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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

VÜCUT KİTLE İNDEKSİ, ADİPONEKTİN VE CRP'NİN PREMENOPOZAL KADINLARDA MİGREN SIKLIĞI VE ŞİDDETİNE ETKİSİ

THE IMPACT OF BODY MASS INDEX, ADIPONECTIN AND C-REACTIVE PROTEIN ON FREQUENCY AND SEVERITY OF MIGRAINE ATTACKS IN PREMENOPAUSAL WOMEN

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ÖZET

AMAÇ: Enflamasyon, migren için olası bir mekanizma olarak araştırılmaktadır. Obezite ve adipokinlerin enflamasyondaki rolü ve migrenle ilişkisi üzerine birçok çalışma yürütülmektedir. Bu çalışmada amacımız, premenopozal kadınlarda interiktal dönemde plazma adiponektin (ADP) düzeyleri, vücut kitle indeksi (VKİ) ve C-reaktif protein (CRP) ile migren ataklarının sıklığı ve şiddeti arasındaki ilişkiyi belirlemektir.

GEREÇ VE YÖNTEM: Çalışmaya 38 ayaktan tedavi gören premenopozal kadın ve yaş uyumlu 32 sağlıklı kontrol dahil edilmiştir. Hastalara Uluslararası Başağrısı Derneği kriterlerine göre migren tanısı konulmuştur. Hastaların baş ağrısız dönemdeki CRP, ADP düzeyleri, lökosit sayıları ve VKİ değerleri kontrol grubu ile karşılaştırılmıştır.

BULGULAR: VKİ ve CRP düzeylerinin hasta ve kontrol grubunda karşılaştırılmasında pozitif ve istatistiksel olarak anlamlı bir korelasyon gözlenmiştir (sırasıyla p=0.01, p=0.03). Her iki grupta da VKİ ve ADP düzeylerinin karşılaştırılmasında bir korelasyon saptanmamıştır (kontroller için p=0.053, hastalar için p=0.285). Migren atak sıklığının hastaların VKİ, CRP ve ADP düzeyleri ile karşılaştırılmasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır (sırasıyla p=0.669, p=0.989, p=0.201). VKİ ile ağrı şiddeti arasında pozitif ve anlamlı bir ilişki saptanmıştır (p=0.017). CRP, ADP ve ağrı şiddeti arasında ise ilişki bulunamamıştır (sırasıyla p=0.827, p=0.359).

SONUÇ: Bir enflamasyon belirteci olan CRP, VKİ'nin artışı ile ilişkili olarak artmaktadır. Yüksek VKİ, şiddetli migren ataklarını destekleyebilir. Sonuç olarak, kilo alımını önlemek ve kilo vermeyi önermek, şiddetli baş ağrısı ataklarını yönetmede terapötik bir yol olabilir.

ANAHTAR KELİMELER: Adiponektin, Vücut kitle indeksi, C-reaktif protein, Migren, Premenopozal periyot.

ABSTRACT

OBJECTIVE: Inflammation has been investigated as a possible mechanism for underlying migraine. Many studies continue to be conducted on the role of obesity and adipokines in inflammation and their relationship with migraine. Our objective was to determine the relationship between plasma adiponectin (ADP) levels, body mass index (BMI), and C-reactive protein (CRP), with the frequency and severity of migraine attacks in premenopausal women during the interictal period.

MATERIAL AND METHODS: The study included 38 premenopausal women receiving outpatient treatment for migraine and 32 age-matched healthy controls. The patients were diagnosed with migraine according to the International Headache Society criteria. The patients' CRP, ADP levels, leukocyte counts during the headache-free period, and BMI were compared with those of the control group.

RESULTS: A positive and statistically significant correlation was observed in the comparison of BMI and CRP levels in both the patient and control groups (p=0.01, p=0.03, respectively). No correlation could be established in terms of the comparison of BMI and ADP levels in either group (p=0.053 for controls, p=0.285 for patients). No statistically significant association was found in the comparison of the frequency of migraine attacks with the BMI, CRP, and ADP levels of the patients (p=0.669, p=0.989, p=0.201, respectively). A positive and significant relationship was determined between BMI and pain severity (p=0.017). However, no relationship between CRP, ADP levels, and pain severity was found (p=0.827, p=0.359, respectively).

CONCLUSIONS: CRP, as an established marker of inflammation, increases in relation to a rise in BMI. High BMI may contribute to the development of severe migraine attacks. In conclusion, preventing weight gain and advising weight loss may be a therapeutic strategy for managing severe headache attacks.

KEYWORDS: Adiponectin, Body mass index, C-reactive protein, Migraine, Premenopausal period.

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INTRODUCTION

Migraine, which is common in society, is a complex disease characterized by recurrent and disabling headache attacks. Research by Peterlin et al. suggests that migraine is a neurovascular disease (1). Although it is not clear whether the initial neurological event that causes a migraine attack is due to brainstem activation or cortical spreading depression, it is known that migraine pain occurs due to meningeal vasodilation and neurogenic inflammation. Vasodilation develops as a result of the secretion of inflammatory neuropeptides from activated trigeminal system nerve terminals, followed by plasma extravasation and mast cell degranulation, which lead to neurogenic inflammation. Calcitonin gene-related peptide, substance P, interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α have all been reported as neuropeptides involved in the pathway leading to neurogenic inflammation in migraine attacks (1,2).

Adipose tissue is suggested to be involved in immunity and insulin sensitivity, in addition to inflammation (1,2). It is also known that adipose tissue produces chemokines and cytokines, as well as adipocytokines such as leptin, resistin, and adiponectin (ADP). ADP is an adipocytokine involved in energy homeostasis. In addition to preventing insulin resistance and having protective effects against the development of atherosclerosis, it also has anti-inflammatory effects. In migraine, insulin sensitivity is reported as impaired. Insulin resistance is associated with obesity, a condition suggested to be a predominant risk factor for the transformation of episodic migraine into a chronic form. For this reason, ADP may be considered as having a preventive role in the pathological progression of migraine (1).

ADP is the most abundant adipocytokine in circulation. Structurally, it belongs to the complement 1q family and is also a structural homolog of the TNF-α family. Primarily, it is secreted from adipocytes (1,3). Plasma ADP levels are inversely correlated with BMI and vary from 3.0 to 30 microg/ml (3,4). ADP concentrations in cerebrospinal fluid (CSF) have been reported to be 1–4% of serum concentrations (5). It is unclear whether ADP acts as an anti-inflammatory hormone or only modulates innate immunity. However, ADP is known to act as a modulator of many cytokines (6). In mouse studies, it has been reported that ADP reduces IL-6 secretion and down-regulates the production and activity of TNF-α through its effect on brain endothelial cells. IL-6 and TNF-α are both pro-inflammatory cytokines known to play a role in the pathogenesis of insulin resistance, obesity, coronary artery disease, and possibly migraine (1). Abnormal C-reactive protein (CRP) levels have been reported in migraine patients (7). Oxidative stress, leukocyte activation, and inflammatory vasodilation are thought to be the mechanisms associated with increased CRP levels in migraine (8). It has been suggested that high BMI is associated with migraine. In population-based studies, BMI has been found to be associated with the transformation of migraine from an episodic to a chronic form (9).

Given that migraine is a common and debilitating disease, in this study we aimed to investigate whether body mass index, adiponectin, and C-reactive protein (CRP) have an impact on the frequency and severity of migraine attacks in premenopausal women. By doing so, we aimed to explore potential therapeutic approaches to alleviate or reduce the frequency of attacks.

MATERIAL AND METHODS

We included in our study 38 premenopausal outpatient women attending the hospital outpatient clinic, along with 32 age- and gender-matched healthy controls. Patients were diagnosed with migraine according to the International Headache Society (IHS) criteria (10). The control group was screened for vascular-type headache, and individuals who had not experienced this type of headache throughout their lives and matched by age and gender were selected as controls. Male patients, menopausal female patients, and those with a history of atherosclerotic coronary artery disease, hypertension, or diabetes mellitus were excluded from the study. CRP, ADP levels, leukocyte count during the headache-free period, and BMI were compared between the patient and the control group.

Patients were asked about headache type, duration, frequency, severity, the average number of headache attacks per month, as well

as the occurrence of nausea, vomiting, photophobia, and phonophobia, and the existence of a family history of migraine. BMI was calculated in both groups using the formula: BMI = weight (kg) / height (m^2) and categorized based on the World Health Organization categories: <18.5 (underweight), 18.5 to 24.9 (normal weight), 25 to 29.9 (overweight), and ≥30 kg/m^2 (obese). The Wong-Baker Face Scale (11) was used to assess pain intensity. The pain intensity was categorized as follows: a score of 0 indicated no pain, 1 indicated mild pain, 2 indicated more than mild pain, 3 indicated moderate pain, 4 indicated severe pain, and 5 indicated the worst pain **(Figure 1)**.

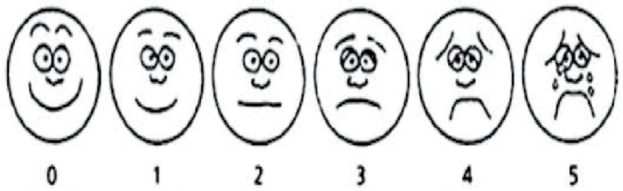

Figure 1: Wong-Baker Face Scale

Venous blood samples taken to detect CRP levels and leukocyte count were analyzed on the same day, while those for ADP levels in both groups were preserved frozen at -80 °C until the day of analysis. After being kept at room temperature for 20 minutes, the samples were centrifuged for 10 minutes at 1500 rpm to separate the serum. The ELISA method was used to analyze ADP levels. Evaluations of symptoms and blood samples were performed during the interictal (headache-free) period.

Ethical Committee

Ethics committee approval for the study was obtained from Ankara Numune Education and Research Hospital (Approval No: 637/2008).

Statistical Analysis

Statistical analysis of the data was performed using the SPSS software package. Descriptive statistics for continuous variables were presented as mean ± standard deviation or median (min-max), while the frequencies of nominal variables were expressed as percentages. The normality of the variables was assessed using the Shapiro-Wilk test. The Mann-Whitney U test and paired-samples t-test were used to determine whether there was a significant difference between groups for variables obtained by measurement. Pearson's correlation test was applied for variables following a normal distribution, and Spearman's correlation test was used for variables not following a normal distribution. Statistical significance was set at $p<0.05$.

RESULTS

The median age of the patients was 34 years (range 16-41 years), and that of the controls was 31.5 years (range 21-50 years). No statistical significance was found between the two groups regarding median age (p=0.364).

The median BMI of the patients was 24.3 kg/m^2 (range 18-39.9 kg/m^2), and for the controls, it was 22.4 kg/m^2 (range 16.2-31.8 kg/m^2). This difference was not statistically significant (p=0.113). A positive family history of migraine was reported by 13 patients (34.2%) and 1 control subject (3.1%), which was statistically significant (p=0.001) **(Table 1)**. In both groups, all relatives with a positive family history were first-degree relatives.

Table1: Comparement of demographic characteristics and laboratory findings of the patients and controls

	Patients	Controls	p
Median age	34 (range 16-41 yrs)	31.5 (range 21-50 yrs)	0.364
Median BMI	24.3 kg/m (18-39.9)	22.4 kg/m (16.2-31.8)	0.113
Positive family history of migraine	n=13 (34.2%)	n=1 (3.1%)	0.001*
ADP levels	8.60 µg/ml (4.06-14.39)	9.03 µg/ml (4.55-14.04)	0.684
CRP levels	3.19 mg/dl (3.19-18.2)	3.19 mg/dl (3.02-8.00)	0.423
Median leucocyte count	6700 /µL (3500-12800)	6950 /µL (3500-14300)	0.701
Smoking	n=12 (31.6%)	n=13 (40.6%)	0.431
Alcohol	n=1 (2.6%)	n=2 (6.3%)	0.581

* ; shows statistical significance: Migraineurs have statistically significant family history of migraine

According to the IHS criteria (10), 2 patients (5.3%) were classified as having migraine with aura, and 36 (94.7%) were classified as having migraine without aura **(Table 2)**.

Table 2: The characteristics and ratio of migraine headache in patients

	N	%
Migraine with aura	2	5.3
Migraine without aura	36	94.7
Occurrence of photophobia during attack	34	89.5
Occurrence of phonophobia during attack	34	89.5

The median number of pain attacks per month was 3 (range 1-8 per month). In the patient group, the median CRP level was 3.19 mg/dl (range 3.19-18.2 mg/dl), and in the control group, it was also 3.19 mg/dl (range 3.02-8.00 mg/dl). No statistical significance was found between the two groups regarding median CRP levels (p=0.423).

Similarly, no significance was found in terms of median adiponectin levels (p=0.684), with a median ADP level of 8.60 µg/ml (range 4.06-14.39 µg/ml) for patients and 9.03 µg/ml (range

4.55-14.04 µg/ml) for controls. When the groups were compared regarding leukocyte count, no significant difference was found (p=0.701). The median leukocyte count was 6700/µL (range 3500-12800/µL) for patients and 6950/µL (range 3500-14300/µL) for controls. No correlation could be established in either group between BMI and ADP levels (p=0.053 for controls, p=0.285 for patients) (Table 1). The intensity of pain during attacks was described as moderate by 11 patients (28.9%), severe by 19 patients (50%), and the worst by 8 patients (21.1%), according to the Wong-Baker Face Scale (11). A positive and statistically significant correlation was observed between BMI and CRP levels in both the control and patient groups (p=0.01, p=0.03, respectively). In this study, no statistical association was found between the frequency of migraine attacks and BMI, CRP, or ADP levels in the patients (p=0.669, p=0.989, p=0.201, respectively) **(Table 3)**.

Table 3: Correlation analyses between attack frequency, BMI, CRP and ADP of the patients

N=38	Attack frequency	BMI	CRP	ADP
Attack frequency		r= 0.72 p=0.669	r= -0.002 p=0.989	r= -0.212 p=0.201
BMI	r= 0.72 p=0.669		r= 0.353 p=0.030*	r= 0.178 p= 0.285
CRP	r= -0.002 p=0.989	r= 0.353 p=0.030*		r= - 0.053 p= 0.754
ADP	r= -0.212 p=0.201	r= -0.178 p=0.285	r= -0.053 p=0.754	

*There is a positive statistical correlation between BMI and CRP.

On the other hand, a positive and significant relationship was found between BMI and pain severity (p=0.017) **(Table 4 and Figure 2)**. No relationship was found between CRP, ADP, and pain severity (p=0.827, p=0.359, respectively).

Table 4: Correlation analyses between pain severity and BMI, CRP and ADP

N=38	Pain Severity
BMI	r= 0.384 p=0.017*
CRP	r= 0.037 p= 0.827
ADP	r= -0.153 p= 0.359

*There is a positive statistical correlation between BMI and pain severity

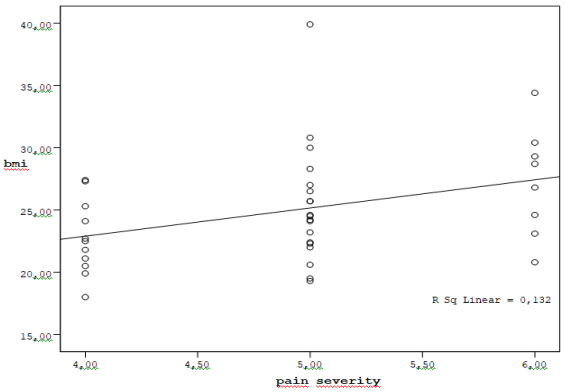

Figure 2: Positive correlation between BMI and pain severity

DISCUSSION

The previous and current data have shown that adipose tissue is not only a depot for fat storage but also plays an active role in multiple physiological processes and pathological events related to inflammation and immunity. Adipose tissue is known for secreting a variety of growth factors, complement factors, cytokines, and adipocytokines, including ADP. ADP is an adipocytokine, primarily secreted from adipocytes in adipose tissue. It has both anti-inflammatory and pro-inflammatory properties. The HMW-ADP form of adiponectin, which is detected in the circulation in three forms (high, medium, and low molecular weight), has been shown to have pro-inflammatory properties, and the LMW-ADP form has anti-inflammatory properties (2,12). It is known that plasma levels of ADP are inversely correlated with BMI. At normal levels, ADP has anti-inflammatory activities, such as inhibition of IL-6 and IL-8 formation induced by TNF-α, as well as the ability to induce IL-10 and IL-1, which are also anti-inflammatory cytokines. ADP levels are also inversely correlated with C-reactive protein, TNF-α, and IL-6 levels (9,12).

One study, although the sample size was small, mentions three clear relationships between migraine and adipose tissue. The first is that in headache-free periods, serum total ADP levels were found to be increased in women suffering from chronic daily headaches compared to episodic migraineurs and control subjects. This finding has been considered to support the likely pro-inflammatory role of ADP in the neurogenic inflammatory pathway in migraine chronification. Secondly, the levels of medium and high adiponectin, which are forms of adiponectin, increase, and finally, the area in the body where fat tissue increases is associated with migraine (2). Plasma ADP levels have been found significantly lower in obese subjects than in non-obese ones (13). While the ADP molecule at normal levels has an anti-inflammatory effect, it begins to show pro-inflammatory properties at low levels. According to new hypotheses, obesity leads to a decrease in ADP production and chronic inflammation, which, in turn, causes the inflammatory state to persist in migraine (14).

Irregularities in adipokine levels have been associated with many diseases, such as obesity,

cardiovascular disease, and Type 2 diabetes (15). Population-based studies have shown that obesity plays a major role as a risk factor in the progression of migraine and the transformation from episodic headache to chronic daily headache. Obesity can increase the frequency of headache attacks to ≥15 days per month (8). One study has shown that there is no relationship between migraine and BMI when BMI is <29.71 kg/m^2, but when it is above this value, the risk of migraine increases, regardless of age and gender. In addition, while this positive relationship was more significant when there was concurrent diabetes, the relationship was detected at lower levels in the group without diabetes (16). In our study, although a significant positive relationship was observed between migraine severity and high BMI, no association was detected between attack frequency and BMI. Yu et al. (17) found in the Chinese population that morbid, but not lesser, levels of obesity are related to increased migraine prevalence. However, they did not find any correlations between obesity and the severity, frequency, or disability related to migraine attacks. In a study conducted in Iran, similar to ours, it was observed that headache severity increased with increasing BMI, as did frequency and duration, causing higher disability scores (18).

Bigal et al. (19) did not find a notable difference with respect to the mean decrease in headache frequency following preventive treatment in distinct weight groups. However, the reduction in the number of severe headache attacks was higher in the obese group compared with the normal weight group, suggesting that obese migraineurs may respond better to preventive medication than patients of normal weight. Peterlin et al. (20) reported that migraine and obesity are associated in reproductive ages, but they also reported that it was not correlated with obesity in post-reproductive ages. On the other hand, it is thought that some preventive medications may modulate adiponectin levels more significantly in overweight patients, causing higher continuous levels. Topiramate, which is used in epilepsy and migraine prophylactic treatment, is one such preventive drug and causes weight reduction as an adverse effect (1). In a study by Schütt et al. (21), it was reported that topiramate increased adiponectin concentrations and reduced body mass index in patients with migraine after 20 weeks of treatment.

In our study, we found a negative correlation between BMI and ADP levels; however, this correlation was not statistically significant. This insignificance is thought to be related to the small sample size, unlike some other studies conducted on chronic migraine patients with high total ADP levels, and the inclusion of only the interictal period of episodic headache migraineurs in the study.

In migraineurs, who are possibly exposed to repeated vascular inflammation, C-reactive protein has been reported as abnormal (8). In the study by Welch et al., it was reported that 43% of all migraine patients have elevated hs-CRP. This elevation was found to be more prominent in migraineurs without aura, and in those with atypical, severe, or complex features presenting as aura (22). Vanmolkot and de Hoon (23) showed CRP elevation in patients with migraine without aura. In our study, in accordance with the Reykjavik study (8), no statistical significance was found between migraineurs and non-migraineurs in respect to CRP levels. However, if we had performed the study during migraine attacks, when neuroinflammation is evident, we might have found differences between the groups.

Several studies have researched the relationship between ADP levels and pro-inflammatory markers in different populations. Plasma CRP levels were found to be inversely correlated with plasma ADP levels in men. In another study, ADP levels in plasma and adipose tissue were shown to be inversely correlated with CRP levels in healthy overweight women. CRP levels were reported to be positively related to BMI, suggesting that CRP is a useful biomarker for obesity-related chronic inflammatory conditions (13). In line with this, we also found a positive and statistically significant correlation between BMI and plasma CRP levels in our study. Finding a positive association between the severity of migraine attacks and BMI also led us to consider the presence of an inflammatory relationship, with CRP as one of the potential

mediators between obesity and migraine. No association could be established between ADP and CRP levels in migraineurs and controls.

Further and larger studies are needed to understand the impact of ADP levels in migraine, so its role in migraine pathophysiology can be clarified. In conclusion, our study suggests that a reduction in body weight may lead to at least a reduction in the severity of migraine attacks and the daily life functional disability related to severe headache attacks. Individual therapeutic approaches related to body mass index may be an effective treatment method, at least to reduce the severity of migraine attacks.

REFERENCES

1. Peterlin BL, Bigal ME, Tepper SJ, Urakaze M, Sheftell FD, Rapoport AM. Migraine and adiponectin: is there a connection? Cephalalgia. 2007;27(5):435-46.

2. Peterlin BL, Alexander G, Tabby D, Reichenberger E. Oligomerization state-dependent elevations of adiponectin in chronic daily headache. Neurology. 2008;70(20):1905-11.

3. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, et al. Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol. 2003;14(6):561-6.

4. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. 1999;257(1):79-83.

5. Qi Y, Takahashi N, Hileman SM, et al. Adiponectin acts in the brain to decrease body weight. Nat Med. 2004;10(5):524-9.

6. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005;115(5):911-20.

7. Gudmundsson LS, Aspelund T, Scher AI, et al. C-reactive protein in migraine sufferers similar to that of non-migraineurs: the Reykjavik Study. Cephalalgia. 2009;29(12):1301-10.

8. Hamed SA. The vascular risk associations with migraine: relation to migraine susceptibility and progression. Atherosclerosis. 2009;205(1):15-22.

9. Bigal ME, Lipton RB, Holland PR, et al. Obesity, migraine, and chronic migraine: possible mechanisms of interaction. Neurology. 2007;68(21):1851-61.

10. Olesen J. International Classification of Headache Disorders. Lancet Neurol. 2018;17(5):396-7.

11. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs. 1988;14(1):9-17.

12. Joshi SS, Nemichandra SC, Harsha S, et al. Assessment of Alteration of Serum Adiponectin Levels in Migraineurs: An Interventional Case Control Study. Ann Neurosci. 2020;27(3-4):148-52.

13. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clin Chim Acta. 2007;380(1-2):24-30.

14. Eidlitz Markus T, Toldo I. Obesity and Migraine in Childhood. Curr Pain Headache Rep. 2018;22(6):42.

15. Abbasi M, Noori-Zadeh A, Seidkhani-Nahal A, et al. Leptin, adiponectin, and resistin blood adipokine levels in migraineurs: Systematic reviews and meta-analyses. Cephalalgia. 2019;39(8):1010-21.

16. Tian S, Cheng Z, Zheng H, et al. Interaction between diabetes and body mass index on severe headache or migraine in adults: a cross-sectional study. BMC Geriatr. 2024;24(1):76.

17. Yu S, Liu R, Yang X, et al. Body mass index and migraine: a survey of the Chinese adult population. J Headache Pain. 2012;13(7):531-6.

18. Togha M, Haghdoost F, Khorsha F, et al. Body Mass Index and its Association with Migraine Characteristics in Female Patients. Arch Iran Med. 2019;22(10):554-9.

19. Bigal ME, Gironda M, Tepper SJ, et al. Headache prevention outcome and body mass index. Cephalalgia. 2006;26(4):445-50.

20. Peterlin BL, Rosso AL, Rapoport AM, Scher AI. Obesity and migraine: the effect of age, gender and adipose tissue distribution. Headache. 2010;50(1):52-62.

21. Schütt M, Brinkhoff J, Drenckhan M, et al. Weight reducing and metabolic effects of topiramate in patients with migraine an observational study. Exp Clin Endocrinol Diabetes. 2010;118(7):449-52.

22. Welch KM, Brandes AW, Salerno L, et al. C-reactive protein may be increased in migraine patients who present with complex clinical features. Headache. 2006;46(2):197-9.

23. Vanmolkot FH, de Hoon JN. Increased C-reactive protein in young adult patients with migraine. Cephalalgia. 2007;27(7):843-6.