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Research Article

Association of General Obesity With Hyperhomocysteinemia in Patients With Migraine

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Background: Recent evidences have shown that obesity may affect homocysteine concentration. In addition, other studies reported that migraine is associated with high homocysteine concentration and obesity.
Objectives: The purpose of this study was to assess any association between general obesity and homocysteine levels in patients with migraine.
Patients and Methods: This cross-sectional study was conducted on 121 patients with migraine, aged 15-67 years, referred to Isfahan Khorshid and Imam Mosua Sader clinics in 2013. Fasting serum homocysteine concentration and anthropometric measurements such as weight, height, Body Mass Index (BMI), Body Fat Mass (BFM) and Lean Body Mass (LBM) were measured. The association between anthropometric measurements and homocysteine levels was examined with linear regression test, using SPSS software (version 18.0).
Results: Obesity and overweight were found in 14% and 43% of patients, respectively. In addition, hyperhomocysteinemia was observed in 19.6% of women, but none of men had homocysteine levels higher than 15 μm/L. There was a significant positive association between BMI ($P = 0.002$), BFM ($P = 0.007$) and LBM ($P < 0.001$) with serum levels of homocysteine. These associations remained significant even after adjustment for confounding variables. Moreover, in sex-stratified analyses, we found significant associations between BMI and BFM with homocysteine levels either in crude and adjusted models. However, such association was not significant for LBM ($P = 0.31$ for men; $P = 0.06$ for women).
Conclusions: Body mass index, BFM and LBM were significantly associated with high homocysteine levels in patients with migraine. Further studies are needed to confirm our findings.

*Keywords:*Obesity; Body Mass Index; Homocysteine; Migraine

1. Background

General obesity, usually defined by Body Mass Index (BMI), is a complex multifactorial chronic disease that has increased dramatically in the past decades (1, 2). Today, developed and developing countries both face general obesity epidemic in children and adults (2). In the United States, 35.5% of men and 35.8% of women have general obesity (3). In Spain, 24.4% of men and 21.4% of women have general obesity (4). In Iran, it is estimated that about 42.9% and 56.9% of men and women have general obesity, respectively (5). Studies showed that general obesity is associated with the risk of type II diabetes, hypertension, dyslipidemia, cardiovascular diseases, cancer and migraine (1). Moreover, obesity can induce the abnormal levels of insulin, total cholesterol level, Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C), triglycerides, glycosylated hemoglobin (HbA1c) and inflammatory cytokines such as C-Reactive Protein (CRP), fibrinogen and tumor necrosis factor (TNF-α). (6-9). Besides, recent investigations have shown that obesity may cause hyperhomocysteinemia (10-13), which is associated with endothelial damages and several disorders including cardiovascular diseases, ischemic stroke and spontaneous abortion (14-16). Based on the literature, investigations have shown a significant association between obesity and migraine (17). Other studies reported that migraine is associated with high homocysteine levels, which is considered as a leading cause of several disorders (18). Therefore, the association between obesity and homocysteine levels is important in patients with migraine, because high homocysteine levels in patients with migraine together with obesity reported to increase characteristics of migraine attacks such as severity, frequency and duration (19, 20). Therefore, there are conflicting results regarding obesity and high homocysteine levels (12, 13, 21-23), and also most studies emphasized on BMI and data on the relation between body fat mass (BFM) and lean body mass (LBM) with homocysteine levels is scarce. Besides, recent studies reported obesity and high homocysteine levels as risk factors of migraine attacks.

2. Objectives

The purpose of the present study was to assess any association between general obesity (BMI, BFM and LBM) and serum levels of homocysteine in patients with migraine.

3. Patients and Methods

In this cross-sectional study, we recruited 136 patients with migraine aged 15-67 years, from Khorshid and Emam Mosa Sadr Clinics, Isfahan, Iran in 2013. All participants who had long-term migraine disorder with one year history of severe, recurrent migraine attacks confirmed by neurologist according to International Headache Society (IHS) criteria (24) were enrolled. Disorders related to homocysteine level variation such as type II diabetes, chronic renal failure, hypertension, cardiovascular diseases and ischemic stroke as well as history of taking vitamin-B supplementation were considered as exclusion criteria.

This study was approved by the Ethics Committee of School of Nutrition, Isfahan University of Medical sciences, Isfahan, Iran. An informed consent was obtained from all participants. We collected general information about age, gender, medical history, anti-migraine drugs consumption, taking vitamin and mineral supplements and family history of migraine from all patients. In addition, BMI, BFM and LBM, as the indicators of general obesity, were measured for each participant. Body weight was measured by a digital scale with minimum clothing and without shoes with accuracy of 0.5 kg. Height was taken by a non-stretchable tape and bare foot with accuracy of 0.5 cm. Subject's BMI was calculated using the following formula; weight in kg/square of height in m^2. Body mass index values were categorized as underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30) and obese (BMI ≥ 30). Body fat mass and LBM were determined by body composition analyzer (Plus Avis 333, Korea). Lean body mass comprised muscle, internal organs and body water or whole body mass except the BFM and bone mass. Lean and obesity defined as BFM ≤ 15% and BFM ≥ 25% of total body mass for males and BFM ≤ 20% and BFM ≥ 35% of total body mass for females, respectively. Blood samples were collected from all patients in the morning after 12 hours fasting. Serum homocysteine level was analyzed using enzyme immunoassay (ELISA) method (Liquid Stable 2-part homocysteine reagent kit: Roche Company, Germany). Hyperhomocysteinemia was considered as serum homocysteine concentration more than 15 and 10 μm/L in men and women, respectively. Data was analyzed using SPSS statistical software (version 18.0; SPSS, Inc. Chicago, IL, USA). Quantitative variables were shown as mean and standard deviation of mean, and qualitative variables were represented as number of frequency and their percent. Age, anthropometric indices and homocysteine levels were compared in men and women using independent sample t-test. Moreover, we evaluated family history of migraine and long-term anti-migraine drug consumption in men and women by chi-square test. To examine the association between BMI, BFM and LBM with serum homocysteine levels, we used linear regression in crude and three adjusted models. In the first model, we adjusted age as a continuous variable to see the mentioned associations independent of subjects' age. In the second model, we additionally adjusted for long-term anti-migraine drug consumption such as corticosteroids and analgesic drugs. Further adjustment was performed for family history of migraine in the final model. Significant levels were considered as P value < 0.05.

3.1. Ethical Considerations

This study was conducted after obtaining a confirmation from the Ethics Committee of School of Nutrition, Isfahan University of Medical sciences, Isfahan, Iran and taking consent from all participants.

4. Results

In this study, from 136 patients, we had completed data of 24 men and 97 women with a mean age of 35.12 ± 12.23 and 33.93 ± 10.68 years, respectively. Hyperhomocysteinemia was observed in 19.6% of women, but none of men had homocysteine levels higher than 15 μm/L. Obesity and overweight were seen in 14% and 43% of patients, respectively. Anthropometric measurements, homocysteine levels and other characteristics of patients with migraine were compared between men and women and presented in Table 1. Weight, height, BMI, LBM and homocysteine levels were higher in men than women, but women had higher BFM. Age, family history of migraine and proportion of anti-migraine drugs consumption were not significantly different between men and women. Results of multiple linear regression tests for association between BMI, BFM and LBM with homocysteine levels in crude and adjusted models are shown in Table 2. Based on this table, a significant positive association was observed between BMI and BFM with homocysteine levels. This association remained significant even after adjustment for age, family history of migraine and long-term anti-migraine drugs consumption. Moreover, we found a significant association between LBM and homocysteine levels either in crude or multiple adjusted models. Gender-stratified analyses revealed significant positive associations between BMI and BFM with homocysteine levels in either men or women. Adjustment of confounding variables caused no changes in these associations. In both men and women, there was no significant association between LBM and serum homocysteine concentration. This association remained non-significant even after adjustment of different confounding variables (Table 3).

Table 1. Anthropometric Measurements, Homocysteine Levels and Other Characteristics of Men and Women [a, b]

Variables	Men	Women	P Value
Age, y	35.12 ± 12.23	33.93 ± 10.68	0.63
Weight, kg	70.97 ± 13.71	64.56 ± 11.03	0.01
Height, cm	169.29 ± 11.60	158.56 ± 5.90	< 0.001
BMI, kg/m^2	24.75 ± 4.08	25.72 ± 4.47	0.33
Body fat, kg	18.27 ± 6.87	21.62 ± 7.13	0.04
LBM, kg	52.21 ± 8.76	43.34 ± 4.37	< 0.001
Homocysteine, μm/L	10.04 ± 3.62	8.01 ± 2.42	0.015
Family history of migraine	18 (75)	62 (63.9)	0.21
Drug consumption [c]	19 (79.2)	83 (85.6)	0.31

[a] Data are presented as Mean ± SD or No. (%).
[b] Abbreviations: BMI, body mass index; LBM, lean body mass.
[c] Considered as long-term anti-migraine drug consumption such as corticosteroids and analgesic drugs.

Table 2. Multiple Linear Regression for Association Between Anthropometric Measurements and Homocysteine Levels in Total Population[a, b]

	BMI		Body Fat		LBM	
	β (SE)	P Value	β (SE)	P Value	β (SE)	P Value
Crude	0.175 (0.05)	0.002	0.095 (0.03)	0.007	0.134 (0.03)	< 0.001
Model 1	0.147 (0.06)	0.016	0.077 (0.03)	0.040	0.127 (0.03)	0.001
Model 2	0.140 (0.06)	0.021	0.073 (0.03)	0.052	0.129 (0.03)	0.001
Model 3	0.146 (0.05)	0.013	0.079 (0.03)	0.029	0.129 (0.03)	< 0.001

[a] Abbreviation: β (SE), β (standard error).
[b] Model 1, Adjusted for age; Model 2, Further adjusted for long-term anti-migraine drug consumption such as corticosteroids and analgesic drugs; Model 3, Additionally controlled for family history of migraine.

Table 3. Multiple Linear Regression for Association Between Anthropometric Measurements and Homocysteine Levels in Men and Women[a]

	BMI		Body fat		LBM	
	β (SE)	P Value	β (SE)	P Value	β (SE)	P Value
Men						
Crude	0.423 (0.16)	0.019	0.258 (0.09)	0.016	0.113 (0.08)	0.19
Model 1	0.355 (0.17)	0.056	0.221 (0.10)	0.040	0.09 (0.08)	0.29
Model 2	0.399 (0.18)	0.045	0.243 (0.10)	0.034	0.088 (0.08)	0.32
Model 3	0.435 (0.18)	0.031	0.240 (0.10)	0.039	0.090 (0.08)	0.31
Women						
Crude	0.147 (0.05)	0.007	0.090 (0.03)	0.009	0.078 (0.05)	0.16
Model 1	0.140 (0.05)	0.018	0.085 (0.03)	0.024	0.074 (0.05)	0.18
Model 2	0.132 (0.05)	0.025	0.080 (0.03)	0.033	0.081 (0.05)	0.14
Model 3	0.131 (0.05)	0.022	0.084 (0.03)	0.020	0.098 (0.05)	0.06

[a] Model 1: Adjusted for age; Model 2, Further adjusted for long-term anti-migraine drug consumption such as corticosteroids and analgesic drugs; Model 3, Additionally controlled for family history of migraine.

5. Discussion

Findings of this study showed significant positive associations between BMI, BFM and LBM with high levels of homocysteine in patients with migraine. These associations remained significant even after adjustment of different confounding variables. Moreover, in gender-stratified analyses, we found significant associations between BMI and BFM and serum homocysteine levels in men and women in either crude or adjusted models. However, such association was not significant for LBM in both genders. In this study, we found a significant positive association between general obesity and homocysteine levels in patients with migraine. In line with our findings, a case control study conducted by Konukoglu et al. showed that homocysteine concentration is higher in obese normotensive subjects than non-obese ones (12). In another similar study, Ercan et al. indicated that obese women have higher homocysteine levels compared to normal weight women (13). Besides, in a prospective cohort study Park et al. demonstrated a significant positive association between BFM and homocysteine concentration (25), which is consistent with our finding. Another similar study conducted by Sanlier et al. showed that as weight and BFM increase, homocysteine levels increase as well (26). In contrast to our findings, some studies indicated no association between BMI and homocysteine levels (22, 25). In a cross-sectional study conducted by Elshorbagy et al., BMI and BFM were inversely associated with homocysteine concentration (23). Inconsistent results in different studies may be due to differences in subjects' diet, physical activity level and their health status. In our study, we found a significant association between LBM and homocysteine levels in total population, but there were non-significant associations between men and women, which can be due to small number of participants in both genders. Our findings regarding the association between LBM and homocysteine levels are consistent with Battezzati et al. study, which reported a positive association between homocysteine and LBM (27). In contrast, there are some reports indicating no such association (23, 28).

Mechanism of obesity role in increasing homocysteine levels is unknown. Obesity is associated with insulin resistance; lack of insulin may increase homocysteine production in patients with obesity. Moreover, oxidative stress occurred in insulin resistance increases the angiotoxicity effects of homocysteine in obese subjects and leads to various disorders related to endothelial damages (12). Furthermore, evidences demonstrated a significant inverse association between BMI and plasma folate concentration (22, 29). Therefore, folate deficiency in obese subjects inhibits methionine synthetase and increases homocysteine levels. Moreover, investigations indicated that a high LBM entails high creatine turnover, which subsequently enhanced homocysteine formation (30).

The present study had several limitations. First was the cross-sectional nature of our study, hence, we could not confer a causal link between general obesity and homocysteine levels. Moreover, further studies are needed to confirm our findings. Second, low sample size in this study may have caused insufficient power to detect associations. Third, in this study analyses were performed without correction of plasma vitamin levels such as folate and B12 vitamin. However, a single measure of homocysteine may not be reflective of its long-term status. Therefore, it is suggested to consider these limitations in further studies. The strength of this study was that we assessed the association between general obesity and homocysteine levels in patients with migraine for the first time. Body mass index, BFM and LBM were significantly associated with high homocysteine levels in patients with migraine. Subsequently, further studies are needed to confirm our findings.

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Authors' Contributions

Sadeghi O, Ghiasvand R, Maghsoudi Z, Nasiri M devised the concept for the study, developed the study design, collected data, performed the study intervention, involved in the conception of study and performed the analyses and final preparation of the manuscript. Khorvash F and Askari Gh supervised data collection and analysis, contributed to the study design and intervention. Sadeghi O and Nasiri M assisted in data gathering and involved in study coordination and manuscript revision.

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