Progress in Nutrition 2020; Vol. 22, N. 3: e2020010 DOI: 10.23751/pn.v22i3.8332

Original article

Serum Orexin-A, Oestrogen, Leptin, RBP-4 Levels, body composition and cardiovascular risk parameters in migraine

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Summary. *Objective:* Tension-type headache and migraine are common health disorders recently associated with increased risk of obesity and chronic diseases. In the present study, comparison of anthropometric measurements, body composition, and cardiovascular parameters as well as serum orexin-A, oestrogen, leptin and retinol binding protein-4 levels as whether being a potential clinical markers in females with migraine and tension-type headache (TTH) with healthy controls was aimed. *Methods:* This case-control study conducted on female individuals with migraine without aura (n:30), TTH (n:29) and a control group (n:27) in Ankara between 2016-2017. Anthropometric measurements and body compositions were taken and blood pressures, serum glucose, insulin, lipid profile, orexin-A, leptin, oestrogen, retinol binding protein-4 and Homeostatic Model Assessment-Insulin Resistance levels were measured. The participants in the migraine group were asked about frequency of attacks, attack duration and pain severity. *Results:* In the migraine group, higher serum cholesterol levels than the tension-type headache group and higher systolic and diastolic blood pressure levels than the control group were observed. A significant increase in attack duration was related with the increased blood pressures in migraine patients. There was no difference found between the groups in terms of anthropometric measurements, serum orexin-A, oestrogen, leptin and retinol binding protein-4 levels. *Conclusion:* Monitoring the migraine patients for cardiovascular risk is essential. Further studies should be conducted to evaluate differences between headache groups in terms of peptide levels.

Key words: migraine, tension-type headache, cardiovascular risk, orexin-A, retinol binding protein-4

Introduction

According to the World Health Organization (WHO), headache is the most common nervous system disease and was reported in a majority of adults (18 to 65 years of age, about 50% to 75%) worldwide during recent years. Tension-type headache (TTH) is the most common type (1). Migraine is a chronic neurovascular disease progressing with episodic attacks and is observed four times more often in females than males (2). Although, pathophysiology of migraine is not clear, findings such as specific neurovascular dysfunction, endothelial dysfunction, hypercoagulability and pathological vascular reactivity are considered possible associations between migraine and cardiovascular risk parameters (2,3) A meta-analysis concluded that ischemic strokes increase twofold in migraine sufferers, and females who receive oral contraceptive drugs have a higher risk (3). Furthermore, it is known that risk for obesity, hypertension, diabetes and hyperlipidemia increases in individuals with migraine, especially migraine with aura (2).

When pathogenesis of migraine and obesity is reviewed, both disorders may be related to orexigenic and anorexigenic peptides associated with appetite metabolism and released from the hypothalamus.

Regulation of release of hypothalamic peptides and proteins may trigger the headache or contribute to the formation of migraine (4). Although the outcomes of the studies investigating the association between TTH and obesity are contradictory (5,6). There are a limited number of studies analysing the levels of certain peptides, such as orexin-A (OXA), leptin and retinol binding protein-4 (RPB-4), in migraine and TTH. Therefore, this study focused on comparison of anthropometric measurements, body composition and cardiovascular risk parameters as well as OXA, leptin and RBP-4 levels whether being a potential clinical markers in migraine patients with those in the TTH and control groups. Furthermore, it aims to evaluate the possible relation between homeostasis model assessment for insulin resistance (HOMA-IR), plasma OXA, oestradiol, leptin, RBP-4 levels and blood pressures and attack frequency, duration and severity in migraine patients.

Methods

General Plan of the Study

Patients who had migraine without aura (n:30) and patients with TTH (n:29) between 20 and 55 years of age who were diagnosed according to the International Classification of Headache Disorders, 3rd edition beta version (ICHD-3) at the Headache Research and Implementation Centre of the Neurology Clinic, Gazi University, Ankara between 2016-2017 were enrolled in the present case-control study. Age-matched healthy adults who were selected by a specialist physician's examination were taken as a control group (n:27). Females on their menstrual period, using antihypertensive, hypoglycaemic or oral contraceptive agents, receiving hormone replacement treatment, pregnant and breastfeeding females and pre and post menopausal females were excluded. Also, patients did not enrolled to the study as the time that they have a seizure.

The patients were followed up using a form used at the Headache Research and Implementation Centre. After the individuals to be enrolled were identified, the study data were collected by the researchers using a questionnaire form. The pain severity score was calculated using the Visual Analogue Scale (VAS), with individuals evaluating the severity of their pain.
Ethics committee approval was obtained from the Clinical Research Ethics Committee at Gazi University (number: 25901600/2448). The study was according to principles of Helsinki Declaration.

Anthropometric Measurements and Evaluation of Body Composition

Body weight (kg), height (cm) and waist and hip circumference measurements of all individuals were taken by well-trained researchers according to the appropriate technique and body composition (fat mass, fat-free mass, total body water, intracellular and extracellular body water) was analysed using a bioelectrical impedance analysis device (InBody 720). Body mass index (BMI) was calculated using the formula body weight / height^2 (kg/m^2) and waist/hip ratio was calculated from waist and hip circumference measurements. Basal metabolic rate was calculated by Harris Benedict formula.

Biochemical Measurements and Blood Pressure

Blood samples were collected from all participants after a fasting period of at least 12 hours, centrifuged according to the kit procedure and stored at -32˚C until analysis. Fasting serum glucose and lipid profile (total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol and VLDL cholesterol) were analysed in the biochemistry laboratory at the Gazi University Faculty of Medicine. Fasting plasma insulin, OXA, leptin, oestradiol and RBP-4 analyses were performed using the enzyme-linked immunosorbent assay (ELISA) method. Fasting serum blood glucose and insulin values were utilised to calculate insulin resistance using the formula fasting blood glucose (mg/dL) x fasting insulin (μU/mL)/405, known as HOMA-IR (7)
Blood pressure was measured for each individual according to the appropriate method and patient group, during the pain-free period.

Statistical Analysis

The quantitative data obtained from the participants were evaluated in count (N) and percentage (%) values; statistical significance was evaluated using the chi-square test by Statistical Package for Social Studies version 21 (SPSS 21) (8). For qualitative data, median

values and an interquartile range (IQR) were obtained and the differences between groups were evaluated using the Kruskal-Wallis test. Analysis of the differences between the two groups were conducted using the Mann-Whitney U test. Relationships between biochemical parameters and attack frequency, pain duration and severity of pain were analysed using Spearman's correlation test. The statistical significance level was given within a confidence interval of 95%.

Results

General information about the participants is presented in Table 1. Smoking statuses of the individuals were not statistically significant in three groups (p=0.987). Attack severity for participants in the migraine group was found to be higher than for those in the TTH group (p=0.000).

Anthropometric measurements and body composition data of the participants are shown in Table 2. Although, body weight, waist circumference and fat mass of the migraine patients were not statistically significant, these values were higher than in the TTH and control groups (p values respectively; p=0.262, p=0.136 and p=0.263).

Biochemical findings and blood pressures of the participants are given in Table 3. Total serum cholesterol levels of the migraine patients were higher than those of the TTH group (p=0.030). Furthermore, systolic blood pressure (SBP) values of the individuals in the migraine group were higher than those of the con-

Table 1. General characteristics of participants.

Characteristics	Migraine (n:30)	TTH (n:29)	Control (n:27)	Chi square/KW	p
Age (years)[1]	36.0±13.00	32.0±19.00	29.0±19.00	0.640	0.726
Smoking[2]					
Yes	4 (13.3%)	4 (13.8%)	4 (14.8%)	0.027	0.987
No	26 (86.7%)	25 (86.2%)	23 (85.2%)		
Attack severity (VAS score)[1]	8.0±1.75	5.0±2.50	-	14.717	0.000
Attack frequency (mo)[1]	2.5±3.00	-	-	-	-
Attack duration (h)[1]	12.0±18.75	-	-	-	-

TTH: Tension-type headache; KW: Kruskal Wallis test; mo: month; h: hour
[1]Kruskal Wallis test (median±IQR), [2] Chi-square test

Table 2. Anthropometric measurements and body composition of individuals.

Measurements	Migraine (n:30)	TTH (n:29)	Control (n:27)	KW	p
	Median±IQR	Median±IQR	Median±IQR		
Height (cm)	162.0±11.00	162.0±7.00	164.0±9.50	1.055	0.590
Body weight (kg)	63.0±29.85	58.9±13.40	56.1±15.05	2.679	0.262
Body mass index (kg/m^2)	24.0±8.14	22.5±2.56	21.6±7.13	2.342	0.310
Waist circumference (cm)	85.0±22.00	80.0±7.00	73.0±10.00	3.995	0.136
Hip circumference (cm)	95.0±25.00	99.0±11.00	95.0±13.00	0.970	0.616
Waist/hip	0.82±0.11	0.80±0.07	0.75±0.10	2.879	0.237
Body fat percentage (%)	33.3±10.35	33.0±4.90	31.8±15.20	2.789	0.248
Body fat mass (kg)	21.3±15.55	19.6±6.30	17.8±13.25	2.672	0.263
Fat free mass (kg)	39.4±14.25	43.2±5.50	38.7±6.30	1.068	0.586
Total body water (%)	28.9±10.50	31.7±4.00	28.4±4.60	0.958	0.620
Extracellular body water (%)	11.1±4.30	12.0±1.30	10.8±1.70	1.095	0.578
Intracellular body water (%)	17.8±6.20	19.5±2.70	17.6±2.85	0.915	0.633
Basal metabolic rate (kcal)	1221.0±308.50	1302.0±119.00	1205.0±136.50	1.139	0.566

TTH: Tension-type headache, KW: Kruskal Wallis test

Table 3. Biochemical findings and blood pressure of individuals.

	Migraine (n:30)	TTH (n:29)	Control (n:27)	KW	p
	Median±IQR	Median±IQR	Median±IQR		
Fasting glucose (mg/dL)	74.2±11.75	78.4±5.90	81.0±12.15	1.085	0.581
Total cholesterol (mg/dL)*	184.6±64.50[a]	165.0±49.10[b]	176.2±53.25[a,b]	7.045	0.030
HDL-C (mg/dL)	57.0±27.00	63.9±12.00	56.0±14.65	0.236	0.889
LDL-C (mg/dL)	121.0±52.65	98.0±31.40	96.6±41.80	5.941	0.051
VLDL-C (mg/dL)	14.8±16.50	12.4±7.92	13.2±5.74	0.535	0.765
Triglyceride (mg/dL)	74.4±82.50	65.0±76.50	66.0±28.70	1.080	0.583
Insulin (mIU/mL)	7.2±5.20	6.1±4.50	6.5±3.80	1.381	0.501
HOMA-IR	1.1±0.93	1.1±0.75	1.1±0.80	1.552	0.460
Orexin-A (ng/mL)	0.2±0.44	0.1±0.81	0.1±1.36	0.015	0.992
Estradiol (pg/mL)	108.0±135.50	65.0±142.00	116.0±116.50	1.091	0.580
Leptin (ng/mL)	6.7±8.32	11.1±4.96	5.4±10.95	2.314	0.314
RBP-4 (µg/mL)	36.0±13.50	37.0±24.00	35.0±11.50	0.789	0.671
SBP (mmHg)*	100.0±20.00[a]	90.0±10.0[a,b]	90.0±7.50[b]	6.312	0.043
DBP (mmHg)*	70.0±13.00[a]	60.0±0.00[b]	60.0±0.00[b]	8.734	0.013

KW: Kruskal Wallis test, *Mann- Whitney U test (for comparisons between two groups), Statistically significant values has marked with different letters [a] or [b]. TTH: Tension-type headache, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, VLDL-C: Very low density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment of insülin resistance, RBP-4: Retinol binding protein 4, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

trol group (p=0.043), whereas diastolic blood pressure (DBP) values were higher than both the TTH group and the control group (p=0.013). There was no statistically significant difference between the three groups in terms of other biochemical parameters (Table 3).

The association between HOMA-IR levels, plasma OXA, oestrogen, leptin, RBP-4 levels, blood pressures and attack frequency, severity and duration of migraine patients are shown in Table 4. A positive significant correlation was detected between blood pressures and attack duration (p=0.011 for systolic blood pressure and p=0.038 for diastolic blood pressure). However, there were no statistically significant relationships between HOMA-IR levels, biochemical parameters and attack frequency, duration and severity.

Discussion

Today, along with the increase in incidence of migraine and other headache types (9) studies of the factors associated with pathophysiology and treatment have increased (6,10-12). The most common headache type investigated is the migraine; however, studies conducted on TTHs are limited. The present study compared female migraine and TTH patients with the control group in terms of obesity, cardiovascular risk parameters, insulin resistance and peptides, which may be considered related to headache.

Outcomes of cross-sectional or large community-based studies in which obesity states of individuals exposed to migraine and other headache types were evaluated depending on anthropometric measurements are contradictory (5,13-16). A study conducted on 3722 females diagnosed with migraine reported that obese females have a 1.48 times higher risk of migraine compared with females with normal BMI (13). It was concluded in another study of 53 females with migraine and 36 healthy individuals including 25 females that there was no difference in BMI between the groups; however, duration of migraine attacks was similarly associated with BMI (14). However, in the study by Bigal et al. in which 30.215 individuals were monitored, no association was found between migraine incidence and obesity (16), and obesity was not a risk factor in the group including 2051 individuals with episodic

Table 4. Relationships between HOMA-IR, plasma orexin-A, estrodiol, leptin, RBP-4 levels, blood pressures with attack frequency, duration and severity of migraine patients**.**

	Attack frequency	Attack duration	Attack severity
HOMA-IR			
r	0.016	-0.318	0.039
p	0.935	0.099	0.773
Orexin-A (ng/mL)			
r	0.205	0.304	0.026
p	0.626	0.464	0.915
Estradiol (pg/mL)			
r	-0.006	0.094	0.041
p	0.974	0.634	0.755
Leptin (ng/mL)			
r	0.106	0.167	-0.140
p	0.590	0.395	0.289
RBP-4 (µg/mL)			
r	0.129	-0.288	0.202
P	0.513	0.137	0.125
SBP (mmHg)			
r	0.106	0.472	0.033
p	0.590	0.011	0.803
DBP (mmHg)			
r	0.164	0.394	0.070
p	0.404	0.038	0.598

Spearman correlation test, HOMA-IR: Homeostasis model assessment of insulin resistance, RBP-4: Retinol binding protein 4, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

xTTH (5). A prospective cohort study by Winter et al. that followed overweight or non-obese females for 12.9 years and evaluated their body weight changes and migraine states concluded migraine is not a factor affecting overweight or obesity (15). Similarly, in the present study, body weights and BMI values of the individuals in the migraine, TTH and control groups were evaluated and there was no statistically significant difference between the groups (Table 2).

Since Winter et al., suggested that the data associating the attack number and migraine type with BMI is insufficient (17) and there are conflicting results for association between BMI and migraine, some studies focused on measurement of waist circumference, which is an indicator of obesity (4,18). Peterlin et. al. (4) reported that migraine prevalence increased in line with BMI and abdominal obesity. Another study evaluating abdominal obesity demonstrated that daily migraine attack is higher with higher BMI, but not associated with abdominal obesity (18). In the present study, waist circumference of all individuals was found to be similar (Table 2).

It is known that subcutaneous fat tissue increases in obesity and that levels of leptin and adiponectin in female individuals diagnosed with migraine also increase; such increases cause disruption in insulin sensitivity and contribute to migraine formation by affecting the inflammatory response (19). Jahromi et al. investigated the association between body composition (fat mass, lean body mass and lean truncal mass) and risk of migraine on 1510 middle-aged females and emphasised that lower lean body tissue increases the risk of migraine in overweight and obese individuals and higher fat tissue may be a protecting factor against migraine (20). However, there was no difference between body fat mass and lean tissue mass of all individuals in the present study (Table 2).

Alterations in biochemical parameters may be detected in headache, especially in migraine. There are data showing possible association between migraine and hypertension, dyslipidaemia and insulin resistance in the literature (3,19,21). According to the results of a meta-analysis conducted by Schürks et al. (3), risk of ischemic stroke increases twofold in patients with migraine with aura, and such risk increased more in females under age 45 years who use oral contraceptive agents. In the present study, total serum cholesterol levels were found to be higher in the migraine group than the TTH group ($p<0.05$). Furthermore, systolic blood pressure is higher in the migraine group than in the control group, whereas diastolic blood pressure is higher in the migraine group than in the TTH and control groups ($p<0.05$) (Table 3). In addition, increased attack numbers were obtained by observing an increase in systolic and diastolic blood pressure in the migraine group (Table 4). Although, there is no statistically significant difference found for other cardiovascular risk parameters, LDL-C and triglyceride levels were detected with a tendency to increase in the migraine group (Table 3). In a large cohort study, a requirement of monitoring the risk of hypertension in patients with migraine was reported Deaths due to car-

diovascular diseases increased in female patients with migraine after a follow-up period of 20 years in study (21). High blood pressure and total serum cholesterol level are the important risk factors for the cardiovascular disease and the increased age, body weight and BMI can adversely affect the blood pressure and total cholesterol (2,21). However, in our study the median BMI of all groups were in the normal range and the groups were similar in terms of age and BMI. Therefore, the patients with migraine should be followed for cardiovascular risk independent of age and BMI (10). In terms of TTH, no association was shown between TTH and hypertension (19). Since, similar data to that found in the literature was obtained in the present study, migraine without aura was found to be associated with increased risk for hypertension and cardiovascular disease.

There was no difference for migraine incidence between genders during childhood; however, the difference increases twofold in girls over boys after puberty and remains higher in females at reproductive age than in males (22). In the present study, serum oestrogen levels were found to be lower in the migraine and TTH groups; however, no statistical difference was detected between these groups compared with the controls (Table 3). In a review it is emphasised that the effect of oestrogen is higher in females than males for risk of migraine; and it is also reported that higher oestrogen levels are protective against migraine attacks and such attacks are mostly affected by fluctuations of oestrogen (23). Detection of no difference in oestrogen levels in the present study may be caused by enrolment of female individuals with migraine without aura during the non-menstrual period.

Leptin is one of the adipokines circulating in proportion with body fat mass and is found in many tissues, including the brain. Although, both increased and decreased leptin levels were observed in migraine patients, (24,25) in this study we did not find any difference between the groups in terms of serum leptin levels (Table 3). It is reported that migraine patients do not differ from the control group in terms of BMI; however, body fat mass is lower in patients with migraine (25). Bernecker et al. (24) showed higher leptin levels in 40 non-obese females when compared with the control group. Peterlin et al. (26) reported that leptin levels decreased in migraine patients and no significant difference was detected in leptin levels of migraine patients compared with the control group in four different studies. However, leptin is a peptide which is generally secreted from adipose tissue; therefore, some differences appeared in serum leptin levels between the groups after corrections were made according to body composition (26). It was considered in the present study that similarity of BMI values of all participants removed the factors that may affect serum leptin levels. Therefore, it was concluded that changes in leptin levels in migraine are associated with the presence of obesity.

OXA was another peptide analysed in the present study. Higher levels of OXA were detected in cerebrospinal fluid, especially in chronic migraine and high-dose drug-induced migraine (27). It is considered that OXA has a role in pain, with its vasodilator effect in human and animal studies (28). In a study where circulating OXA levels were analysed, serum samples were obtained from the patients with episodic migraine during attack periods and attack-free periods and compared with the patients with TTH and the control group. At the end of the study, serum OXA levels were shown to be lower in the episodic migraine group than in the other groups, with no change during attacks (11). There was no difference detected for OXA levels between the groups in the present study (Table 3).

It is known that RBP-4, which plays a role in appetite metabolism and energy homoeostasis, is associated with metabolic syndrome, obesity, insulin resistance and increased cardiovascular disease risk (29). The only study where serum RBP-4 levels were analysed in migraine patients considered the association of RBP-4 with inflammation, and 48 patients with migraine as well as 48 individuals in the control group were evaluated together with high sensitivity C-reactive protein. Serum RBP-4 levels were found to be lower in migraine patients, whereas C-reactive protein levels were found to be higher than in the control group (12). There was no significant difference for serum RBP-4 levels between the groups in the present study (Table 3). Since, no association was established between inflammatory indicators with serum RBP-4 analysis, it may be concluded that more studies considering in-

flammation parameters are needed in TTH with migraine patients.

No statistically significant difference for serum fasting glucose, insulin levels and HOMA-IR values between the groups were shown in this study (Table 3). However, insulin resistance is considered to have a role in pathology of migraine according to the studies conducted (30,31) Bhoi et al. (30) reported an association between HOMA-IR levels, which is an indicator for insulin resistance, and migraine duration as well as attack frequency. A case-control study determined that HOMA-IR values significantly increased in chronic migraine only; however, there was no difference between the groups in fasting serum glucose and in second-hour glucose levels using an oral glucose tolerance test (OGTT) (31). Headache types investigated in the other studies are mostly different from the present study and there are no consistent outcomes.

In summary, we didn't find statistically significant difference between groups in terms of serum OXA, oestrogen, leptin and RBP-4 levels. However cardiovascular risk parameters (serum cholesterol and blood pressure) were different between the TTH and control groups. Therefore migraine patients should be assessed for cardiovascular risk.

Conclusions

Consequently, when females with migraine and TTH were compared with the control group in this study, obesity, insulin resistance, serum OXA-A, oestrogen, leptin and RBP-4 levels were shown to be similar between groups. However, significant differences were found for total cholesterol and blood pressure, which are cardiovascular risk parameters, between the TTH and control groups. It was concluded that increased blood pressure was associated with the increase in attack period for migraine. Therefore, it would be useful to monitor the individuals with migraine for cardiovascular risk factors. When results in the literature were reviewed with the data obtained from this study, conflicting outcomes may be attributed to reasons such as the method selected for diagnostic criteria for migraine and TTH, diversity of the headache groups (migraine with aura, migraine without aura, TTH etc.) and sample size. The present study compared the patients diagnosed with migraine without aura and TTH according to the ICD3-beta version. Furthermore, insulin, leptin and RBP-4 hormones, which influence body composition, may be analysed in detail in further studies. Since studies including patients with TTH are scarce in the literature, planning of longitudinal studies with larger sample sizes would be useful.

Limitations

The main limitation of this study is the sample size. Although, it cannot be generalized for all headache patients, present data is valuable as a pilot study in this important disease. Therefore, further studies need to be conducted on a large sample.

Acknowledgement
We would like to thank www.anadiltercume.com for English language editing.

Disclose of Benefit
Authors have no conflict of interests

Funding
This study was supported by TUBITAK (The Scientific and Technological Research Council of Turkey) with project number SBAG-114S928.

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