Jentashapir J Health Res. 2014 December; 5(6): e26653. DOI: 10.5812/jjhr.26653
Published online 2014 December 25. **Research Article**

Association Between Abdominal Obesity Indicators and Serum Levels of Homocysteine in Migraine Patients: A Cross-Sectional Study

Omid Sadeghi [1]; Zahra Maghsoudi [1]; Morteza Nasiri [2,*]; Fariborz Khorvash [3]; Reza Ghiasvand [1]; Gholamreza Askari [1]

[1]Food Security Research Center, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, IR Iran
[2]Student Research Committee, Nursing and Midwifery School, Jundishapur University of Medical Sciences, Ahvaz, IR Iran
[3]Neurology Research Center, Isfahan University of Medical Sciences, Isfahan, IR Iran

*Corresponding author: Morteza Nasiri, Student Research Committee, Nursing and Midwifery School, Jundishapur University of Medical Sciences, Ahvaz, IR Iran. Tel: +98-9171745485, Fax: +98-7726223012, E-mail: mortezanasiri.or87@yahoo.com

Received: December 4, 2014; **Accepted:** December 20, 2014

Background: The current studies showed that obesity could lead to hyperhomocysteinemia as well as migraine.
Objectives: Thus, this study aimed to assess the association between abdominal obesity and serum levels of homocysteine in migraine patients.
Patients and Methods: This cross-sectional study was conducted on 120 migraine patients, aged 15-67 years, who were referred to Isfahan Korshid and Imam Mosua Sader clinics in 2013. Abdominal obesity indicators such as waist circumference (WC), hip circumstance (HC), waist-hip ratio (WHR) and waist-height ratio (WHtR) as well as fasting homocysteine concentration were measured for all patients. Data was analyzed by the SPSS 19 software using t-test, χ^2 and regression.
Results: In this study, 7.7% of men and 18.8% of women had hyperhomocysteinemia. Abdominal obesity was prevalent in 3.8% of men and 27.1% of women. In the entire population, homocysteine concentration was positively associated with WC ($P \leq 0.001$), WHR ($P \leq 0.001$) and WHtR ($P \leq 0.001$), either in crude or adjusted models. In addition, such relationship was seen in women. Amongst men, a significant association was found between WC and homocysteine levels ($P = 0.03$), yet the association between WHR ($P = 0.06$), WHtR ($P = 0.08$) and homocysteine concentration was marginally significant.
Conclusions: Waist circumference, WHR and WHtR were positively associated with homocysteine concentration in migraine patients. However, further studies particularly of prospective nature are required to confirm our findings.

*Keywords:*Abdominal Obesity; Homocysteine; Migraine

1. Background

Homocysteine is a sulfur-containing amino acid, which is derived from demethylation of methionine (1). Elevated plasma levels of homocysteine is an independent risk factor for cardiovascular diseases (2, 3), stroke (4), hypertension (2, 3), recurrent pregnancy loss (5), diabetes (1) and high severity and frequency of migraine attacks (6, 7). Many factors have been found to be important in increasing plasma levels of homocysteine (8, 9). Genetic mutations, which induce alteration in the function of enzymes such as methylene tetra hydro folate reductase (MTHFR) and cystathionine beta synthase (CBS), are involved in the incidence of hyperhomocysteinemia (10). Moreover, changes in the endocrine system can affect homocysteine concentration and cause hyperhomocysteinemia (11). Nutritional factors such as low intake of folic acid, B_{12} and pyridoxine vitamin, heavy coffee and alcohol consumption as well as life style factors including smoking and lack of exercise are other causes of hyperhomocysteinemia (12-14). Also, recent investigations have shown that obesity may affect homocysteine levels (15-20). However, the main reason for the association between obesity and homocysteine levels is unknown; some studies have suggested a connection with 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-χ), which are prevalent in individuals with obesity, especially abdominal obesity (21-24). Furthermore, obesity as an increasing problem in the world is associated with different chronic conditions such as diabetes mellitus, cardiovascular diseases (CVDs), hypertension and different forms of cancers, which may affect homocysteine levels (25, 26). Several studies have investigated the association between obesity and homocysteine concentration in healthy and patient populations, yet no studies have examined the association between abdominal obesity and homocysteine levels in migraine patients. Thus, the association between obesity and homocysteine levels is important in migraine patients, because high homocysteine levels in migraine patients following an obese status can increase characteristics of migraine attacks such as its severity, frequency and duration (6, 7). We performed this study as most previous studies have only focused on the association between general obesity and homocysteine concentration, and due to conflicting results in this regards (27, 28).

2. Objectives

The purpose of the present study was to assess the probable relationship between abdominal obesity and serum levels of homocysteine in patients with migraine.

3. Patients and Methods

In this cross-sectional study, we recruited 136 migraine patients aged between 15 and 67 years, from Khorshid and Emam Mosa Sadr clinics, Isfahan, Iran, during the year 2013. All participants had long-term migraine disorders with one year history of severe recurrent migraine attacks that were confirmed by a neurologist according to the International Headache Society (IHS) criteria (29). We excluded participants who had chronic diseases such as diabetes mellitus, cardiovascular disorders, hypertension, renal diseases and those who had a history of taking vitamin B supplements. After approval from the ethics committee of the School of Health of Isfahan University of Medical Sciences, Isfahan, Iran and obtaining the consent of all participants, we collected patient's general information about age, medical history, consumption of anti-migraine drugs, vitamins and mineral supplements, and family history of migraine. Also, waist circumstance (WC), hip circumstance (HC), waist-hip ratio (WHR) and waist-height ratio (WHtR) as indicators of abdominal obesity were measured for each participant. Waist circumference was measured (in centimeters) at the mid-point between the top of the iliac crest bone and the last floating rib in the midaxillary surface using a non-elastic tape. The same measurement was done at the widest part of the buttock or hip as the subjects' HC. Height was measured by a standard tape, without shoes. Waist-hip ratio (cm/cm) was determined by dividing WC by HC. We also calculated the WHtR by this formula: WC/height. Abdominal obesity was considered as WC more than 102 and 88 cm in men and women, respectively. Blood samples were collected from all patients in the morning and after 12 hours of fasting. Serum homocysteine levels were analyzed by the enzyme-linked immunosorbent assay (ELISA) (liquid stable 2-part homocysteine reagent kit: Roche Company, Germany). Hyperhomocysteinemia in men and women was considered as a serum homocysteine concentration higher than 15 and 10 μm/L, respectively. Data analysis was conducted using the SPSS statistical software (version 18.0; SPSS, Inc. Chicago, IL, USA). Quantitative variables were expressed as means and standard deviations (SD), and qualitative variables were expressed as frequencies (percentages). To compare quantitative variables between men and women, we used the independent sample t-test. Moreover, we used the chi-square test to compare qualitative variables between genders. To examine the association of WC, WHR and WHtR with serum homocysteine levels, we used multiple linear regression in crude and adjusted models. In the first model, we adjusted the mentioned relationships for the participants' age (continuous). In the second model, we additionally controlled for long-term anti-migraine drugs consumption such as corticosteroid and analgesic drugs. Further adjustment was done for family history of migraine in the last model. Results were considered significant when P value was lower than 0.05.

4. Results

Form the 136 migraine patients, 14 patients refused to participate and we had completed data on 122 subjects (26 men and 96 women) with mean age of 34.31 ± 10.58 years. The results showed that 7.7% of men and 18.8% of women had hyperhomocysteinemia. In addition, abdominal obesity was prevalent in 3.8% of men and 27.1% of women. Differences between men and women regarding age, abdominal obesity indicators and homocysteine levels are indicated in Table 1. Based on this table, WHR and HC were higher in men compared with women. Moreover, men had higher homocysteine concentration in comparison with women. There was no difference between men and women regarding age, WHtR, family history of migraine and long-term anti-migraine drugs consumption. The association between abdominal obesity indicators and homocysteine levels is shown in Table 2. There was a significant positive association between WC, WHR and WHtR, and homocysteine levels. Adjustment for potential confounding variables such as age, long-term anti-migraine drugs consumption and family history of migraine creates no change in this relationship, and one unit increase in WC, WHR and WHtR causes 0.11, 17.21 and 12.39 units increase in homocysteine concentration. Sex-stratified analysis revealed that a significant positive association was found between WC, WHR and WHtR, and homocysteine levels among women. This relationship was significant even after adjustment of potential confounding variables, and one unit increase in WC, WHR and WHtR caused 0.06, 11.06 and 10.12 units increase in homocysteine concentration, respectively. Waist circumference was significantly associated with homocysteine levels in both crude and adjusted models in men. In addition, there was a positive association between WHR and WHtR, and homocysteine concentration in men; however, this relationship was marginally significant. Adjustment for potential confounders did not change this relationship.

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

Variables	Men	Women	P Value
Age, y	36.15 ± 10.75	33.86 ± 10.52	0.32
WC, cm	90.84 ± 9.75	82.17 ± 9.25	< 0.001[c]
WHR, cm/cm	0.89 ± 0.08	0.83 ± 0.07	< 0.001[c]
WHtR, cm/cm	0.52 ± 0.06	0.51 ± 0.06	0.49
HC, cm	101.35 ± 6.35	98.81 ± 5.06	0.03 [c]
Homocysteine, μm/L	10.50 ± 3.42	7.80 ± 2.28	0.001 [c]
Family history of migraine	19 (73.1)	64 (65.3%)	0.44
Drug consumption[d]	22 (84.6)	84 (87.5)	0.45

[a] abbreviations: WC, Waist circumstance; WHR, Waist-hip ratio; WHtR, Waist-height ratio; HC, Hip circumstance.
[b] Data are presented as Mean ± SD or No. (%).
[c] P <0.05; statistically significant.
[d] Considered as long-term anti-migraine drugs consumption such as corticosteroid and analgesic drugs.

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

	WC		**WHR**		**WHtR**	
	B (SE)	**P Value**	**B (SE)**	**P Value**	**B (SE)**	**P Value**
Total						
Crude	0.119 (0.02)	< 0.001[c]	15.51 (2.98)	< 0.001[c]	14.57 (3.92)	< 0.001[c]
Model 1	0.112 (0.02)	< 0.001[c]	17.52 (3.71)	< 0.001[c]	13.07 (4.19)	0.002[c]
Model 2	0.112 (0.02)	< 0.001[c]	17.59 (3.78)	< 0.001[c]	12.70 (4.25)	0.003[c]
Model 3	0.110 (0.02)	< 0.001[c]	17.21 (3.68)	< 0.001[c]	12.39 (4.14)	0.003[c]
Men						
Crude	0.144 (0.06)	0.038[c]	15.43 (8.02)	0.067[d]	18.63 (10.43)	0.087[d]
Model 1	0.137 (0.06)	0.053[c]	15.87 (9.85)	0.121	17.23 (10.81)	0.125
Model 2	0.190 (0.07)	0.021[c]	20.45 (11.07)	0.080[d]	23.10 (12.25)	0.074[d]
Model 3	0.186 (0.07)	0.026 [c]	21.70 (11.03)	0.064[d]	23.75 (12.23)	0.067[d]
Women						
Crude	0.074 (0.02)	0.004[c]	10.79 (3.20)	0.001[c]	11.88 (3.67)	0.002[c]
Model 1	0.066 (0.02)	0.015[c]	11.66 (4.14)	0.006[c]	10.90 (4.00)	0.008[c]
Model 2	0.063 (0.02)	0.023[c]	11.22 (4.25)	0.010[c]	10.40 (4.10)	0.013[c]
Model 3	0.065 (0.02)	0.015[c]	11.06 (4.13)	0.009[c]	10.12 (3.98)	0.013[c]

[a] Abbreviations: WC, Waist circumstance; WHR, Waist-hip ratio; WHtR, Waist-height ratio.
[b] Model 1, Adjusted for age; Model 2, Further adjusted for long-term anti-migraine drugs consumption such as corticosteroid and analgesic drugs; Model 3, Additionally controlled for family history of migraine.
[c] P < 0.1; marginally significant.
[d] P < 0.05; statistically significant.

5. Discussion

In this study, we found a significant positive association between WC, WHR and WHtR, and homocysteine concentration in both crude and adjusted models. In addition, sex-stratified analysis showed such relationship in women, as well. Among men, we observed that WC is significantly associated with homocysteine levels, but the association between WHR and WHtR, and homocysteine concentration was marginally significant. This study is the first research that assessed the association between abdominal obesity and serum homocysteine levels in migraine patients. Homocysteine is a non-essential amino acid that is involved in methionine metabolism. High level of homocysteine is associated with various vascular diseases such as cardiovascular diseases, hypertension and ischemic stroke (1-4). It seems that several factors including genetic mutations, low intake or deficiencies of B vitamins, impaired renal function, nutritional and lifestyle factors are involved in the etiology of hyperhomocysteinemia (10-14). Among these factors, obesity, especially abdominal obesity has long been a concern for researchers. Although, some studies have demonstrated that abdominal obesity can affect homocysteine levels, data on the association between abdominal obesity and homocysteine levels is scarce and conflicting, especially in migraine patients. Recent studies showed that hyperhomocysteinemia can increase severity and frequency of migraine attacks (6, 7). In addition, studies in this regard have mostly focused on WC and WHR and there is no evidence on the association between WHtR and homocysteine levels. In this study, we found a significant association between WC, WHR and WHtR, and homocysteine levels, however, among men, the association between WHR and WHtR, and homocysteine levels was marginally significant, which can be due to the small number of men with abdominal obesity. In line with our findings, Vaya et al. conducted a case control study on 66 morbid obese patients and 66 normal weight subjects. This study showed that abdominal obesity is an independent predictor for hyperhomocysteinemia (18). In another cross-sectional study, homocysteine concentration was positively associated with WC, which is in concordance with our results (19). In a similar study conducted on patients with coronary artery disease, it was shown that WHR, but not BMI, is a strong independent predictor of total homocysteine levels (20). In contrast to our findings, some studies showed no significant association between abdominal obesity and homocysteine levels. Konukoglu et al. reported that there is no significant correlation between total homocysteine levels and WHR (28). In a cross-sectional study, there was an inverse association between WC and homocysteine concentration, which is not in agreement with our results (27). Inconsistent findings of the current study compared with previous studies may be due to differences in dietary patterns, health status, physical activities and psychological abnormalities of the participants. However the exact mechanism by which abdominal obesity affects homocysteine concentration is still unknown, while there are some hypotheses in this regard. Several studies have shown that abdominal obesity is associated with insulin resistance. Decreased function of insulin may increase the production of homocysteine in obese subjects by unidentified mechanisms (28). Evidences have demonstrated a significant inverse association between obesity and plasma folate concentration (16, 30). Therefore, folate deficiency in obese subjects inhibits methionine synthetase and increases homocysteine levels.

This study had a number of limitations, which should be considered. The first limitation was the cross-sectional nature of our study, which does not allow a causal link between abdominal obesity and homocysteine levels. Thus, further studies are needed to confirm our findings. Second, the low sample size in this study may have caused insufficient power to detect associations. Third, despite several adjustments, further control for confounding variables such as physical activity, vitamin B sufficiency and diet will be needed to reach an independent association between abdominal obesity and homocysteine levels. Moreover, it is possible that a single measure of homocysteine may not be reflective of long-term status. Thus it is suggested for other researchers to pay more attention to these limitations in future studies. The strength of this study was that we assessed the association between abdominal obesity and homocysteine levels among migraine patients for the first time. Waist circumference, WHR and WHtR were positively associated with homocysteine concentration in migraine patients. Further studies, particularly of prospective nature are required to shed light on our findings.

Acknowledgements

This article was adopted from the MSc dissertation of Mr Omid Sadeghi, which was supported by the Isfahan University of Medical Sciences, Iran (grant number 392363). We hereby appreciate the assistance and support of the Deputy Vice-Chancellor for research affairs of Isfahan University of Medical Sciences and all patients who participated in this study.

References

1. Dominguez LJ, Galioto A, Pineo A, Ferlisi A, Ciaccio M, Putignano E, et al. Age, homocysteine, and oxidative stress: relation to hypertension and type 2 diabetes mellitus. *J Am Coll Nutr.* 2010;**29**(1):1–6.
2. Bautista LE, Arenas IA, Penuela A, Martinez LX. Total plasma homocysteine level and risk of cardiovascular disease: a meta-analysis of prospective cohort studies. *J Clin Epidemiol.* 2002;**55**(9):882–7.
3. Homocysteine Studies C. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA.* 2002; **288**(16):2015–22.
4. Casas JP, Bautista LE, Smeeth L, Sharma P, Hingorani AD. Homocysteine and stroke: evidence on a causal link from mendelian randomisation. *Lancet.* 2005;**365**(9455):224–32.
5. Micle O, Muresan M, Antal L, Bodog F, Bodog A. The influence of homocysteine and oxidative stress on pregnancy outcome. *J Med Life.* 2012;**5**(1):68–73.
6. Lea R, Colson N, Quinlan S, Macmillan J, Griffiths L. The effects of vitamin supplementation and MTHFR (C677T) genotype on homocysteine-lowering and migraine disability. *Pharmacogenet Genomics.* 2009;**19**(6):422–8.
7. Menon S, Lea RA, Roy B, Hanna M, Wee S, Haupt LM, et al. Genotypes of the MTHFR C677T and MTRR A66G genes act independently to reduce migraine disability in response to vitamin supplementation. *Pharmacogenet Genomics.* 2012;**22**(10):741–9.
8. Lussier-Cacan S, Xhignesse M, Piolot A, Selhub J, Davignon J, Genest J, Jr.. Plasma total homocysteine in healthy subjects: sex-specific relation with biological traits. *Am J Clin Nutr.* 1996;**64**(4):587–93.
9. Jacobsen DW. Determinants of hyperhomocysteinemia: a matter of nature and nurture. *Am J Clin Nutr.* 1996;**64**(4):641–2.
10. Alessio AC, Siqueira LH, Bydlowski SP, Hoehr NF, Annichino-Bizzacchi JM. Polymorphisms in the CBS gene and homocysteine, folate and vitamin B12 levels: association with polymorphisms in the MTHFR and MTRR genes in Brazilian children. *Am J Med Genet A.* 2008;**146A**(20):2598–602.
11. Fonseca V, Guba SC, Fink LM. Hyperhomocysteinemia and the endocrine system: implications for atherosclerosis and thrombosis. *Endocr Rev.* 1999;**20**(5):738–59.
12. de Bree A, Verschuren WM, Blom HJ, Kromhout D. Lifestyle factors and plasma homocysteine concentrations in a general population sample. *Am J Epidemiol.* 2001;**154**(2):150–4.

13. Krishnaswamy K, Lakshmi AV. Role of nutritional supplementation in reducing the levels of homocysteine. *J Assoc Physicians India.* 2002;**50 Suppl**:36–42.
14. Chrysohoou C, Panagiotakos DB, Pitsavos C, Zeimbekis A, Zampelas A, Papademetriou L, et al. The associations between smoking, physical activity, dietary habits and plasma homocysteine levels in cardiovascular disease-free people: the 'ATTICA' study. *Vasc Med.* 2004;**9**(2):117–23.
15. Huemer M, Vonblon K, Fodinger M, Krumpholz R, Hubmann M, Ulmer H, et al. Total homocysteine, folate, and cobalamin, and their relation to genetic polymorphisms, lifestyle and body mass index in healthy children and adolescents. *Pediatr Res.* 2006;**60**(6):764–9.
16. Nakazato M, Maeda T, Takamura N, Wada M, Yamasaki H, Johnston KE, et al. Relation of body mass index to blood folate and total homocysteine concentrations in Japanese adults. *Eur J Nutr.* 2011;**50**(7):581–5.
17. Ercan M, Konukoglu D. Role of plasma viscosity and plasma homocysteine level on hyperinsulinemic obese female subjects. *Clin Hemorheol Microcirc.* 2008;**38**(4):227–34.
18. Vaya A, Rivera L, Hernandez-Mijares A, de la Fuente M, Sola E, Romagnoli M, et al. Homocysteine levels in morbidly obese patients: its association with waist circumference and insulin resistance. *Clin Hemorheol Microcirc.* 2012;**52**(1):49–56.
19. da Silva NP, de Souza FI, Pendezza AI, Fonseca FL, Hix S, Oliveira AC, et al. Homocysteine and cysteine levels in prepubertal children: association with waist circumference and lipid profile. *Nutrition.* 2013;**29**(1):166–71.
20. Lin YH, Pao KY, Yang WS, Wu VC, Chen YJ, Lin YL, et al. Waist-to-hip ratio correlates with homocysteine levels in male patients with coronary artery disease. *Clin Chem Lab Med.* 2008;**46**(1):125–30.
21. Da Costa LA, Arora P, Garcia-Bailo B, Karmali M, El-Sohemy A, Badawi A. The association between obesity, cardiometabolic disease biomarkers, and innate immunity-related inflammation in Canadian adults. *Diabetes Metab Syndr Obes.* 2012;**5**:347–55.
22. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature.* 2006;**444**(7121):875–80.
23. Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006;**444**(7121):860–7.
24. Westphal SA. Obesity, Abdominal Obesity, and Insulin Resistance. *Clin Cornerstone.* 2008;**9**(1):23–31.
25. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health.* 2009;**9**:88.
26. Khorvash F, Mottaghi T, Askari G, Maracy MR, Ghiasvand R, Maghsoudi Z, et al. The association between serum vitamin d levels with general and abdominal obesity among patients with migraine. *Int J Prev Med.* 2013;**4**(Suppl 2):S313–7.
27. Park SB, Georgiades A. Changes in body composition predict homocysteine changes and hyperhomocysteinemia in Korea. *J Korean Med Sci.* 2013;**28**(7):1015–20.
28. Konukoglu D, Serin O, Ercan M, Turhan MS. Plasma homocysteine levels in obese and non-obese subjects with or without hypertension; its relationship with oxidative stress and copper. *Clin Biochem.* 2003;**36**(5):405–8.
29. *The International Classification of Headache Disorders.* 2th ed: Cephalalgia; 2004.
30. Mojtabai R. Body mass index and serum folate in childbearing age women. *Eur J Epidemiol.* 2004;**19**(11):1029–36.