | -0.11 | 0.50 | -0.05 | 0.73 | -0.02 | 0.89 |
| **SBP** | 0.46 | 0.002 | 0.01 | 0.97 | 0.02 | 0.90 |
| **DBP** | 0.37 | 0.02 | 0.20 | 0.19 | 0.28 | 0.07 |

*Data were adjusted for age, BMI and WC.*
*TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBS, fasting blood sugar; SBP and DBP, systolic and diastolic blood pressure.*
*[a] Pearson correlation test, [b] Spearman correlation test*

not correlated with serum levels of S100A1 and ZAG in men (Table 4).

As shown in Table 5, in women, none of metabolic and clinical parameters correlated with serum levels of S100B. In women, S100A1 serum levels significantly and negatively was associated with serum levels of TG (r= -0.37, *P*= 0.01), insulin (r= -0.31, *P*= 0.04), and HOMA-IR (r= -0.32, *P*= 0.03). In women, serum levels of ZAG did not correlated with metabolic (TC, TG, LDL-c, HDL-c, FBS, insulin, HOMA-IR) and clinical (SBP and DBP) parameters (Table 5).

**Table 5.** Correlation of serum levels of S100B, S100A1 and ZAG with metabolic and clinical parameters in women.

| | S100B[a] | | S100A1[b] | | ZAG[b] | |
|---|---|---|---|---|---|---|
| | r | *p* | r | *p* | r | *p* |
| **TC** | 0.05 | 0.72 | -0.18 | 0.22 | -0.05 | 0.75 |
| **TG** | 0.06 | 0.68 | -0.37 | 0.01 | -0.19 | 0.22 |
| **HDL-c** | -0.03 | 0.84 | 0.22 | 0.15 | -0.05 | 0.73 |
| **LDL-c** | 0.05 | 0.76 | -0.18 | 0.23 | -0.02 | 0.91 |
| **FBS** | -0.01 | 0.95 | -0.26 | 0.08 | -0.06 | 0.68 |
| **Insulin** | -0.07 | 0.63 | -0.31 | 0.04 | -0.13 | 0.38 |
| **HOMA-IR** | -0.06 | 0.67 | -0.32 | 0.03 | -0.14 | 0.35 |
| **SBP** | -0.18 | 0.24 | 0.04 | 0.79 | 0.11 | 0.45 |
| **DBP** | -0.02 | 0.90 | 0.16 | 0.30 | 0.25 | 0.10 |

*Data were adjusted for age, BMI and WC.*
*TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBS, fasting blood sugar; SBP and DBP, systolic and diastolic blood pressure.*
*[a] Pearson correlation test, [b] Spearman correlation test*

*Association of Serum Levels of S100B, S100A1 and ZAG with Each Other*

As shown in figure 1, there was strong positive association between serum levels of ZAG and S100A1 both in men (r= 0.86, $P < 0.0001$) and women (r= 0.67, $P< 0.0001$). Serum levels of S100B did not correlated significantly with serum levels of S100A1 and ZAG either in men or women (figure 1).

## Discussion

In the present work, serum S100B, S100A1 and ZAG level were comparable between women and men. In respect to S100B, Wiesmann et al. in a study on healthy adults have reported plasma concentration of S100B is sex-independent (18), which is in agreement to the finding of present study. O'Connell et al. in a study on schizophrenia patients have indicated higher level of S100B in women than men (6). In contrast, Nygaard et al. reported a sex-related dependency of S100B in cer-

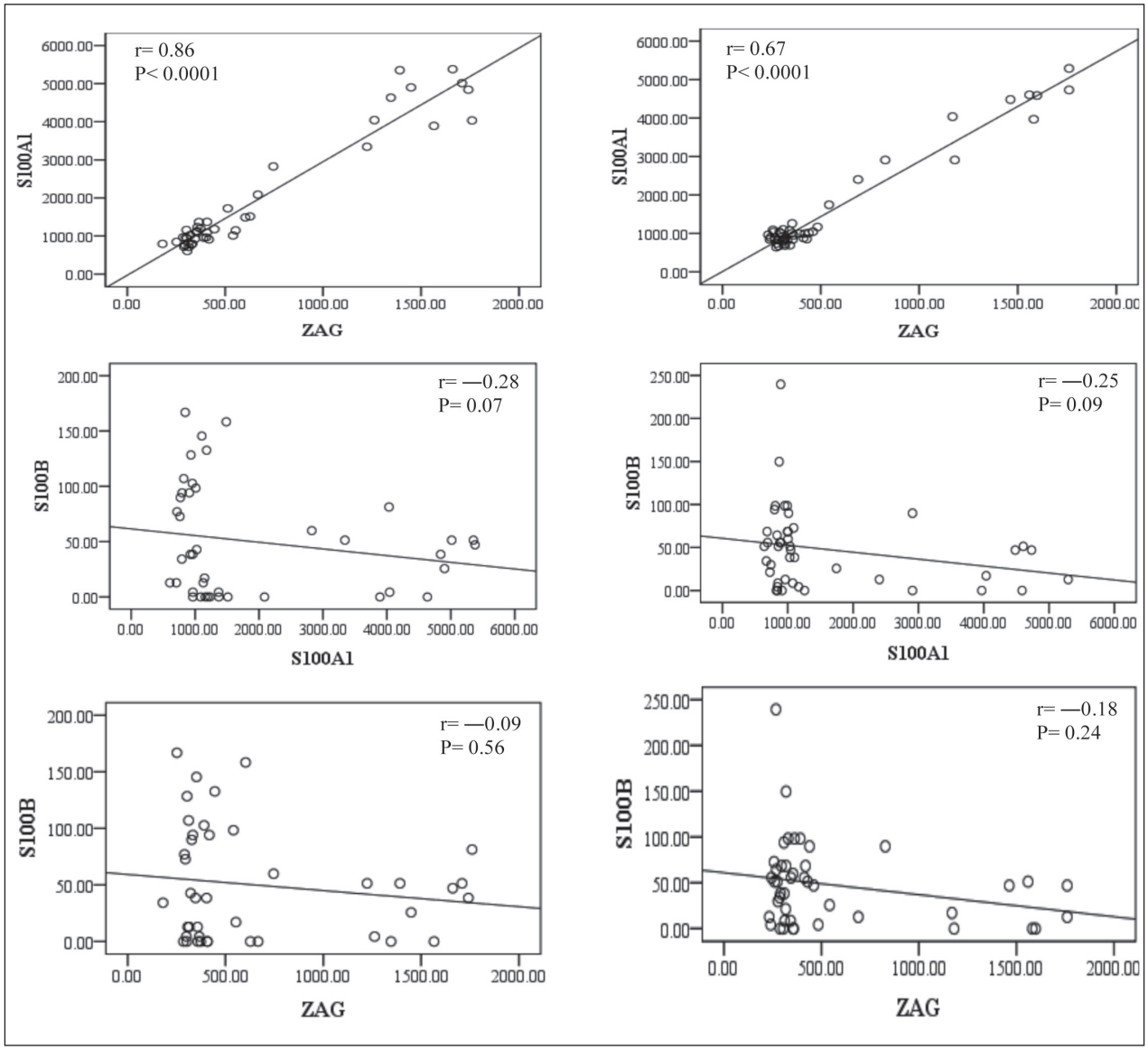


**Figure 1.** Correlation between serum S100B, S100A1 and ZAG levels in men and women.

ebrospinal fluid of patients with no previous history of neurological disorder, with significantly higher levels in men than in women (19). Different physiological and physical conditions of subjects studied in the above investigations and also difference in place of S100B measurement (plasma, serum or CSF) might lead to different observations. Regarding S100A1, the result is in agreement with the sole earlier finding reported by Bennett et al. which have indicated no differences in S100A1serum levels between men and women with normal structure and function hearts (20). In case of serum levels of ZAG among men and women findings are inconsistent across different studies. Zhu et al. and Stejskal et al. in accordance to our finding, did not observe a significant difference in serum ZAG level between men and women in healthy individuals, hypertensive patients and patients with metabolic syndrome (21, 22). Yeung et al. in a study on 258 Chinese subjects found that serum ZAG levels were higher in men than women (23). In contrary, Yang et al. reported lower levels of serum ZAG in men than women (24). The observed differences across the different studies might be related to the fact that these studies had not been designed specifically for gender differences of serum ZAG levels. Therefore, they did not match the groups of men and women for possible confounding effect of factors such as BMI, WC, age and etc.

In the present work, S100B level marginally and positively correlated with WC and WHR in men. TG levels and systolic and diastolic blood pressure positively, but HDL-c negatively associated to serum levels of S100B in men. As far as we aware, there is no study to show relationship between S100B with lipid profile, anthropometric indices or blood pressure. However, some sporadic evidences are indirectly supporting the findings of the current work. Buckman et al. in an animal study showed that S100B level increases in obese mice (25). A close correlation between S100B blood level and BMI was reported by Steiner et al. (26). Steiner et al. in another study indicated that overweight and visceral obesity might be contributed in elevated S100B serum levels[2]. Schmidt et al. revealed that eclampsia patients (characterized by high blood pressure) had higher levels of serum S100B (27). However, further studies with larger samples and different degrees of obesity and with special reference to visceral obesity are essential to confirm the observed correlations.

In the current study, serum S100A1 levels negatively correlated with WC, TG, insulin and HOMA-IR only in women. But serum ZAG levels were not correlated with measured variables. In our knowledge, there is no study to investigate correlation of S100A1 with anthropometric or metabolic factors. However, regarding ZAG, several studies have demonstrated an inverse relationship between ZAG with adiposity (BMI, WHR and WC) and metabolic (FBS, insulin, insulin resistance) criteria and also lipid profile in humans (21, 24, 28). Conversely, in some other investigations, serum ZAG level has been shown to be unrelated to the above mentioned factors (22, 29). It is of interest to note that the observed correlations in the present work were specific to female sex. Previous studies did not differentiate sex groups from each other and did not consider gender differences. Hence, alteration in sex ratio might lead to the observed discrepancy among various studies. It is possible that S100A1 has gender-specific activity or regulation, or because of other factors, such as higher body fat percentage, hormonal interactions in women it may play a role in the correlations. Further researches are needed to address this issue.

An interesting finding of the current study is determination of a strong positive association between serum levels of S100A1 and ZAG independent from age, BMI and WC, both in women and men. Since, in the present work, the two proteins interrelated with same variables with same direction and also similar function has been reported for the peptides in separate investigations, it appears that the two peptides connected together in some way. It has been shown that S100A1 expression from mouse 3T3-L1 cells was in the greatest level during differentiation of the adipocytes (30). Also, Bing *et al.* have found that ZAG mRNA was present in 3T3-L1 cells and its level increased gradually after the differentiation process (11). Thus, it is speculated that production or function of these two peptides might be linked together and act in same biological pathway.

## Conclusions

Serum S100B, S100A1 and ZAG levels did not differ between men and women. S100B positively associated with visceral obesity, TG level and

blood pressure and negatively with HDL-c in men. S100A1 inversely correlated with WC, TG, insulin and HOMA-IR in women. The findings suggest that S100B and S100A1 proteins might have gender-specific activity or regulation. Visceral obesity attenuates S100A1 protein in serum, while enhancement of the protein leads to improved metabolic status in women. In contrary, S100B increases with visceral obesity and increment of this protein aggravates metabolic status and blood pressure in men. Positive correlation between S100A1 and ZAG indicates that these two proteins may act in a same biological pathway.

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Correspondence:
Sorayya Kheirouri
Department of Nutrition, Faculty of Nutrition
Tabriz University of Medical Sciences
Attar Nishabouri St., Tabriz, I. R. Iran.
Postal code: 5166614711, POBOX: 14711
qFax: 0098-41-33340634
E-mail: kheirouris@tbzmed.ac.it