Original Research

The Association Between Migraine, Metabolic Syndrome, Insulin Resistance, and Obesity in Women: A Case-Control Study

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Abstract

Objectives: The aim of this study was to examine the relationship between migraines and obesity, insulin resistance (IR), and metabolic syndrome in female migraineurs.

Methods: A total of 141 female patients who experience migraines and a control group of 141 sex- and age-matched individuals who do not were enrolled in this case-control study. The migraine group was composed of patients from the Gebze Fatih Community Hospital (Kocaeli, Turkey) neurology outpatient service and the control group included hospital staff and friends who volunteered to participate. Descriptive statistics and multivariate logistic regression analyses were performed. Migraine was designated as a dependent variable. Family history of migraine, stroke, metabolic syndrome, cardiac disease, hypertension, hyperlipidemia, and diabetes mellitus; cigarette use; alcohol consumption; and the presence of hypertension, IR, hypertriglyceridemia, low level of high-density lipoprotein (HDL), central obesity, metabolic syndrome; as well as homeostasis model assessment and quantitative insulin sensitivity check index results were selected as independent variables.

Results: The mean waist circumference, mean height, mean weight, and central obesity were greater in the control group (p=0.009, 0.004, 0.036, and 0.015, respectively). A multivariate logistic regression model of migraine presence showed that a family history of migraine (odds ratio [OR]: 1.542, 95% confidence interval [CI]: 2.451-8.905; p<0.0001), family history of stroke (OR: 1.043, 95% CI: 1.214-6.633; p=0.016), and no central obesity (OR: -0.705, 95% CI: -0.290-0.843; p=0.010) were statistically significant variables in our study.

Conclusion: The results of our study indicated that IR and metabolic syndrome were not associated with migraine in women. There was an inverse relationship between central obesity and migraine. Additional research with larger participant groups should be performed to further explore the complex relationship between migraine, obesity, IR, and metabolic syndrome.

Keywords: Co-morbidity; insulin resistance; metabolic syndrome; migraine; obesity.

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Migraine headache is a complicated, repetitive headache disorder that is a very pervasive complaint in neurology. The overall prevalence is 5% to 15%,[1, 2] and it is more frequent among females than males.[3] Migraines are thought to be related to various comorbid disorders, such as epilepsy, depression, anxiety, ischemic stroke, Raynaud's phenomenon, iron deficiency anemia, obesity, in-sulin resistance (IR), and metabolic syndrome.[4–6] However, the relationship between migraines and these comorbid disorders is not yet clear,[7] particularly any association with obesity, IR, or metabolic syndrome.

Some researchers have found an association between metabolic syndrome and migraine;[4, 8] however other studies have had different results.[9] Guldiken et al.[4] found that

more migraineurs had diabetes mellitus (DM), increased body mass index (BMI), and a greater waist circumference (WC) when compared with those who did not suffer from migraines. They discussed possible mechanisms responsible for a relationship between DM and migraine, but due to conflicting study results in the literature they could not reach a definitive answer to the precise relationship. For example, Split et al.[10] demonstrated a higher frequency of migraine in 154 non-insulin-dependent DM patients than in control subjects. In contrast, it was speculated in some other studies that diabetic polyneuropathy can reduce cerebrovascular reactivity and vasodilatation, which are part of the mechanisms leading to migraine headache.[11] Furthermore, various neurotransmitters, like nitric oxide, noradrenalin, and substance P, have been reported to be decreased in the nerve terminals in cases of diabetic neuropathy,[12, 13] which may have an effect on the decreased frequency of migraine attacks. On the other hand, there are 2 large population-based studies in which no connection was found between migraine and DM.[14, 15] Guldiken et al.[4] recommended that patients with migraine should be carefully evaluated for impaired glucose metabolism.

Rainero et al.[16] and Fava et al.[17] found an association between migraine and IR, although their methodologies were different. Yet a study by Sacco et al.[18] did not demonstrate any association between IR and migraine.

A relationship between obesity and migraine is also controversial. Some studies have shown a correlation between obesity and migraine,[4, 19, 20] while others found no direct correlation but did identify a relationship between being overweight and migraine.[21] A positive correlation between weight and headache frequency has been demonstrated.[22] Studies reporting a relationship between obesity and migraine have yielded different theories. Some have proposed that adipose tissue may act like an endocrine gland and produce several inflammatory cytokines, including interleukin-6 and tumor necrosis factor-α, which might have a role in migraine pathogenesis.[23] Peterlin et al.[24] concluded that the level of adiponectin may be reduced in obesity and, because it is nociceptive at low levels, this might have an unfavorable effect on the intensity of the migraine attacks. Some other studies have explored a possible genetic connection between obesity and migraine. For example, the plasma level of calcitonin gene-related peptide is sometimes elevated in people with obesity and is also known to be a postsynaptic mediator of migraine-related trigeminovascular inflammation.[25]

The aim of this study was to examine the relationship between migraine and obesity, IR, and metabolic syndrome in female migraineurs living in Turkey.

Methods

Participants and Study Design

The research was designed as a case-control study. A total of 141 female patients with migraine and 141 age- and sex-matched healthy subjects were enrolled. The migraine patients were assembled from patients of Gebze Fatih Community Hospital neurology outpatients service, and the control group comprised volunteers from the hospital staff and friends. Enrollment continued between December 2014 and May 2015. Primary and secondary headaches were identified by an expert neurologist to determine underlying diagnoses. Patients considered to be suffering from any headache-related disease were excluded.

Determination of the Sample Size

The sample size was defined using OpenEpi software version 3.01 (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com) designed for epidemiologic statistics.[26] The module to calculate a sample size for case-control studies with a 1:1 matched control group in which the endpoint is a qualitative variable was used. The population size was 350.000 (the population of Gebze, Kocaeli county), the hypothesized percentage frequency of outcome factor in the population was 20% based on previous literature,[27] a 95% confidence interval was calculated, and the design effect was determined to be 1. Using the appropriate formula, the estimated minimum sample size was 246 and migraine and control groups of 123:123 were planned. The number of participants recruited to the study was greater than the estimated sample size in order to maintain the appropriate size in the event of any withdrawals.

Covariate Assessment

The study participants completed a headache questionnaire and were interviewed by an expert neurologist. Age was recorded as a continuous variable. Smoking status was dichotomized as present smokers and non-smokers. Alcohol use was defined by identifying the quantity consumed in the previous month. Headache features, such as the presence of aura, severity, location, and duration, and migraine history of the family was acquired from participants' own reports. The length of time experiencing migraine headaches was registered in years (from first experience until report). The severity of pain was scaled between 0 and 10, and the mean number of attacks per month (within the last year) and mean attack duration (in minutes) were also recorded as measures of headache characteristics. Migraine-associated symptoms were also probed. A migraine

diagnosis was established according to the International Classification of Headache Disorders-3 beta (ICHD-3 beta) diagnostic criteria.[28]

Details of a family history of hypertension, DM, hyperlipidemia, obesity, stroke, or cardiac disease were acquired from patients' self-reports. Medication usage (including anti-hypertensive medication, anti-diabetic medication, and oral contraceptives) was also recorded.

Blood Pressure and Body Composition

Systolic and diastolic blood pressure values were measured using a standard aneroid sphygmomanometer. The weight and height of the subjects were recorded, and the BMI (kg/m^2) was calculated. The WC was measured and recorded.

Biochemical Measurements and Insulin Sensitivity

The levels of fasting glucose, fasting insulin, glycated hemoglobin (Hba1c), total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured. Fasting glucose and insulin concentrations were used to calculate the substitute marker of IR, which was evaluated according to the homeostasis model assessment (HOMA) using the formula developed by Matthews et al.[29] Insulin sensitivity was also calculated using the quantitative insulin sensitivity check index (QUICKI),[30] which is a better correlate of the hyperinsulinemic-euglycemic clamp technique than other methods.

Inclusion and Exclusion Criteria

Female subjects between the ages of 18 and 65 years were included in the study. To exclude drug-induced metabolic syndrome, patients and controls taking any immunosuppressive, antiepileptic or antipsychotic medications, beta-blockers, thiazide diuretics, or oral contraceptives were excluded. Additionally, participants with any cardiac, bariatric, or aesthetic operations to the abdominal area were not included. Finally, patients suspected of having possible medication overuse headache (MOH) were excluded. The subjects were those with a headache frequency of more than 15 days per month for a period of more than 3 months, despite treatment with painkillers.[28]

Diagnosis of Metabolic Syndrome

Metabolic syndrome was diagnosed using the International Diabetes Federation (IDF) criteria,[31] which have been widely accepted. According to the recent IDF definition, the criteria needed to diagnose a person with metabolic syndrome are having central obesity (men: WC ≥94 cm, women: ≥80 cm) plus any 2 of the following 4 factors: fasting plasma glucose ≥100 mg/dL or under treatment for type 2 diabetes, elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or using medication for previously diagnosed hypertension, triglyceride level ≥150 mg/dL or current triglyceride treatment, and an HDL cholesterol level <40 mg/dL in males and <50 mg/dL in females or cholesterol-related treatment. These criteria have been reported to be valid for Eastern Mediterranean populations.

Standard Protocol Approvals, Registration, and Patient Consent

Written, informed consent was provided by all of the participants enrolled in this study. The research was carried out in conformity with the Declaration of Helsinki and was approved by the Ethics Committee of the Community Hospitals Association of the Turkish Ministry of Health.

Data Analysis and Statistical Methods

The descriptive tests applied to study the qualitative variables were Fisher's exact test and a chi-square test. To compare the quantitative variables of 2 groups (migraine vs. control), Student's t-test and the Mann-Whitney U test were used. After adjusting for confounding variables, multivariate analysis was performed to identify significant factors of the migraine model. Migraine was designated the dependent variable and a family history of stroke, obesity, hypertension, cardiac disease or migraine; alcohol consumption; cigarette smoking; presence of hypertension, hyperlipidemia, obesity, IR, or metabolic syndrome; and HOMA index and QUICKI index values were chosen as independent variables. SPSS Statistics for Windows, Version 17.0. (SPSS, Inc., Chicago, IL, USA) was used to perform all of the statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Based on the ICHD-3 beta criteria, 131 (93%) members of the migraine group had migraine without aura (MwoA), 10 (7%) had migraine with aura (MwA), 85 (60%) had migraine associated with menses, and 6 (4%) had chronic migraine (Table 1). A family history of migraine, obesity, or stroke were significant characteristics among the migraine pa-

Table 1. Headache classification based on ICHD-3 beta

Characteristic	Migraine (n=141)
Migraine without aura, n (%)	131 (93)
Migraine with aura, n (%)	10 (7)
Pure menstrual migraine, n (%)	0
Migraine associated with menses, n (%)	85 (60)
Chronic migraine, n (%)	6 (4)

ICHD-3 beta: International Classification of Headache Disorders-3 beta.

tients (Table 2). The other demographic data did not differ significantly between the migraine and control groups (Table 2). The mean WC, mean height, and mean weight were greater in the control group (p=0.009, 0.004, and 0.036, respectively). Central obesity was also more prevalent in the control group (p=0.015) (Table 4). In contrast, there was no significant difference in the mean BMI between groups (Table 3). Similarly, the mean systolic and diastolic blood pressure, mean fasting glucose, mean fasting insulin, mean Hba1c, mean total cholesterol, mean LDL, mean HDL, and HOMA index and QUICKI index values did not differ significantly between groups (Tables 3 and 4). In addition, the presence of IR, hyperlipidemia, low HDL, hypertension, and metabolic syndrome did not differ significantly between groups (Table 4). Correlation analysis was used to evaluate headache characteristics

(pain intensity and headache frequency) against variables related to metabolic syndrome (weight, obesity, WC, IR, hypertriglyceridemia, and metabolic syndrome), but found no statistical relationship between any of these factors (Table 5).

In all, 23.4% of the migraineurs experienced bilateral headaches. More than 90% had exogenous and endogenous triggers. Allodynia was present in 80% of the migraine group. Other migraine characteristics are summarized in Table 6.

A family history of migraine [odds ratio (OR): 1.542, 95% confidence interval (CI): 2.451–8.905; p<0.0001), family history of stroke (OR: 1.043, 95% CI: 1.214–6.633; p=0.016), and no central obesity (OR: -0.705, 95% CI: -0.290–-0.843; p=0.010) were statistically significant factors in the multivariate logistic regression model of migraine (Table 7).

Table 2. Demographic and clinical characteristics

Demographic and clinical characteristics	Migraine (n=141)	Control (n=141)	p
Mean age, years (SD)	33.6 (9.3)	34.07 (8.9)	0.660
Cigarette smoking, n (%)	26 (18)	27 (19)	0.879
Alcohol consumption, n (%)	1 (0.7)	1 (0.7)	1
Family history of migraine, n (%)	57 (40)	16 (11)	<0.0001
Family history of HT, n (%)	85 (60)	89 (63)	0.624
Family history of DM, n (%)	73 (51)	75 (53)	0.812
Family history of HL, n (%)	68 (48)	64 (45)	0.633
Family history of obesity, n (%)	17 (12)	7 (5)	0.030
Family history of stroke, n (%)	29 (20)	9 (6)	<0.0001

DM: Diabetes mellitus; HL: Hyperlipidemia; HT: Hypertension. P≤0.05 indicates significance.

Table 3. Clinical measurements, mean blood pressure, BMI, and blood biochemistry

Clinical measurements	Migraine (n=141)	Control (n=141)	p
Waist circumference, cm (SD)	83.0 (11.7)	86.2 (11.4)	0.009
Mean height, cm (SD)	158.3 (6.9)	161.0 (6.7)	0.004
Mean weight, kg (SD)	64.4 (11.3)	67.5 (12.7)	0.036
Mean systolic blood pressure (SD)	108 (13)	109 (14)	0.55
Mean diastolic blood pressure (SD)	66 (9)	66 (9)	0.92
BMI (SD)	26.9 (5.1)	27.0 (4.9)	0.718
Mean fasting blood glucose (SD)	93.3 (9.3)	92.8 (13.9)	0.169
Mean fasting blood insulin (SD)	12.7 (7.9)	14.9 (14.5)	0.118
Mean Hba1c (SD)	5.5 (0.4)	5.9 (3.7)	0.183
Mean CRP (SD)	0.45 (0.46)	0.46 (0.42)	0.940
Mean triglycerides (SD)	183.7 (36.9)	183.4 (37.8)	0.893
Mean HDL (SD)	48 (11.5)	49.1 (9.6)	0.283

BMI: Body mass index; CRP: C-reactive protein; Hba1c: Glycated hemoglobin; HDL: High-density lipoprotein. P≤0.05 indicates significance.

Table 4. Components of metabolic syndrome, HOMA index, and QUICKI index

Components of metabolic syndrome and associated indices	Migraine (n=141)	Control (n=141)	p
Mean HOMA index (SD)	2.7 (1.7)	3.1 (2.2)	0.229
Mean QUICKI index (SD)	0.3 (0.02)	0.3 (0.02)	0.430
Insulin resistance according to HOMA, n (%)	98 (69)	96 (68)	0.797
Insulin resistance according to QUICKI, n (%)	72 (51)	71 (50)	0.905
Metabolic syndrome, n (%)	24 (17)	28 (19)	0.501
Central obesity, n (%)	74 (52)	94 (66)	0.015
Hypertriglyceridemia, n (%)	23 (16)	19 (13)	0.503
Low HDL, n (%)	82 (58)	81 (57)	0.904
HT, n (%)	9 (6)	7 (5)	0.607
DM, n (%)	23 (16)	24 (17)	0.873

DM: Diabetes mellitus; HL: Hyperlipidemia; HT: Hypertension; HOMA: Homeostasis Model Assessment Index; QUICKI: Quantitative insulin sensitivity check index. P≤0.05 indicates significance.

Table 5. Relationship between migraine characteristics and metabolic syndrome parameters

Metabolic parameters	Headache frequency (n=141), p	Headache severity (n=141), p
Weight	0.945	0.597
Waist circumference	0.891	0.356
Obesity	0.703	0.319
Hypertriglyceridemia	0.643	0.289
Metabolic syndrome	0.904	0.885

Table 6. Migraine characteristics and treatment habits of the migraineurs

Migraine characteristics	Migraine (n=141)
Severity of pain, mean (SD)	7.4 (0.7)
Frequency of pain per month, mean (SD)	5.9 (4.3)
Duration of pain during the attack, hours, mean (SD)	18.3 (14.4)
Time since onset of attacks, years, mean, (SD)	6.8 (6.0)
Unilateral headache, frequency, (percent)	108 (76.6)
Bilateral headache, frequency, (percent)	33 (23.4)
Nausea, frequency, (percent)	140 (99.3)
Vomiting, frequency, (percent)	74 (52.5)
Photophobia, frequency, (percent)	137 (97.2)
Phonophobia, frequency, (percent)	137 (97.2)
Exogenous trigger, frequency, (percent)	131 (92.9)
Endogenous trigger, frequency, (percent)	133 (94.3)
Allodynia, frequency, (percent)	114 (80.9)
Static mechanical allodynia, frequency, (percent)	110 (78)
Dynamic mechanical allodynia, frequency, (percent)	90 (63.8)
Thermal allodynia-hot, frequency, (percent)	69 (48.9)
Thermal allodynia-cold, frequency, (percent)	20 (14.2)
Cephalic allodynia, frequency, (percent)	87 (61.7)
Extracephalic allodynia, frequency, (percent)	25 (17.7)
Medical treatment during attack, frequency, (percent)	133 (94.3)
Simple analgesic usage during attack, frequency, (percent)	13 (9.2)
NSAID usage during attack, frequency, (percent)	93 (66)
Anti-emetic treatment during attack, frequency, (percent)	20 (14.2)
Prophylactic treatment, frequency, (percent)	20 (14.2)

NSAID: Nonsteroidal anti-inflammatory drug.

Table 7. Parameters and significance level for a multivariate logistic regression model of migraine

Parameter	Beta coefficient	OR	95% CI	p
Family history of migraine	1.542	4.672	2.451–8.905	<0.0001
Family history of stroke	1.043	2.837	1.214–6.633	0.016
Central obesity	-0.705	0.494	0.290–0.843	0.010

CI: Confidence interval; OR: Odds ratio.

Discussion

In our study, obesity, IR, and metabolic syndrome were not associated with migraine in female patients. Among 141 female migraineurs, 17% had metabolic syndrome, 52% had central obesity, 16% had hypertriglyceridemia, 58% had low HDL, 6% had hypertension, and 16% had IR. Among the control group, 19% had metabolic syndrome, 66% had central obesity, 13% had hypertryglicerdemia, 57% had low HDL, 5% had hypertension, and 17% had IR according to the IDF 2012 criteria. When metabolic syndrome and its components were compared between the study groups, only 1 significant difference was found: the presence of central obesity, and surprisingly, it was more common in the control group (66%; p=0.015). A Turkish study performed in 2004[27] found that the presence of metabolic syndrome and obesity (according to IDF criteria) was 19.2% and 50.4%, respectively, among women between the ages of 30-39 years (mean age was 33.6 years in our migraine group). Therefore, the mean values in our migraine and control groups were similar to the general population in Turkey, with the exception of the presence of central obesity in the control group.

Guldiken et al.[4] found that among 215 patients with metabolic syndrome, 19.5% had migraines and their data led to the conclusion that migraine prevalence in metabolic syndrome was higher than in the general population. Bhoi et al.[8] reached the same conclusion, finding that among 135 migraine patients, 31.9% had metabolic syndrome. Salmasi et al.[9] performed an age- and sex-matched case-control study that included 200 migraine patients (161 females and 39 males) and 200 healthy controls. Within the migrainous group, 34 (17%) had metabolic syndrome compared with 30 (15%) members of the control group. However, a greater WC and BMI (as components of metabolic syndrome) were more frequent in the migrainous group than in the control group (p=0.003 and 0.005, respectively). Thus, they concluded that metabolic syndrome and migraine headache demonstrated no significant correlation, yet a greater BMI and WC did correlate with migraine headache.

Other studies have detected an association between migraine and obesity. Horev et al.[19] found 13 migraine patients among 27 obese women. Ford et al.[20] reported that BMI was associated with the prevalence of severe headaches or migraines in a non-linear manner. Similarly, Pinhas-Hamiel et al.[22] evaluated the association between obesity and primary headaches in 273 children and adolescents aged 9-17 years and found that there was an almost 4-fold excess risk of headaches in overweight females when compared with normal-weight girls. In our sample, we found no association when headache characteristics (pain intensity and headache frequency) were compared with variables related to metabolic syndrome (weight, obesity, WC, IR, hypertriglyceridemia, and metabolic syndrome) (Table 5).

Telleze-Zenteno et al.[21] studied 1.371 migraine patients and 612 sex-matched controls with a similar percentage of females in both groups (approximately 82%). They found more obese patients (BMI 30-34.5 kg/m²) in the control

group (13.6% vs. migraine group: 10.3%), while migraine was associated with being overweight (BMI 25-29.9 kg/m^2) (38.3% vs. controls: 33.7%). There was no association between severity of migraine and BMI.

There have been studies that determined no relationship between migraine and obesity.[32–36] However, although Bigal et al.[32] found that the presence of migraine was not associated with obesity, obesity increased the number and intensity of migraine attacks and was a stronger risk factor for transformed migraine.

In terms of the association between obesity and migraine, different pathophysiological mechanisms have been linked to the conclusions of these conflicting study results.

It has been demonstrated that some inflammatory cytokines, such as interleukin-6 and tumor necrosis factor, which are produced in adipose tissue, might cause a prothrombotic state by inducing an inflammatory reaction in the vascular system.[23] These 2 cytokines intervene in the mechanism of migraine formation, and the levels increase just before the initiation of a migraine headache.[33] Guldiken et al.[4] suggested that obesity is a risk factor for chronic migraine. Researchers have postulated that weight loss might prevent migraine development and decrease the number of migraine attacks. However, in our study, there was no association between obesity and migraine or obesity and headache frequency.

Studies have also examined the association between migraine and IR. Rainero et al.[16] compared migraine patients (n=30) with a healthy control group (n=15). They performed an oral glucose tolerance test in both groups and observed that plasma glucose concentrations were higher in the migraine patients than in the controls. This result suggested that insulin sensitivity is impaired in migraine patients.

Split et al.[10] compared 154 non-insulin-dependent DM patients with controls and diagnosed a larger number of migraineurs in the DM(+) group. Fava et al.[17] compared episodic migraine patients (n=83) with chronic migraine patients (n=83) and healthy controls (n=83). They found a significant prevalence of IR in the chronic migraine group, while obesity (BMI >30 kg/m^2) was associated with increased risk of chronic migraine. They concluded that chronic migraine is associated with IR status, especially when it is found together with obesity. Sacco et al.[18] used a different methodology to explore the subject: They compared 50 patients with MwA, 50 patients with MwoA, and 50 controls. However, their results did not demonstrate any association between migraine and IR. Similarly, no relationship was demonstrated between migraine and DM in 2 other broad, population-based studies.[14, 15]

In our sample, according to the IDF 2012 criteria, impaired glucose metabolism (fasting plasma glucose >100 mg/dL or usage of anti-diabetic medication) was present in 16% of the migraine group and 17% of the control group. According to the HOMA index, 69% of the migraine group and 68% of the control group had IR, while 51% of the migraine group and 50% of the control group had IR based on the QUICKI index. Hence, both groups had similar proportions of those with impaired glucose metabolism. A review of the literature tells us that there are studies linking the presence of IR and migraine[10, 16, 17] and others that do not find a connection.[14, 15, 18] The interaction between DM and migraine is still uncertain, and the results are contradictory about the frequency of migraine in DM. Even those studies that found an association between impaired glucose metabolism and migraine were unable to provide a clear pathophysiological explanation to their findings. Bic et al.[37] suggested that high levels of blood lipids and free fatty acids in the circulation were one of the triggering factors in development of migraine headaches. The researchers speculated that biological conditions that increase the levels of circulating free fatty acids and blood lipids, such as stress, smoking, obesity, IR, heavy exercise, hunger, consumption of alcohol and caffeinated beverages, and use of oral contraceptives can lead to migraine attacks. They suggested that elevated blood lipids and free fatty acids might lead to increased aggregation of the platelets, decreased levels of serotonin, and elevated prostaglandin levels, causing vasodilatation that precedes a migraine attack. Mitsias et al.[11] postulated that diabetic polyneuropathy might decrease cerebrovascular reactivity and also prevent the vasodilatation that promotes a migraine headache. Furthermore, Cameron et al.[12] and Kihara et al.[13] reported that numerous neurotransmitters, like substance P, nitric oxide, and noradrenalin, are reduced in the nerve terminals in diabetic neuropathy and might be involved in the pathophysiology of migraine.

In contrast, Aamodt et al.[38] demonstrated that the frequency of migraines was lower in elderly patients who have been diabetic for more than 13 years. DM might be protective against migraine, or the exact opposite might be true. As already mentioned, the results of studies examining the relationship between impaired glucose metabolism and migraine remain controversial.

Despite the complexity, the literature does allow us to form some theories about the results of our study. The characteristics of our migraine group revealed that 92.9% of the group had exogenous migraine triggers while 94.3% had endogenous triggers. Among the exogenous migraine triggers that could have an interaction within the individual's metabolic status, 9.4% of the group mentioned chocolate, 2% wine, 4.3% cheese, 3% onion, 12% spicy food, 11.3% tea, and 19.9% coffee. Since central obesity was observed

more frequently in our control group (migraine: n=74/141, 52%; control: n=94/141, 66%; p=0.015). It is possible that the migraineurs may be more concerned about the ingredients and quantity of the food they consume in order to avoid migraine attacks, and thus be more meticulous about weight gain.

Also generally speaking, patients who begin to suffer from migraines at a young age are often individuals exposed to various kinds of medications that have various side effects. Some of these medications (e.g., anti-epileptics, antidepressants) interfere with glucose metabolism and cause the subjects to gain weight. This may not have been sufficiently considered in previous research demonstrating that migraineurs are more obese or have a more impaired glucose metabolism. In our migraine group, the mean length of time since onset of attacks was 6.8 years and the mean frequency of the migraines was 5.9 per month. In spite of this, only 14.2% received prophylactic treatment. The mean antiepileptic usage was 2.1%, antidepressants 2.8%, beta-blockers 5%, and calcium channel blockers 5%. We recommend that there be new studies exploring the reasons some migraine patients are more prone to have a disrupted glucose metabolism and designed to include the effect of certain kinds of medication used in the migraine population.

A limitation of our study is that we were unable to compare different subgroups of migraine (episodic migraine vs. chronic migraine or MwA vs. MwoA) because there were too few patients in some of the subgroups (e.g., MwA patients: n=10, chronic migraine patients: n=6). Also, we did not have information about the physical exercise habits of either group and could not consider its effect on metabolic status.

Conclusion

This research indicated that IR, obesity, and metabolic syndrome were not associated with migraine in women. Further research examining the complicated relationships between migraine, impaired glucose metabolism, obesity, and metabolic syndrome is needed to determine the reasons underlying the mixed study results.

Disclosures

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