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Title: Evaluation of metabolic risk markers: Calcium/magnesium ratio, lipoproteins and insulin resistance in patients with obstructive sleep apnea syndrome

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ABSTRACT

Objectives: Obstructive sleep apnea syndrome (OSAS) is described as repetitive apnea episodes that lead to inflammation, ischemia/hypoxia and may also have effects on mineral and metabolic markers. We aimed to examine the relationships between calcium (Ca), magnesium (Mg), Ca/Mg ratio, insulin sensitivity-resistance markers (glucose, insulin, HOMA-IR), cardiovascular markers (lipids,lipoproteins), their relationships with each other, and to find out the possible influence of Ca/Mg ratio on metabolic markers in OSAS.

Material and Methods: Male patients' metabolic markers and mineral levels were compared with those of control subjects.

Results: In OSAS group fasting glucose and insulin levels were statistically significantly higher (P= 0.004 and 0.003, respectively) and fasting glucose levels were correlated with Ca, Mg and Ca/Mg ratios (0.012, 0.001 and 0.000, respectively). Calcium levels were correlated with HOMA-IR (P= 0.015). Severe OSAS patients had statistically significantly higher Ca/Mg ratios (P = 0.017) and HOMA-IR levels (P = 0.003) than mild/moderate group but correlation between Ca/Mg ratio and HOMA-IR wasn't statistically significant.

Conclusion: Mg and Ca levels were appear related to insulin resistance markers in patients. Severe OSAS patients had statistically higher Ca/Mg ratios than mild/moderate group's so they might represent a risk group with respect to diabetes.

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Key words: Calcium to magnesium ratio; insulin resistance; lipoproteins; obstructive sleep apnea syndrome; male patients

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a widespread sleep disorder with excessive daytime sleepiness. Its prevalance is 2-4% and male:female ratio is approximately 3:1 (1). OSAS is described as iterative obstructions of the upper airway. The average number of oxygen desaturation incidents every hour during performing polysomnography is called as oxygen desaturation index (ODI). A complete cessation of the upper airway for at least 10 seconds during (PSG) is called as an apnea and a reduction in airflow with an aurosal is called as a hipopnea. When the apnea-hypopnea index (AHI) is greater than five, OSAS can be diagnosed (2). OSAS is associated with metabolic abnormalities such as diabetes, obesity, dyslipidemia, metabolic syndrome (MetS); and also cardiovascular diseases (CVDs) (3,4). Intermittent ischemia and/or hypoxia of tissues -caused by airway obstruction- enhanced oxidative stress and sympathetic activation, so those metabolic abnormalities may be induced in OSAS patients. It is well known that there is an increasing public health issue called Type 2 diabetes mellitus (T2DM), worldwide. Increased risk of developing insulin resistance and T2DM have been reported in OSAS patients (5) and 50-70% of people with diabetes have been stated to be with a sleep disorder (6).

Calcium (Ca) is an essential cation in many metabolic processes of the body and works as a second messenger in transmitting signals. The Ca^{2+} ion is involved in contraction, secretion and regulation of

cell proliferation and differentiation (7). Extracellular Ca is a cofactor for clotting factors and adhesion molecules. In the body magnesium (Mg) is the most abundant second cation in intracellular space and the fourth most abundant cation. Like Ca, in numerous biological processes, Mg plays essential roles: an essential macroelement for the synthesis of proteins and fatty acids, played a part as a cofactor in the metabolism of carbohydrates and lipids. Insulin has some signal transduction pathways and Mg is included in these various steps: secretion, binding and receptor activities of insulin. For example, if the insulin receptor activity decreases, the post-receptor action will be inhibited and so an increase in insulin resistance can be seen (8). Hypomagnesemia often coexists with insulin resistance, T2DM, hypertension and MetS. For example, if dietary intakes of Mg and Ca are higher, individually, MetS risk will be decreased (9-12).

Mg has an antiplatelet, antiarrhythmic, antivasospastic and other CV protective effects (13), too. Despite the reports on its potential CV benefits, a direct relationship between serum and/or dietary Mg and CVD risk and its effective prognostic value is still not clearly established.

The calcium to magnesium (Ca/Mg) ratio is found more informative than that of Ca and Mg ions evaluated separately, because Mg has a physiological calcium antagonist role. In this study we investigated the concentrations of Ca, Mg , lipoprotein parameters including total cholesterol (TC), high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), triglyceride (TG), and also parameters of carbohydrate metabolism as insulin, fasting serum glucose (FSG), insulin resistance (IR), and also an anthropometric parameter- body mass index (BMI)- of patients with OSAS. We aimed to assess all these metabolic markers, especially Ca/Mg ratio, and their relationship with OSAS and the disease severity.

MATERIALS AND METHODS

Patients

The study comprised seventy newly diagnosed male OSAS patients (mean age 47.57 ± 12.15) and thirty male non-apneic controls (mean age 43.23 ± 10.50). The participants of the study were informed about the process of this study and they gave written informed consent. BMI was calculated for each participant before the sleep study. Patients were classified as two groups according to their AHI: severe OSAS as Group 1 (AHI >30), mild/ moderate OSAS as Group 2 ($5 < AHI \leq 30$). There were fifty-five and fifteen patients in these groups, respectively.

Central sleep apnea, upper airway resistance, lung disease, heart failure, chronic renal failure, systemic steroid therapy, hormone replacement therapy and cerebrovascular disease were the exclusion criterions of our study. Using a standardized questionnaire, the participants' datas (age, history of chronic and/or metabolic diseases, drugs, habits and cigarette smoking status) were noted. All of the participants were current smokers. Seven of the patients and three of the control subjects were diabetic. Only one participant in patients group was hypertensive.

Evaluation of biochemical tests

Between 7.30 a.m. to 9.00 a.m, we took fasting venous blood samples from participants. We collected blood samples into tubes containing a coagulator and gel separator. We obtained serum by centrifuging these blood samples for 5 minutes at 3,500 rpm in order to analyse biochemical and hormone tests (FSG, lipoproteins, insulin) and to determinate concentrations of bioelements (Mg and Ca). We determined the concentrations of Mg, Ca, FSG, TC, HDL-c, LDL-c and TG, using the spectrophotometric method, reagents and kits (AU 2700 instrument, Beckman Coulter, California, USA). Insulin levels were measured in all patients with DXI 800 Beckman Coulter equipment. We performed all assays by using calibrators and both internal and external quality controls. The minimum detectable concentrations were 0.12 mg/dL for Ca, 0.09 mg/dL for Mg, 2.70 mg/dL for TC, 0.88 mg/dL for TG, 0.07 mg/dL for HDL-c, 1.93 mg/dL for LDL-c, 0.72 mg/dL for glucose and 0.03

μIU/mL for insulin. The intra-assay and inter-assay variation coefficients were 0.7 % and 1 % for Ca, 1.03 % and 1.3 % for Mg, 0.1 % and 1.5 % for TC, 1.1 % and 1.8 % for TG, 0.9 % and 2 % for HDL-c, 0.7 % and 2.2 % for LDL-c 0.7% and 1.3% for glucose and 1.7% and 4.4% for insulin, respectively. Patients' insulin resistance (IR) values were calculated according to the formula: Homeostatic model assessment indicator of insulin resistance (HOMA-IR) = FSG (mg/dL) × fasting insulin levels (μIU/mL) / 405.

Statistical analyses

Statistical analyses were carried out using SPSS software version 23.0 for Windows (SPSS Inc., USA). The results of groups with normal distribution are presented as mean ± SD, and the median was use to present results that showed abnormal distribution. We used t-test for data with normal distribution and Mann-Whitney U test for data with non-normal distribution to determine significant differences between the groups. To estimate the correlations between serum Ca, Mg, Ca/Mg ratio and BMI, lipid profile and HOMA-IR for each group, we used Spearman's correlation coefficients. The $P \leq 0.05$ values of the obtained results were confirmed as statistically significant.

Table 1 shows anthropometric characteristics, PSG diagnostic indices (including AHI, oygen desaturation index (ODI), lowest O_2 saturation levels), means/medians, standard deviations, lipoproteins, minerals and insulin sensitivity/resistance markers of patients and control subjects. Table 2 shows Spearman's correlations between the studied minerals (Ca and Mg) and BMI, lipoproteins and HOMA-IR. Table 3 shows the significant difference (P= 0.039) of Ca/Mg ratios between the OSAS subgroups.

RESULTS

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Serum levels of TG, TC and LDL-c were higher but HDL-c levels were lower in patients but only the TG levels between two groups were statistically significantly different (P= 0.036). Although the patients had numerically higher Ca/Mg ratios (4.72 (4.36-4.84); 4.61 (4.33- 4.81)), there were no statistically significant differences in serum magnesium, calcium and Ca/Mg ratios between OSAS patients and controls. But, serum fasting glucose, insulin levels and as a matter of course their HOMA-IR levels were statistically significantly higher than controls (P= 0.004, P= 0.003 and P= 0.000, respectively) (Table 1).

Patients' calcium, magnesium and Ca/Mg ratios were positively correlated with their FSG levels (P= 0.012, 0.001 and 0.000, respectively). In addition their calcium levels were positively correlated with homeostatic model assessment indicator of insulin resistance (HOMA-IR) (P= 0.015) (Table 2).

Furthermore, when we analyse the subgroups of OSAS, we found that the patients with severe OSAS had significantly higher mean levels of Ca/Mg ratio, FSG, insulin and HOMA-IR levels as compared with mild/moderate OSAS group (P= 0.017, 0.033, 0.036 and 0.003, respectively) (Table 3).

DISCUSSION

OSAS is characterized by hypoxemia and carbon dioxide retention during sleep because of complete or partial upper airway obstruction (14). This intermittent ischemia and/or hypoxia enhanced oxidative stress and sympathetic activation so that OSAS is related with metabolic abnormalities like diabetes, obesity, dyslipidemia, MetS, and also CVDs (3,4). It is known that OSAS promotes inflammatory responses and has a negative effect on proatherogenic lipid levels. The study of Gozal et al. suggested that after adenotonsillectomy, serum apoB, triglyceride and CRP levels decreased proportionally to the AHI in children with OSAS (15). In our study, serum TG, TC and LDL-c levels were higher and HDL-c levels were lower in patients. Between two groups we also found a statistically significant difference in terms of TG levels (P= 0.036).

A growing evidence shows that OSAS is independently associated with insulin resistance and T2DM (16). In development of T2DM, the role of magnesium has been increasingly mentioned, too. Mg is included in various stages of signal transduction pathways of insulin. Mg has roles in secretion of insulin, binding and receptor activity. Studies suggest that lowering intracellular Mg^{2+} levels, decreases insulin receptor activity, inhibits the post-receptor action, causes an increase in insulin resistance; in brief, hypomagnesemia affects insulin resistance and is a risk factor for T2DM (17). According to the study of Song and co-workers, Mg supplementation has beneficial effects on glucose control in patients with T2DM (18). As Mooren FC et al. suggested in their study, Mg improves insulin sensitivity in subjects without diabetes (19). Ca and Mg have antagonistic roles, so the Ca/Mg ratio is found more informative than evaulating both ions individually (14). In our study, patients' serum Ca levels were numerically higher, Mg levels were lower, thereby their Ca/Mg ratios were higher than control group's. But the differences between these levels were not statistically significant (P> 0.05). When we evaulated these levels between OSAS groups (mild/ moderate and severe), we found that the ratio of Ca/Mg was significantly associated with severe OSAS. Mg levels or Ca levels alone, in contrast, were not constantly associated with severe OSAS. Mg deficiency is also related to oxidative stress and the inflammatory response. In contrast, Mg supplementation reduces insulin levels and also improves insulin sensitivity. Magnesium works like a physiologic antagonist to ionized calcium, so low levels may further activate ionized calcium (20). In our study, patients' Mg and Ca levels were in reference interval, but numerically different from controls'. Hence, we suggest to check these levels intermittently in especially severe OSAS patients. A recent study suggest that a higher intra-cellular Ca/Mg ratio, that can be induced by a low Mg- high Ca diet, may lead to insulin resistance or hypertension (21). Similarly to this study, in our study severe OSAS patients had statistically significantly higher Ca/Mg ratios (P= 0.017) and also statistically significantly higher serum FSG (P= 0.033) and insulin levels (P= 0.036) than mild/ moderate group. In addition their

Ca/Mg ratios were statistically significantly positive correlated with their FSG levels (P=0.000). Also, patients' HOMA-IR levels were statistically significantly higher than control group's (P= 0.001) and statistically positive correlated with their Ca levels (P= 0.015). We investigated the association between serum calcium, magnesium, Ca/Mg ratio of OSAS patients. We further investigated the interaction between Ca, Mg and Ca/Mg ratios on mild/moderate and severe OSAS patients and their diabetes risk, hypothesizing that insufficient serum Mg levels reflected by a high serum ratio of Ca/Mg ratio will be related with severe OSAS.

Studies showed that, patients with longer duration of T2DM, having micro- and/or macrovascular chronic complications of the disease, were also identified as having increased prevalence of Mg deficits. The results of serum fasting glucose and insulin levels of OSAS indicated that patients had statistically significantly higher levels than control group's (P< 0.01). In addition, patients had statistically higher HOMA-IR levels (P< 0.01). These results told that OSAS patients showed increased risk of developing insulin resistance and T2DM as previously reported by Rasche et al (5). There are studies in the general population about the relationship between Mg levels and the development of T2DM (22). Possible link between reduced insulin sensitivity and Mg deficiency is existing inflammation and/or oxidative stress. It is mentioned that in T2DM free radicals are often increased and also associated with Mg deficits (23). Serum fasting glucose, insulin and HOMAIR levels of patients with OSAS in our study were statistically higher than the controls. Ca/Mg ratios also predict inflamatory situation, these levels were not statistically significantly different between our study groups but while evaulating the difference of mean levels between severe and mild/moderate OSAS groups, we found that severe group had statistically higher levels (P= 0.017). As supporting previous studies mentioned about increased metabolic risks in OSAS, our study showed the increased risk of diabetes in severe OSAS patients.

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Our study has certain limitations. First, the study population consisted of only males. Our study results may not therefore reflect all individuals with OSAS. However, this was not planned beforehand; the patients were included consecutively. We attribute this to OSAS being more common in males than females in Turkish society. Second, this study had a relatively small sample size. So, larger and further studies are needed to search this association.

To conclude, results of the current study indicate that increased Ca/Mg ratios and relatively lower Mg levels are more notable in severe OSAS patients. This information is noteworthy because documentation of the role of Ca/Mg ratio and insulin resistance in severe OSAS may have important implications regarding diagnosis, monitoring, treatment and prognosis of T2DM.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University Medical Faculty (96681246/189).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: MU. Performed the experiments or case: IÇ, MU. Analyzed the data: IÇ. Wrote the paper: IÇ. All authors have read and approved the final manuscript.

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Table 1: Biochemical, polysomnographic parameters and anthropometric characteristics of the study groups.

	Reference range	Case group	Control group	P
Number of subjects	-	70	30	-
Age (years)	-	47.57 ± 12.15	43.23 ± 10.50	**NS**
Cigarette smoking (current)	-	70	30	**NS**
Comorbidity; Hypertension	-	1	-	**NS**
Diabetes mellitus	-	7	3	**NS**
AHI groups 0-4.9	-	-	30	-
5-14.9	-	4 (5.71%)	-	-
15-29.9	-	11 (15.71%)	-	-
> 30	-	55 (78.57%)	-	-
Oygen desaturation index (ODI) Mild/ moderate/ severe	-	86/ 82.36/ 76.07	-	-
Lowest O_2 saturation levels Mild/ moderate/ severe	-	18.4/ 16.46/ 59.11	-	-
BMI (kg/m^2)	< 24.9	10 %	10 %	
	25 - 29.9	20 %	30 %	

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	30 - 34.9	40 %	40 %	**NS**
	35 - 39.9	20 %	10 %	
	> 40	10%	10 %	
Fasting serum glucose (mg/dL)	70 - 110	[a]94 (88- 107)	[a]84 (74.5- 99)	**0.004**
Serum fasting insulin (µIU/mL)	1.9 - 23	[a]9.31 (6.27- 13.11)	[a]5.95 (3.53- 7.16)	**0.003**
HOMA-IR	> 2.6	[a]2.09 (1.33- 3.69)	[a]1.24 (0.66- 1.56)	**0.000**
Serum calcium (mg/dL)	8.4 - 10.6	9.72 ± 0.32	9.57 ± 0.47	**NS**
Serum magnesium (mg/dL)	1.9 - 2.5	2.0 ± 0.12	2.04 ± 0.19	**NS**
Ca/Mg ratio	-	[a]4.72 (4.36- 4.84)	[a]4.61 (4.33- 4.81)	**NS**
Serum TG (mg/dL)	35 - 150	[a]211 (136- 284)	[a]160 (104- 184)	**0.036**
Serum TC (mg/dL)	0 - 200	[a]213 (183- 242)	[a]197 (179- 218)	**NS**
Serum HDL-c (mg/dL)	40 - 60	[a]40 (36- 48.5)	[a]43 (39.5- 48.5)	**NS**
Serum LDL-c (mg/dL)	0 - 135	[a]132 (114- 158.5)	[a]126 (112.5- 148.5)	**NS**

mean ± SD, [a]Mann-Whitney U test was used, data are median and interquartile range (25%; 75%). NS, non significant. BMI: Body mass index, HOMA-IR: Homeostatic model assessment-insulin resistance.

Table 2: P values of Spearman's correlations between the studied minerals (Ca and Mg) and BMI, lipids, fasting serum glucose, insulin, HOMA-IR in patients.

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	Ca		Mg		Ca/Mg ratio	
	r	P	r	P	r	P
BMI	0.07	0.565	-0.012	0.92	0.097	0.426
TG	0.15	0.21	-0.035	0.775	0.133	0.272
TC	0.169	0.162	0.052	0.671	0.154	0.202
HDL-c	-0.03	0.808	-0.016	0.895	0.074	0.542
LDL-c	0.161	0.184	0.133	0.272	0.049	0.685
Fasting serum glucose	0.297	0.012*	-0.384	0.001**	0.438	0.000**
Insulin	0.218	0.07	-0.091	0.453	0.176	0.145
HOMA-IR	0.395	0.015*	0.045	0.793	0.071	0.604

*P ≤ 0.05, ** P ≤ 0.01. BMI: Body mass index, HOMA-IR: Homeostatic model assessment-insulin resistance. For units see Table 1.

Table 3: Ca/Mg ratio, FSG, insulin and HOMA-IR levels of OSAS groups.

	Group 1	Group 2	Sig. (2-tailed)
Number of patients	Severe OSAS n= 55	Mild/moderate OSAS n= 15	-
Ca/Mg ratio	4.83 ± 0.48	4.51 ± 0.39	**0.017***
Fasting serum glucose	105.25 ± 28.42	88.66 ± 14.27	**0.033***
Insulin	12.82 ± 5.83	7.29 ± 3.12	**0.036***
HOMA-IR	[a]2.47 (1.42 - 4.37)	[a]1.23 (1.07 - 2.28)	**0.003***

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HOMA-IR: Homeostatic model assessment-insulin resistance. [a]Mann-Whitney U test was used, data are median and interquartile range (25%; 75%). *P < 0.05

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