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Effect of Obesity and Leptin Level on Migraineurs

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Background: The aim of this study was to analyze the effects of obesity and leptin levels on patients with migraine, and to observe the change of leptin levels in migraineurs.

Material/Methods: We enrolled 52 migraine patients from the Headache Clinic in Shandong Provincial Hospital into a randomized controlled trial with another 52 age-, sex-, and BMI-matched healthy subjects as controls. Leptin levels in all subjects were determined by radioimmunoassay.

Results: Compared with the control group, the migraineurs revealed no significant change in leptin levels ($P>0.05$). Multivariate Logistic regression analysis showed that neither abdominal obesity nor leptin had significant impact on migraine clinical features. Total body obesity had a significant effect on the frequency ($OR=4.248$), duration ($OR=3.167$), and intensity ($OR=5.225$) of the headache.

Conclusions: Total body obesity affected headache frequency, intensity, and duration, while leptin levels did not.

MeSH Keywords: Leptin • Migraine Disorders • Obesity, Abdominal

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Background

According to the newly released version of the Global Burden of Disease study of 2010, migraine is responsible for almost 3% of disability attributable to a specific disease worldwide. Indeed, it is considered the most disabling neurological disorder, and the eighth most burdensome disease. Migraine and obesity are two common health problems in today's world [1,2]. Recent studies suggest an association between obesity and mortality. Obesity can be linked to higher risk of mortality, and it affects the frequency of migraine severity and crippling headache attacks, but the mechanism underlying the relationship between obesity and mortality remains unclear. Leptin is secreted chiefly by lipocytes to control trophic behavior, and a study found decreased leptin levels in migraineurs [3–5]. The aim of this study was to detect changes of leptin levels in migraineurs, and to analyze the effects of obesity and leptin level on migraine.

Material and Methods

Subjects

The procedures followed were approved by the Ethics Committee of Shandong Provincial Hospital. Written informed consents were obtained from all subjects before the study. Fifty-two patients who visited the Headache Clinic in Shandong Provincial Hospital from October 2012 to March 2013 were enrolled into the migraine group, including 35 females (67.3%) and 17 males (32.7%). The 52 patients, aged 18–55 years, had been diagnosed with migraine according to the International Classification of Headache Disorders (the International Classification of Headache Disorders 2nd Edition, ICHD-II), which is the latest diagnostic code of migraine; they had at least 1 headache attack per month for at least half a year, revealing no complications demonstrated by cranial computer tomography or magnetic resonance imaging. Patients with the following conditions were excluded: (1) primary headache of other types; (2) Secondary headache caused by craniocerebral trauma, space-occupying lesion, or other diseases; (3) Pregnant and lactating woman; (4) Rheumatic disease.

Based on BMI, 23 migraineurs were assigned to the total body obesity (TBO) subgroup, including 15 females (65.8%) and 8 males (34.2%). The remaining 29 patients were assigned to the non-TBO subgroup, including 20 females (69.0%) and 9 males (31.0%). There was no significant difference in sex between these 2 subgroups (χ^2=0.082, *P*=0.775). Based on waist circumference, these 52 migraineurs were divided into an abdominal obesity (ABd-O) subgroup, including 20 females (64.5%) and 11 males (35.5%), and a non-ABd-O subgroup, including 15 females (71.4%) and 6 males (28.6%); there was no significant difference in sex distribution between these 2 subgroups (χ^2=0.272, *P*=0.602).

Another 52 healthy people matched by sex, age, and BMI to the migraineur group from Shandong Provincial Hospital-Health Physical Examination Center were enrolled into the control group (healthy people: migraineurs=1:1).

All the subjects had been informed of the purpose and significance of sampling, and a venous blood sample of 3~5 ml was obtained with permission from 6:00 to 8:00 a.m.

Indices

1. BMI: BMI=weight(kg)/height(m^2). The classification of obesity by BMI was based on the latest WHO requirements of the Asia Pacific population health guidance [6]: BMI in TBO group ≥25 kg/m^2; BMI in no-TBO group <25 kg/m^2.
2. Waist index: waist circumference in ABd-O group: male >85 cm, female >80 cm [7].
3. Leptin determination: Radioimmunoassay was used in the determination of leptin. Leptin Kit (C-Leptin Kit) was provided by Beijing North Biotechnology Institute. Both intra-assay variation and inter-assay variation were less than 10%.
4. Headache index: with the patients' age, sex, and weight all taken into account, all 52 patients in the case group qualified as migraineurs in this study. Detailed [8] clinical features included the headache site, frequency, severity, duration, and characteristics. The Visual Analogue Scale (VAS) was adopted to assess headache severity, which gives scores ranging from 0 to 10. The frequency of headache was counted as migraine headache attacks within 1 month. The headache duration was counted in hours.

Statistical analysis

SPSS 19.0 was employed to analyze the research data. The unpaired t test was applied to normally distributed data, rank-sum tests were used for abnormally distributed data, and the χ^2 test was used for categorical variables. In addition, multiple logistic regression was used to evaluate the predictors or associated factors for migraine.

Results

Leptin levels of the migraine group and the control group

Leptin levels were 4.98±1.80 (range: 2.07–10.98) μg/L in the migraine group, and 4.91±1.64 (range: 1.97–8.99) μg/L in the control group, showing no significant difference (*P*>0.05).

The effects of TBO on the migraineurs

There was no significant difference between the TBO subgroup and non-TBO subgroup with regard to age (P=0.159), duration

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Table 1. The general information of TBO group and non-TBO group ($\bar{\chi}\pm s$).

Index	TBO group (n=23)		Non-TBO group (n=29)		*t*	*P*
Age (years)	41.73±6.02	(31–52)	38.11±11.28	(18–54)	1.434	0.159
Duration (years)	11.78±9.63	(1–40.64)	9.63±9.61	(0.08–40)	0.741	0.462
Leptin level (μg/L)	5.43±2.07	(3.07–9.57)	4.59±1.45	(2.07–10.98)	1.708	0.094
BMI (kg/m^2)	28.42±1.814	(25.39–32.60)	22.07±2.484	(22.07–24.84)	9.008	<0.001

Figures in brackets show the data range.

Table 2. The difference of headache indices between TBO group and non-TBO group ($\bar{\chi}\pm s$).

Index	TBO group (n=23)		Non-TBO group (n=29)		Statistics	*P*
Headache frequency (times/month)	18.77±9.07	(5–30)	12.00±8.17	(2–30)	*Z*=2.489	0.013*
Duration (hours)	26.34±25.14	(0.5–72)	13.27±19.53	(0.3–72)	*t*=2.049	0.046*
Severity of headache (VAS)	7.05±1.80	(3–10)	5.84±2.19	(1–10)	*t*=2.091	0.042*

Figures in brackets show the data range.

Table 3. General information of Abd-O group and non-Abd-O group ($\bar{\chi}\pm s$).

Index	Abd-O group (n=31)		Non-Abd-O group (n=21)		*t*	*P*
Age (years)	41.96±8.12	(25–54)	37.00±10.26	(18–53)	1.89	0.065
Duration (years)	12.61±11.89	(0.08–40.64)	7.83±7.14	(0.08–23)	1.577	0.122
Leptin level (μg/L)	5.35±2.01	(2.5–10.98)	4.42±1.28	(2.07–6.59)	2.043	0.046*
Waist index (cm)	88.37±6.27	(80.3–106.7)	75.28±5.27	(63.5–84.6)	7.865	0.000

(P=0.462), and leptin level (P=0.094), as shown in Table 1. But there was a significant increase in the headache frequency (P=0.013), severity (P=0.008), and duration (P=0.046) in the patients of the TBO group (Table 2).

The effects of ABd-O on the migraineurs

The ABd-O and non-Abd-O subgroups were comparable in terms of patient age (P=0.065) and headache duration (P=0.122), as shown in Table 3, while leptin levels were significantly higher in the ABd-O subgroup (5.35±2.01) than in the non-Abd-O subgroup (4.42±1.28) (P= 0.046) (Table 3).

There was also a significant increase in headache frequency (P=0.027), severity (P=0.041), and duration (P=0.033) in patients of the ABd-O subgroup in comparison with the non-ABd-O group (Table 4).

The effects of BMI and leptin level on migraineurs

Although the difference of leptin levels between the migraine group and the control group was not significant (*P*>0.05), obese subjects showed an increase in leptin level (Tables 1, 3), so other indices of obesity should be considered to analyze the effects of the leptin levels on migraineurs.

Multiple logistic regression analyses were performed to analyze the effects of BMI, waist index, and leptin and other indices on the migraineurs. Leptin levels and ABd-O caused no significant difference in the headache frequency, duration, or severity between groups, which were sex- and age-adjusted (*P*>0.05). The headache frequency (≥21 attacks per month) (*OR*=4.248), duration (≥24 hour) (*OR*=3.167), and severity (8 to 10 points on VAS) (*OR*=5.225) in the TBO subgroup were 4.248, 3.167, and 5.225 times higher, respectively, than those in the non-TBO subgroup, indicating a close correlation between TBO and headache frequency, duration, and severity (Table 5).

Discussion

In recent years, a many studies have been conducted on obesity and migraines around the world, but it remains unclear whether leptin, as a kind of cell factor closely related to obesity,

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Table 4. Difference of headache indices between Abd-O group and non-Abd-O group ($\bar{\chi}\pm s$).

Index	Abd-O group (n=31)		Non-Abd-O group (n=21)		Statistics	*P*
Headache frequency (times/month)	17.77±9.17	(2–30)	11.68±8.14	(2–30)	*Z*=2.205	0.027*
Duration (hours)	21.57±21.85	(0.5–72)	16.15±24.39	(0.3–72)	*t*=0.812	0.041*
Severity of headache (VAS)	7.10±1.89	(2–10)	5.76±2.28	(1–10)	*t*=2.219	0.033*

Table 5. Effects of obesity indices on migraineurs.

	Obesity index	β	SE	Wald	*P*	*OR*	95% CI for *OR*	
							Lower	Upper
Headache frequency	TBO	1.446	0.712	4.121	0.042	4.248	1.051	17.163
	ABd-O	/	/	/	0.232	/	/	/
	Leptin level	/	/	/	0.812	/	/	/
Duration	TBO	1.153	0.592	3.793	0.051	3.167	0.993	10.101
	ABd-O	/	/	/	0.329	/	/	/
	Leptin level	/	/	/	0.959	/	/	/
Severity of headache (VAS)	TBO	1.653	0.833	3.942	0.047	5.225	1.021	26.728
	ABd-O	/	/	/	0.271	/	/	/
	Leptin level	/	/	/	0.959	/	/	/

is involved in the linkage between obesity and migraine [9]. This study suggested that there were signs of growing leptin levels in patients in the obesity group; the leptin level could be influenced by several factors, including sex, age, androgen, the location of adipose tissue, and the fat mass; androgens can improve the secretion of leptin and testosterones can inhibit it. Increased leptin levels in obese patients could be attributed to leptin resistance, decline in the function of leptin, or the sensitivity of leptin receptors [8].

Diagnosis of obesity is now mainly based on BMI value. But as people become increasingly aware of the effects of ABd-O on their health, it has been indicated that BMI could not entirely replace WC in the diagnosis of obesity since BMI does not reflect sex-related differences [10]. Many studies suggest that, compared with TBO, ABd-O can better forecast some cardiovascular and cerebrovascular diseases and diabetes, which are closely related to obesity [11]. Moreover, TBO people are generally ABd-O, but only a fraction of ABd-O people are TBO. This study found that the effect of ABd-o on migraines disappeared after people got rid of TBO. Similar to previous research, this study found that obesity was positively associated with headache frequency, severity, and duration. Some studies on the link between BMI and migraine frequency proposed the theory of a J-shaped risk curve, which suggests that when BMI ≤18.5kg/m^2 or ≥35 kg/m^2, there will be increased risk of high migraine frequency [12,13]. However, Mattsson et al. [14] did not find any effects of obesity on headache frequency, severity, or duration. A recent Chinese study supported the results of Mattsson et al. [7].

The mechanism for the correlation between obesity and migraine is very complex, and may be related to hypothalamic dysfunction, thrombocytin and feeding orexin, inflammation mediators, and adiponectin [15,16].

The mediators of inflammation involve the transcriptional factor-α (tumor necrosis factor-α, TNF-α), interleukin and calcitonin gene-related peptide (calcitonin gene-related peptide, CGRP) [17], which are related to obesity and can make the central nervous system sensitive; central sensitization can cause permanent damage to the periaqueductal gray, and its reduced ability to modulate pain [18]. Furthermore, constant mild inflammation resulting from obesity can trigger migraine-related inflammatory reactions, as well as increased headache frequency and severity [15].

It was Guldiken et al. [3] who found that, compared with age- and sex-matched healthy people, migraineurs showed significantly lower leptin levels, but with fat mass adjusted, the

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significant difference disappeared; our study came up with similar results. Leptin can regulate the immunoreaction and inflammatory reaction [19], and induce the syntheses of NO, arachidonic acids, interleukin-6 and TNF-α [20,21]. Leptin levels rose sharply in the circulatory response model of acute inflammation; leptin levels were increased in the patients with acute infection, septicemia, and rheumatoid arthritis; but 24 h of stimulation by proinflammatory mediators brought reduced leptin, which was synthesized by human fat cells [22]. Moreover, in another study, mice showed increased sensitivity when they received peritoneal injection of leptin [23], which indicated that leptin could cause pain [24].

This study suggests that leptin had no obvious impact on the index of migraine. Similarly, a previous study on the efficacy of topiramate on migraineurs found that the medicine could bring about weight loss for the patients, but prior-treatment and post-treatment revealed no significant difference in leptin levels, thus indicating that leptin did not take part in the inflammatory mechanism of migraine.

Conclusions

Obesity, especially TBO, can affect the frequency, duration, and severity of migraine, and our study suggests that people with both obesity and migraine should properly control their weight. There was no significant difference in leptin levels in the migraineurs, which indicates that leptin does not affect migraine; it revealed no link to the effects of obesity on the migraineurs. Even with a control group matched by age, sex, and BMI, this study still faced challenges, such as the changes in sex hormone sand the fluctuation of the menstrual cycle could not be scheduled for. Therefore, the function and significance of change of leptin levels in migraineurs need to be studied further. In addition, the sample size might not be sufficient to detect the relationship between obesity and leptin level on susceptibility of the migraineurs, especially when stratifying the sample by sex, because clinical features of migraine, measured by visual analogue scale, could be influenced by the patient's subjective state. Most importantly, this was only an observation study with limited evidence, and no functional study has been performed yet to explain the underlying mechanism.

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