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Migraine in Patients with Metabolic Syndrome: Is there a Relationship to Leptin?

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Abstract

Previous studies have reported association of migraine and metabolic syndrome (MS) and between MS and leptin (a protein product of the obesity gene). This study aimed to determine whether there is a link between MS and its components, leptin and migraine and its covariates (frequency and duration), as data regarding this relationship are still sparse or even controversial. This study included 60 patients with MS and comorbid migraine with mean age of 47.83±7.31 years. Demographic, anthropometric, clinical and lab characteristics were identified. Serum leptin concentrations were also measured. Nearly 58.33% had episodic migraine (MoA=44.64%, MA=16.6%), 35% had chronic migraine and 6.67% had tension type headache (TTH). Obesity, type 2 diabetes mellitus and hypertension and were reported in all patients, of them 80% had hypertriglyceridemia and/or dyslipidemia, 81.67% had insulin resistance (IR) and 58.33% hyperleptinemia. Compared to patients with TTH, patients with migraine had higher measurements for BMI (39.01 ± 6.05), WC (P = 0.058), poor glycemic control (8.11 ± 1.22), SBP (P = 0.052), DBP (P = 0.050) and serum levels of LDL-c (P = 0.0001), fasting insulin (P = 0.0001) and leptin (P = 0.0001). Leptin concentrations were found to be positively correlated with BMI (r = 0.547, P = 0.008), WC (r = 0.445, P = 0.002), HbA1c (r = 0.656, P = 0.001) and fasting insulin (r = 0.613, P = 0.008). The logistic regression to model leptin and headache parameters (frequency and duration) after adjusting age and sex and leptin levels, were found to correlate with BMI, WC and fasting insulin) but this relationship disappeared after adjustment of these covariates. We conclude that comorbid migraine with MS is related to obesity (total body obesity and abdominal adiposity) and insulin abnormalities after adjustment of other covariates.

Keywords: Metabolic syndrome; Obesity; Insulin resistance; Leptin

Abbreviations

MS: Metabolic Syndrome; T2DM: Type 2 Diabetes Mellitus; HTN: Hypertension; TC: Total cholesterol; TG: Triglycerides; LDL-c: Low Density Lipoprotein Cholesterol; HDL-c: High Density Lipoprotein Cholesterol; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TBO: Total Body Obesity; BMI: Body Mass Index; WC: Waist Circumference; IR: Insulin Resistance; FBG: Fasting Blood Glucose; OGTT: Oral Glucose Tolerance Test; HbA1c: Gycolysated Hemoglobin; ICHD: International Classification of Headache Disorders; MA: Migraine with Aura; MoA: Migraine without Aura; ELISA: Enzyme-Linked Immunosorbent Assay; HOMA-IR: Homeostasis Model Assessment Equation for Insulin Resistance

Introduction

Metabolic syndrome (MS) is quite common with an estimated prevalence of 5% of subjects with normal body weight, 22% of overweight subjects and 60% of obese subjects [1,2]. MS is defined according to the single global definition promoted by several international societies as a cluster of conditions with the following features [3]: obesity [total body obesity (TBO) which is indicated by elevated body mass index (BMI) and abdominal adiposity which is indicated by increased WC], insulin resistance (IR) which refers to the diminished cell response to insulin in promoting transport of glucose from blood to muscles and other tissues [4], type 2 diabetes mellitus (T2DM), hypertension (HTN), cholesterol abnormalities (hypercholesterolemia and/or dyslipidemia), and an increased risk for clotting. Epidemiological, longitudinal and cross-sectional case controlled studies have shown increased prevalence of migraine among patients with MS (10-22.5%) [5,6]. Migraine is a frequent medical condition with an estimated prevalence of ~12% of the general population [7]. Migraine is defined according to the definition and criteria of the second edition of the International Classification of Headache Disorders (ICHD-2), as a chronic neurological disorder characterized by episodic attacks of moderate to severe headache and associated symptoms [8]. The highest prevalence occurs between the ages of 25 and 55 years, potentially the most productive period of life [8]. Migraine is divided into six major categories, the two most important of which are: migraine without aura (MoA) and migraine with aura (MA). For MoA, the ICHD-2 requires at least five lifetime headache attacks (often unilateral and pulsating) which accompanied by various combination of features (photophobia/phonophobia and/or nausea/vomiting) which last from 4 to 72 hours. MA is characterized by focal neurological phenomena (aura) that usually proceed, accompany or occur in the absence of headache. Most aura symptoms develop over 5-20 minutes and last ~20-60 minutes. In one-third of patients with MA, visual aura is the most common form (hemianopia, a crescent with a bright, ragged edge and scintillations, scotoma, photopsia or phosphenes, fortification spectra and other visual manifestations), followed by sensory symptoms (numbness and tingling or paraesthesia). Hemi-motor weakness, dysphasia and incoordination and other signs of brainstem dysfunctions are less common aura symptoms. Chronic migraine (which evolved from episodic migraine and was termed chronic daily headache in ICHD-1 classification) is defined if the

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migraine headache attacks occurs at frequency of >15 days/month in a patient not overusing acute medications [9].

MS and migraine are population prevalent and disabling disorders influenced by multifactorial (complex) genetic, environmental and many modifying risk factors (as sedentary lifestyle and progressive weight gain). However, the mechanisms underlying the pathogenesis of MS-related migraine remain unknown. Several studies reported an association between migraine and MS and its different components as obesity (TBO and abdominal adiposity) [10-13], poor glycemic control [14], IR [15], HTN [16] and hypercholesterolemia/dyslipidemia [17].

Recently, a large number of adipocyte-derived adipokines as adiponectin, leptin, resistin, and retinol binding protein 4, and the resident macrophage-derived adipokines and cytokines as tumor necrosis factor (TNF-α) and interleukin 6 (IL-6), have been discovered to play critical roles in variety of endocrine functions which are related to organs such as the brain, liver, pancreas and skeletal muscle to control diverse processes as food intake, energy expenditure, carbohydrate and lipid metabolism, blood pressure, blood coagulation, and inflammation [18]. The dys-regulation of adipokines secretion and action have been found to play an important role in initiation of obesity and its related inflammation, MS, T2DM, inflammatory disorders and vascular disorders [18].

Leptin is the best known adipocyte-derived adipokines and a protein product of the obesity gene [19]. Leptin has been found to be positively and predictively associated with obesity [20-21]. IL-6 (which has an important role in the initiation of obesity-related inflammation) [22], hyperglycemia [23], IR [24,25], HTN [26,27] and lipids [28] which are components of metabolic syndrome. Thus, leptin may form a link between MS and migraine.

Aim of work

This study aimed to determine whether there is a link between MS and its components, leptin and migraine and its covariates (frequency and duration).

Materials and methods

Subjects

This cross-sectional study included consecutive 60 patients with MS and complained of headache. Patients were recruited from the out-patient diabetes clinic of the Internal Medicine department of Assiut University Hospital, Assiut, Egypt throughout a period 6 months (2010-2011), and evaluated by trained physicians according to a standard protocol for the presence of MS and its components [3]. Forty age, sex, socioeconomic status and educationally matched subjects recruited from the general population were included as healthy controls subjects for comparison. The study protocol was carried out according to the Declaration of Helsinki and was in conformity with the local ethical guidelines and informed written consent was obtained from each participant.

Patients were studied during the headache attack-free periods. Headache was classified according to the criteria of the 2nd edition of the International Headache Society [8]. Accordingly, patients with MS were divided into those with episodic migraine (MA and MoA), chronic migraine (evolved from episodic migraine) and other types of primary headaches (e.g. tension type headache or TTH). According to the frequency of migraine attacks, patients with migraine were divided into two groups: a) high frequency group: ≥4 attacks / month, and b) low-frequency group: <4 attacks / month [29].

Excluded were: 1) smokers and alcoholics, 2) patients with other medical, neurologic, psychiatric or systemic diseases as major cardiovascular events (e.g. myocardial infarction, stroke, coronary artery bypass graft/percutaneous transluminal coronary angioplasty revascularization intervention); transient ischemic attacks, cerebrovascular stroke; epilepsy; active gastrointestinal disease; gout; recent infection; chronic inflammation; serum creatinine >150 μmol/l, and malignancies, 3) patients treated with insulin because exogenous insulin might lead to a false high insulin concentration that was used in the calculation of the IR index, 4) patients on regular medications other than non-steroidal anti-inflammatory (NSAIDS), anti-migrainous, anti-diabetic, anti-hypertensive and lipid lowering drugs, and 5) pregnancy, lactation or use of contraceptive pills.

Methods

All participants were subjected to medical, endocrinological and neurological history and examination. The following demographic, anthropometric, cardiovascular, and clinical parameters were collected per subject: age, gender, weight, height, BMI and WC, duration of illness (years), current anti-diabetic, anti-hypertensive and lipid lowering therapies. The body mass index (BMI) is a commonly used anthropometric measure to estimate total body fat and is often calculated based on patient's self-reported height and weight. According to BMI, subjects are divided into 5 categories: i) underweight (<18.5 kg/m^2), ii) normal weight (18.5 to 24.9 kg/m^2), iii) overweight (25 to 29.9 kg/m^2), iv) obese (30 to 34.9 kg/m^2) and v) morbidly obese (>35 kg/m^2) [30]. Abdominal adiposity was defined when WC ≥ 94 cm in males and ≥ 80 cm in females [3]. IR is usually calculated using the homeostasis model assessment equation (HOMA-IR) (formula: Fasting insulin (uIU/mL) X fasting glucose (mmol/L) / 22.5. Patients were consider to have IR if HOMA-IR ≥ 2.6 [31].

Specimen collection and analysis

No medications were taken on the morning of the study day. Venous blood samples (6 ml) were obtained via venipuncture at 8:00-10:00 a.m. after an overnight fast for at least 12 hours. 2 ml of K3EDTA blood was drawn in a vacutainer tube for immediate assessment of complete blood count (CBC) (Cell Dyn 3500, Abbot Diagnostics, Abbott Laboratories. Abbott Park, Illinois, USA) and preparation of hemolysate was kept frozen for estimation of HbA1c, a clinical indicator of glycemic control. HbA1c determination is based on turbidimetric inhibition immunoassay for hemolyzed whole blood and was measured using Hitachi 911 autoanalyzer (Roche Diagnostics, Mannheim, Germany. The remaining 4 ml were immediately centrifuged at 2,500 rpm for 15 minutes and the obtained serum was divided into 3 aliquots: one was utilized for FBG, kidney, liver functions and lipogram, while the other two aliquots were stored at -70°C for latter assessment of serum insulin and leptin. Serum levels of TC, TG, HDL-c, LDL-c were measured by enzymatic colourimetric method [Hitachi 911 autoanalyzer (Roche Diagnostics, Mannheim, Germany]. Insulin was determined by enzyme-linked immunosorbent assay (ELISA) (Diagnostic Systems Laboratory, Webster, TX, USA). Serum leptin was measured by an ELISA (BioVendor Laboratory Medicine, Inc., Modrice, Czech Republic). Two hours after blood withdrawal for estimation of FBG, the patients received formal standard oral glucose and 3 ml blood samples were withdrawn from each participant for estimation of post-prandial blood glucose level (i.e. oral glucose tolerance test or OGTT). The measurements of serum insulin and leptin levels were combined

Demographic and Clinical characteristics	Patients (n = 60)		Control subjects (n = 40)	P1-value	P2-value	P3-value
	Patients with migraine	Patients with TTH				
Male/female; # (%)	22/38	1/3	12/28	-	-	-
Age; years	32.0-55.0 (47.83 ± 7.31)	32.0-55.0 (48.55 ± 7.60)	35.55-55.00 (48.35 ± 7.60)	0.494	0.345	0.255
Patients with episodic migraine; # (%)	35 (62.5%)	-	9 (22.5 %)	-	-	-
	25 (44.64%)	-	5(12.5%)	-	-	-
MoA	10 (17.86%)	-	3 (7.5%)	-	-	-
MA	21 (37.5%)	-	1 (2.5%)	-	-	-
Patients with chronic migraine; # (%)	4 (6.67%)	-	11 (27.5%)	-	-	-
Patients with TTH; # (%)	1.00-22.00 (8.528 ± 4.27)	-	5.00-9.00 (3.325 ± 1.05)	-	-	-
Duration of migraine; years	2.0-18.0 (6.56 ± 1.45)	-	-	-	-	-
Duration of episodic migraine; years	1.00-22.00 (9.328 ± 4.27)	-	-	-	-	-
Duration of chronic migraine; years	-	5.0-20.0 (15.34 ± 6.33)	3.0-15.0 (12.23 ± 4.55)	-	0.255	**0.012**
Duration of TTH; years						
Frequency of headache attacks; #/month (%)						
Low-frequency (<4/month)	5 (8.33%)	1 (1.67%)	4 (10%)	-	-	-
High-frequency (≥4/month)	51 (85%)	3 (5%)	2 (5%)	-	-	-
BMI; kg/m^2	29.07-55.55 (39.01 ± 6.05)	29.07-55.55(28.55 ± 6.56)	26.20-53.50 (30.52 ± 4.59)	0.253	0.865	0.365
Degree of obesity; # (%)						
normal: 18.5-24.9 kg/m^2	0	0	14 (35%)	-	-	-
Overweight: 25.0-29.9 kg/m^2	2 (3.33%)	3 (5%)	16 (40%)	-	-	-
Obese: 30.0-34.9 kg/m^2	21 (35%)	1 (1.67%)	2 (5%)	-	-	-
Morbidly obese: >35.0 kg/m^2	33 (55%)	0	0	-	-	-
WC; cm	93.0-136.0 (126.27 ± 9.84)	93.0-136.0 (108.36 ± 9.99)	100.0-132.0 (87.05 ± 5.32)	**0.050**	**0.053**	0.058
SBP; mmHg	110.0-180.0 (150.92 ± 16.86)	100.0-150.0 (135.060 ± 16.33)	100.0-130.0 (120.0 ± 0.0)	**0.052**	0.432	**0.052**
DBP; mmHg	70.0-110.0 (105.75 ± 6.56)	70.0-100.0 (80.20 ± 8.10)	60.0-85.0 (80.0 ± 0.0)	**0.054**	0.405	**0.050**
Duration of T2DM; years	2.0-20.0 (5.98 ± 3.60)	2.0-20.0 (6.24 ± 2.50)	-	-	-	-
Duration of obesity; years	2.0-20.0 (8.75 ± 4.47)	2.0-20.0 (5.04 ± 2.08)	-	-	0.057	-
Duration of HTN; years	1.0-18.0 (5.12 ± 3.44)	1.0-18.0 (4.92 ± 2.16)	-	-	-	-
Degree of control on anti-diabetics treatment						
Controlled; **#** (%)	23 (38.33%)	3 (5%)	-	-	-	-
Uncontrolled; **#** (%)	33 (55%)	1 (1.67%)	-	-	-	-
Degree of control on anti-hypertensive treatment			-	-	-	-
Controlled; **#** (%)	24 (40%)	2 (3.33%)	-	-	-	-
Uncontrolled**; #** (%)	32 (53.33%)	2 (3.33%)				
Degree of control on lipid lowering treatment						
Controlled; **#** (%)	23 (38.33%)	4 (6.67%)	-	-	-	-
Uncontrolled**; #** (%)	33 (55%)	0	-	-	-	-

Data are expressed as range, mean±SD; number (%); MoA, migraine without aura; MA, migraine with aura; TTH, tension type headache; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 diabetes mellitus; HTN, hypertension
Significance: P1: migraine versus controls; P2: TTH versus controls; P3: migraine versus TTH

Table 1: Demographic, anthropometric and clinical characteristics of the studied groups.

with the cross sectional assessment while clinical evaluation and interviewing with patients and control subjects.

Statistical analysis

Calculations were done with the statistical package SPSS, version 12.0. Data were presented as mean ± SD (standard deviation). In tables 1 and 2, non-parametric methods were used to compare the differences between groups (as there were only four subjects in the group of TTH. In tables 3 and 4, one-way ANOVA with a post hoc test was used to compare the differences between the three groups. We used stepwise forward logistic regression to model leptin and headache parameters adjusting for covariates. In patients with MS and migraine to determine whether migraine covariates had relationships to leptin, the logistic regression model was as follow: First, we carried out correlations between dependent variables (frequency and duration of headache) and the independent variables (as BMI, WC, HbAIc, SBP, DBP, TC, TG, LDL-c, HDL-c and leptin). Second, independent variables which had no significant correlations were excluded (after adjustment of age and sex) followed by adjustment of other positively correlated independent variables. For all tests, values of $p<0.05$ were considered statistically significant.

Results

This study included 60 patients with MS and complained of headache (male = 22; females = 38), with mean age of 47.83±7.31 years. Nearly 93.33% (n = 56) had migraine, 58.33% (n = 35) had episodic migraine (MoA = 44.64%, n = 25; MA = 16.6%, n = 10), 35% (n = 21) had chronic migraine and 6.67% (n = 4) had TTH. In control subjects, migraine was reported in 22.5% (n = 9) while TTH was reported in 27.5% (n = 11). The majority of patients had frequent migraine attacks (91.07%, n = 51). T2DM and HTN were reported in 100% of patients, of them >50% were uncontrolled on anti-diabetics or anti-hypertensive medications, 91.67 (n = 55) were obese/morbidly obese, 80% (n = 48) had hypercholesterolemia and/or hypertriglyceridemia 81.67% (n = 49) had IR and 58.33% (n = 35) had hyperliptinemia. Leptin levels were 2.3 fold higher in women compared with men. Demographic, anthropometric, clinical and laboratory characteristics of the studied groups were shown in tables 1 and 2. Compared to patients with TTH,

Laboratory	Patients (n = 60)		Control subjects	P1-value	P2-value	P3-value
	Patients with episodic and chronic migraine	TTH				
Patients with hypercholesterolemia / dyslipidemia; # (%) **lipid**	48 (80%)	0	0	-	-	-
TC; mg/dl	130.20-395.00 (229.00 ± 53.15)	130.20-195.00 (130.05 ± 48.58)	124.00-195.00 (128.10 ± 70.10)	**0.052**	0.675	0.368
LDL-c; mg/dl	58.80-286.60 (141.89 ± 44.83)	58.80-200.00 (80.56 ± 15.50)	64.00-115.00 (57.30 ± 19.40)	**0.007**	0.432	**0.0001**
TG; mg/dl	48.40-423.00 (189.29 ± 11.08)	48.40-200.00 (150.85 ± 23.56)	49.00-128.00 (92.10 ± 8.20)	**0.006**	**0.001**	0.568
HDL-c; mg/dl	17.00-89.00 (44.52 ± 14.78)	35.00-89.00 (39.50 ± 8.60)	35.00-48.00 (56.90 ± 1.20)	0.537	0.113	0.067
FBG; mmol/l	5.12-21.19 (10.29 ± 3.78)	5.35-10.55 (10.54 ± 3.50)	3.10-5.40 (4.30 ± 0.71)	**0.0001**	**0.0001**	0.235
Post-prandial blood glucose; mmol/l	7.00-16.00 (12.69 ± 2.39)	4.50-16.00 (12.59 ± 5.80)	4.50-6.30 (5.37 ± 0.59)	**0.0001**	**0.0001**	0.432
HbA1c	5.90-10.90 (8.11 ±1.22)	2.00-20.10 (10.50 ± 0.25)	4.00-5.70 (4.86 ± 0.48)	**0.0001**	**0.0001**	0.675
Patients with Insulin resistance; # (%)	49 (81.67%)	0	0	-	-	-
Fasting insulin; µIU/ml	2.00-35.10 (14.17 ± 10.83)	2.00-10.55 (5.56 ± 1.93)	2.00-7.20 (5.56 ± 1.93)	**0.0001**	0.455	0.568
Patients with hyperleptinemia; # (%)	35 (58.33%)	0	0	-	-	-
Leptin; ng/ml	1.00-106.50 (25.32 ± 7.53)	1.00-60.310 (10.60 ± 4.56)	1.00-22.10 (8.49 ± 6.62)	**0.0001**	0.098	**0.0001**

Data are expressed as mean ± SD; number (%)
TTH, tension type headache; FBG, fasting blood glucose; HbA1c, glycolysated hemoglobin; TC, total cholesterol; TG, triglycerides; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol
Significance: P1: migraine versus controls; P2: TTH versus controls; P1: migraine versus TTH

Table 2: Laboratory findings of the studied groups.

Demographic and Clinical characteristics	MoA (n = 25)	MA (n = 10)	Chronic migraine (n = 21)	TTH (n = 4)	P1-value	P2-value	P3-value	P4-value
Male/female; #	9/16	2/8	8/13	1/3	-	-	-	-
Age; years	47.48 ± 8.43	49.87 ± 5.49	49.48 ± 6.10	48.55 ± 7.60	0.144	0.907	0.804	0.115
BMI; kg/m^2	39.01 ± 6.05	36.64 ± 4.75	39.60 ± 5.23	28.55 ±6.56	**0.050**	**0.0.54**	**0.012**	0.133
Degree of obesity; # (%)								
Normal: 18.5-24.9 kg/m^2	0	0	0	1 (1.67%)	-	-	-	-
Overweight: 25.0-29.9 kg/m^2	2 (8%)	0	0	3 (5%)	-	-	-	-
Obese: 30.0-34.9 kg/m^2	15 (60%)	3 (30%)	3 (14.29%)	0	-	-	-	-
Morbidly obese: >35.0 kg/m^2	13 (52%)	7 (70%)	18 (85.71%)	0	-	-	-	-
WC; cm	115.96 ± 8.84	116.20 ± 11.85	118.55 ± 5.67	108.36 ± 9.99	**0.125**	**0.0.50**	0.067	0.856
SBP; mmHg	165.80 ± 10.18	150.00 ± 13.54	150.00 ± 13.33	135.060 ± 16.33	**0.045**	**0.053**	**0.050**	0.462
	100.20 ± 4.98	95.33 ± 7.15	95.20 ± 5.20		**0.024**	**0.050**	**0.050**	0.821
DBP; mmHg				80.20 ± 8.10				
Duration of T2DM; years	5.92 ± 3.84	5.33 ± 3.59	10.67 ± 2.56	6.24 ± 2.50	0.089	0.754	**0.001**	0.675
Duration of overweight/obesity; years	6.72 ± 3.18	10.53 ± 3.18	12.66 ± 3.56	5.04 ± 2.08	**0.053**	**0.0001**	**0.0001**	**0.012**
Duration of HTN; years	4.60 ± 2.18	6.20 ± 3.86	10.78 ± 2.40	4.92 ± 2.16	0.564	0.345	**0.0001**	0.654
Degree of control on anti-diabetic treatment								
Controlled; **#** (%)	12 (48%)	3 (30%)	12 (57.14%)	3 (5%)	-	-	-	-
Uncontrolled; **#** (%)	13 (52%)	7 (70%)	9 (42.86%)	1 (1.67%)	-	-	-	-
Degree of control on anti-hypertensive treatment								
Controlled; **#** (%)	10 (40%)	0	5 (23.81%)	2 (3.33%)	-	-	-	-
Uncontrolled**; #** (%)	15 (60%)	10 (100%)	16 (76.19%)	2 (3.33%)	-	-	-	-
Degree of control on lipid lowering treatment								
Controlled; **#** (%)	12 (48%)	3 (30%)	12 (57.14%)	4 (6.67%)	-	-	-	-
Uncontrolled**; #** (%)	13 (52%)	7 (70%)	9 (42.86%)	0	-	-	-	-

Data are expressed as mean ± SD; number (%)
MoA, migraine without aura; MA, migraine with aura; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure
Significance: P1: MoA versus TTH; P2: MA versus TTH; P3: chronic migraine versus TTH; P4: MoA versus MA; P5: MoA versus chronic migraine; P6: MA versus chronicmigraine

Table 3: Demographic, anthropometric and clinical characteristics of the studied groups according to the type of headache.

patients with migraine had higher measurements for BMI (39.01 ± 6.05), WC (P = 0.058), poor glycemic control (8.11 ± 1.22), SBP (P = 0.052), DBP (P = 0.050) and serum levels of LDL-c (P = 0.0001), fasting insulin (P = 0.0001) and leptin (P = 0.0001). Leptin concentrations were found to be positively correlated with BMI (r = 0.547, P = 0.008), WC (r = 0.445, P = 0.002), HbA1c (r = 0.656, P = 0.001) and fasting insulin (r = 0.613, P = 0.008) (tables 3 and 4). After adjusting age and sex, the logistic regression to model leptin and migraine covariates (frequency and duration), leptin concentrations found to correlate with BMI, WC and fasting insulin) but this relationship disappeared after adjustment of these covariates.

Discussions

The associations between clinical features of migraine and MS and its components have already been reported [1-6]. However, in this study, we reported increased frequency of comorbid migraine in patients with MS and complained of headache (93.33%), of them, 58.33% had episodic migraine (MoA = 44.64%; MA = 16.6%), 35% had chronic

Laboratory	MoA (n = 25)	MA (n = 10)	Chronic migraine (n = 21)	TTH (n = 4)	P1-value	P2-value	P3-value	P4-value
Lipid								
TC; mg/dl	228.54 ± 42.16	210.64 ± 60.04	230.55 ± 58.98	130.05 ± 48.58	**0.001**	**0.001**	**0.001**	0.851
LDL-c; mg/dl	143.39 ± 40.97	122.21 ± 44.91	149.27 ± 40.70	80.56 ± 15.50	**0.001**	**0.001**	**0.001**	0.056
TG; mg/dl	180.38 ± 10.87	207.00 ± 15.66	174.93 ± 33.69	150.85 ± 23.56	**0.047**	**0.001**	**0.050**	0.484
HDL-c; mg/dl	43.54 ± 14.55	46.15 ± 12.89	44.00 ± 12.99	39.50 ± 8.60	0.706	0.700	0.229	0.573
Fasting blood glucose; mmol/l	19.89 ± 3.74	8.16 ± 4.52	15.52 ± 4.22	4.30 ± 0.71	**0.0001**	0.089	**0.0001**	**0.001**
Post-prandial glucose; mmol/l	21.55 ± 5.05	13.23 ± 2.65	20.67 ± 4.75	5.37 ± 0.59	**0.0001**	0.546	**0.0001**	**0.001**
HbA1c	12.35 ± 1.06	9.5 ± 0.56	10.50 ± 0.25	4.86 ± 0.48	**0.0001**	0.432	**0.0001**	**0.035**
Fasting insulin; µIU/ml	15.09 ± 7.63	12.63 ± 5.23	13.54 ± 4.53	5.56 ± 1.93	**0.0001**	**0.0001**	**0.0001**	0.632
Leptin; ng/ml	27.54 ± 6.43	30.45 ± 3.23	30.23 ± 5.67	8.49 ± 6.62	**0.0001**	**0.0001**	**0.0001**	0.654

Table 4: Laboratory findings of the studied groups according to the type of headache

migraine of high frequencies (91.07%), while migraine was reported in 22.5% of healthy control subjects. Although a 58.33% prevalence of episodic migraine in patients with MS seems to be different from the numbers reported previously in many studies (11.9% in men and 22.5% in women), this could be explained by use of different study and methodological designs as follow: a) we chose a cut off age of 55 years old, b) all patients had chronic illness, c) the majority of patients were obese/morbidly obese (35% and 55% respectively) and, d) the majority of patients with episodic and chronic migraine had higher frequencies of IR (81.67%), higher measurements of SBP and DBP with > 50% were uncontrolled on anti-hypertensive or anti-diabetic medications.

Here, we reported an increased risk of TBO and abdominal adiposity in patients with episodic and chronic migraine compared to TTH. Large population-based studies indicated that obesity (TBO and/or abdominal adiposity) is a risk or an exacerbating factor for episodic migraine and migraine progression from episodic to chronic migraine after adjusting for comorbidities, but not for other types of headaches. Obesity is considered as a pro-inflammatory state in which increased inflammatory mediators; vascular hyper reactivity, plasma calcitonin gene-related peptide (CGRP) concentrations and decreased adiponectin concentrations. These alterations may increase the frequency, severity and duration of migraine attacks per se, which in turn would cause central sensitization. Repeated central sensitization may be associated with permanent neuronal damage close to the periaqueductal gray area, with poor modulation to pain and thereafter, chronic migraine [10-13, 20]. In accordance, Horev et al. [10] reported migraine in 48.15% of the studied morbidly obese women (MA = 37.04%, MoA = 11.11%) and 14.81% had TTH. Peres et al. [10] reported headache in 75% of the studied obese women, of them 66% had migraine, 9% had TTH and 48% had incapacitating headaches. Bigal et al. [20] reported migraine in 22.11% in and TTH in 1.71% of studied USA population, of them very frequent headaches (10-14 day/month) was reported in 7.4% with overweight, 8.2% in obese and 10.4% in morbidly obese subjects, compared to 6.5% with normal weight. Keith et al. [12] in their cross-sectional analysis of 11 datasets which included 220,370 adult women (≥18 years), the authors identified that a BMI of ~20 was associated with the lowest risk of headache, BMI of 30 was associated with ~35% increase in the odds for headache whereas BMI of 40 was associated with ~80% increase in odds. In this study, we chose a cut off age of 55 years old. In accordance, Peterlin et al. [13] reported increase in the prevalence of migraine with increase in BMI independent to WC in adult's ≤55 years old and regardless of gender and migraine prevalence is increased with increase in WC and independent of BMI in women. While in adults >55 years old and regardless of gender, migraine prevalence is not associated with WC or BMI. In addition, migraine prevalence is decreased with WC independent of BMI in women. In fact, in normal individuals, adipose tissue distribution patterns are different in women and men, with younger women having more adipose tissue depots in a gluteofemoral distribution than abdominally, while men of all ages and older women have more abdominal adipose tissue depots than young women [31].

In this study, we reported more poor in glycemic control and higher frequencies of IR in patients with episodic and chronic migraine compared to patients with TTH. In accordance, Rainero et al. [24] found that poor glycemic control (indicated by higher glucose plasma concentrations during OGTT) was associated with evaluated insulin sensitivity in adults with migraine. Several studies have revealed that serum leptin concentrations are not only correlated with BMI and body fat but also with fasting insulin concentrations that is independent of body adiposity [4].

In this study, we reported higher measurements of SBP and DBP in patients with episodic and chronic migraine compared to patients with TTH. In accordance, Scher et al. [32] in their Genetic Epidemiology of Migraine Study which included 5,755 subjects from the Netherlands, the authors found higher blood pressure with migraine compared to TTH. Gudmundsson et al. [26] in their population-based study on 10,366 men and 11,171 women, the authors found that patients with migraine had higher DBP and lower SBP and pulse pressure compared to their matched controls. The authors also found that one standard deviation increase in DBP significantly increased the probability of migraine by 30% of women compared to 14% of men, while one standard deviation increase in SBP and pulse pressure significantly decreased the probability of migraine by 19% and 13% of men and 25% and 14% of women, respectively. It has been identified that poor control of blood pressure may exacerbate the frequency and severity of migraine and patients with chronic migraine are more likely to be hypertensive than patients with episodic headaches. More recently, a unifying view among most recent studies suggests that migraine is positively correlated with DBP but negatively correlated with SBP and pulse pressure. It has been suggested that renin-angiotensin system acts as a biological link between HTN and central nervous system (CNS) activities that are relevant for migraine pathogenesis [27].

In this study, we reported elevated concentrations of TC, TG, LDL-C and low concentrations of HDL-C in patients with episodic and chronic migraine compared to patients with TTH. It has been observed that high levels of free fatty acids, hypercholesterolemia and dyslipidemia are important factors involved in triggering migraine headache [33]. The relationship between abnormal lipid profile and migraine is further supported by the following: a) low fat diet was associated with significant decrease in headache frequency, intensity, duration and medication intake [34], b) high fat diet has been considered to underlie platelet aggregability, which is associated with decreased serotonin and heightened prostaglandin levels leading to vasodilation, the immediate

precursor of migraine headache [34], and c) increasing dietary intake of polyunsaturated fatty acids have been found to result in formation of less potent inflammatory mediators, attenuate perivascular and neurogenic inflammatory processes and suppress nitric oxide (NO) production, which play roles in migraine pathogenesis [33].

In this study, patients with migraine had higher leptin concentrations compared to patients with TTH. In logistic regression model, leptin did not account for changes in migraine frequency or duration after adjustment for BMI, WC and fasting insulin. This indicates that hyperleptinemia observed in patients with comorbid migraine in patients with MS, is associated with obesity (TBO and abdominal adiposity) and insulin abnormalities. The observed hyperleptinemia among patients implied a state of leptin resistance [35]. It has been suggested that expansion of adipose tissue during weight gain leads to the recruitment of macrophages as well as the synthesis of various mediators by adipocytes as cytokines (TNF-α and IL-6) and adipocytokines (as adiponectin and leptin) which trigger of migraine headache [36,37]. The conjoint correlation between leptin and insulin is also supported by finding that leptin has a direct effect on insulin activity and regulation of total body sensitivity to insulin and triglyceride levels in lipodystrophic syndromes [37]. Hyperleptinemia in diabetic and obese subjects might be due to the stimulatory effect of insulin on adipose tissues stimulating more expression of obesity gene and more leptin secretion [37,38]. Therefore, the relationship between leptin and insulin should be revealed through their metabolic effects on endocrine disorders and MS. In contrast, Haffner et al. [38] reported low inter-ictal leptin concentrations in patients with migraine compared to their control subjects when unadjusted for fat mass. The authors suggested that hyperleptinemia and hyperinsulinemia might be due to the effect of oral hypoglycemic drugs (as sulphonyl urea and glibenclamide). These drugs are reported to increase the circadian leptin and insulin concentrations.

However, and despite the strength of our findings, this study had a main limitation, which is the higher frequency of migraine (3-fold increase in the prevalence of migraine compared to many previous studies). It might be due to small sample size which may create sample distortion bias. However, we explain this as follow: 1) our main aim was to determine the relationship between MS, leptin and migraine in a group of patients with MS and complain with headache, 2) we chose a cut off age of 55 years old, 3) our majority of patients were MS were obese/morbidly obese, had higher frequencies of IR, had higher measurements of SBP and DBP, with > 50% were uncontrolled on anti-diabetic and anti-hypertensive medications and all had chronic illnesses (migraine) and MS and its components

Conclusion

We conclude that: migraine is a very frequent comorbidity associated with MS. It mainly related to obesity (TBO and abdominal adiposity T2DM, IR HTN and hypercholesterolemia/dyslipidemia) Hyperleptinemia observed in patients with MS and having migraine is associated with obesity (TBO and abdominal adiposity) and insulin abnormalities. Delineation of migraine comorbidity in MS is important, because it can help to improve treatment strategies and the understanding of the possible pathophysiology of migraine.

Conflicts of Interest

We declare that this work has no conflict of interests. There is no involvement of sponsor for this work design, data collection, analysis, interpretation, drafting, nor the decision to submit this paper for publication. All are authors' responsibility.

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