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The Effect of Body Mass Index on Migraine Severity in Female Patients

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Abstract

Background: Both Migraine & nutritional disorders are common disorders with significant health & socioeconomic impacts. We aimed to determine the relationshipbetween BMI and migraine headache severity, frequency, and disability.

Methods: We collected 100 females migraineurs attending the out patient clinic of a tertiary neurology hospital. The patients were divided into four categories, based on BMI: underweight (<18.5), normal weight (18.5 to 24.9), overweight (25 to 29.9), andobese (>30). The headache frequency, severity, duration and disability using MIDAS score were assessed. Multivariate analyses were conducted.

Results: On multivariate analysis, overweight patients represented 62.82% of longer headache (>24 hr) group while they represented only 22.73% among shorter headache (<24 hr) group (OR= 8.09, 95%CI=2.15-30.51, p=0.002). BMI have lost their association in multivariate analysis. Multi-parity of 2-3 and ≥4 were more common in severe headache cases than mild/moderate cases (OR=9.89, 95%CI= 1.4-69.67, p=0.021and OR=11.37, 95%CI=1.36-95.1, p= 0.025 respectively). 70.73% of patients with severe headache were overweight compared with 42.37% of patients with mild/moderateheadache (OR= 4.32, 95%CI=1.34-13.96, p=0.014). About 60% of patients with high MIDAS grade had ≥4 parity compared with 17.86% of patients with low grade who had such parity (OR=7.78, 95%CI=1.27-47.61, p=0.026). The frequency of overweight and obese patients among high grade group was 68.18% and 18.18%, respectively comparedwith 42.86% and 5.36%, respectively among low grade group with significant differences (OR= 3.56, 95%CI=1.15-11.03, p= 0.027 and OR=7.22, 95%CI=1.1-47.14, p=0.039, respectively).

Conclusion: BMI does have significant effects on migraine headache severity and the resulting disability but its effects on headache frequency and duration was not supported.

1.1. Background:

Both Migraine & nutritional disorders are common disorders with significant health &socioeconomic impacts.

1.1.1 Migraine

Migraine is a common disabling primary headache disorder with two major types: 1) Migraine without aura which is a clinical syndrome characterized by headache with specific features and associated symptoms. Typical characteristics of the headache are unilaterality, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Theheadache comes in attacks lasting 4–72 hours. 2) Migraine with aura is primarily characterized by the transient focal neurological symptoms that usually precede or accompany the headache. Some patients experience a prodromal phase, occurring hours or days before the headache, and/or a postdromal phase that occur after headache resolution. Prodromal and postdromal symptoms include hypoactivity, hyperactivity, depression, cravings for particular foods, fatigue, repetitive yawning, and neck stiffness and/or pain [(1)].

1.1.2. Nutritional disorders

Nutritional status, on the other hand, is an important determinant of health & illness worldwide. Nutritional disorders are diseases that occur when a person's dietary intake does not contain the right amount of nutrients for healthy functioning, or when a personcannot correctly absorb nutrients from food. Nutrition disorders can be caused by undernutrition, over-nutrition (leading to obesity) or an incorrect balance of nutrients [(2)].Of these, undernutrition and obesity are important public health problems worldwide.

Overweight and obesity are defined as abnormal or excessive fat accumulation that maylead to health impairment. The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Globally, there hasbeen an increased intake of energy-dense foods that are high in sugars and fat; and an increase in physical inactivity because of the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization. Changes in dietary and physical activity patterns are often the result of societal and environmental changes associated with development and lack of supportive policies in sectors such as health, agriculture, urban planning, environment, transport, food processing, marketing, distribution, and education [(3)].

Nutritional status in adults is measured by body mass index (BMI) (formerly known asthe Quetelet index). BMI is divided into the following categories (applicable for adults
>20 years old): Underweight (Below 18.5), Normal weight (18.5–24.9), Pre-obesity (25.0–29.9), Obesity class I (30.0–34.9), Obesity class II (35.0–39.9) and Obesity classIII (Above 40) [(4)]. Of note, BMI is a measure of total body obesity (TBO) rather than abdominal obesity (AO) which have more precise prediction of metabolic & endocrinepathology. AO is measured by abdominal circumference.

Obesity is classically related to some common conditions like premature death, cardiovascular diseases, high blood pressure, osteoarthritis and diabetes. Of note,Overweight and obesity are linked to more deaths worldwide than underweight.

However, the relation of headache to obesity was probably first identified by Scher andcolleagues in 2003 [(5)]. More frank-titled studies were conducted in the following years with somewhat conflicting.

1.2.Epidemiology:

Migraine has a documented high prevalence and socio-economic and personal impacts. In the Global Burden of Disease Study 2010 (GBD2010), it was ranked as the third mostprevalent disorder in the world. In GBD2015, it was ranked the third-highest cause of disability worldwide in both males and females under the age of 50 years. The estimatedprevalence of migraine is about 15–18% of women and 6% of men occurring most commonly in men and women aged 25-55 years [8]. With regard to obesity and overweight, the prevalence has increased substantially in the last decades, and is now one of the leading risk factors for disease and death worldwide [9]. Although considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings. According to WHO global estimates in 2016, more than 1.9 billion adults aged 18 years and older were overweight.Of these over 650 million adults were obese. 39% of adults aged 18 years and over (39%of men and 40% of women) were overweight. Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. The worldwide obesity prevalence nearly tripled between 1975 and 2016. Globally there are more people who are obese than underweight – this occurs in every region except parts of sub-Saharan Africa and Asia. In Iraq, 2015 nationally representative cross-sectional survey of 3,916 persons 18-years and older found that 31.8% of participants were overweight and 33.9% of them were obese [10].

1.3. Pathophysiology

Although the origin of migraine neuronal mechanisms that underlie the primary condition in susceptible people is not known yet, it is widely accepted that migraine involves sensitization of trigeminovascular pathways, dysfunction of subcortical structures (brain stem and diencephalic centres and primary dysregulation of sensory processing [11,12]. Other suggestionsconsider migraine as a brain state of altered excitability [13].

Migraine's premonitory symptoms; which occur many days before the headache phase;are neurological symptoms of non-nociceptive nature, which points to a brain origin of these symptoms.

The genetic susceptibility or predisposition of migraine is strongly supported by the family studies that pointed to genetic predisposition and the multiple identified genes responsible for familial hemiplegic migraine (which increases the likelihood of severeaura symptoms) [14,15].

While the above-mentioned responses are often explained by the term excitability, theclinical symptoms of migraine would be explained by a state of hypersynchrony [16].

1.4. Clinical features

Migraine symptomatology can be classified into 4 phases: 1) premonitory migraine phase, 2) aura phase, 3) headache phase, and 4) migraine postdrome. These phases mayoccur in a linear sequential order but in most cases, they show a significant overlap.

Nonpainful symptoms occurring hours to days before the onset of headache defines the **premonitory or prodromal phase of migraine**.

These symptoms can include neck stiffness, yawning, thirst, and increased frequency of micturition. Premonitory symptoms precede the headache or during headache itself, and similar symptoms can present in the postdrome after headache resolution. It is important to clinically recognize these symptoms to ensure early and effective attack management. The migraine prodromal phase is likely

more common than is currently reported in the literature [17].

The migraine **aura** (transient neurological deficits) occurs in about one-third of migraineurs in context of their migraine attacks. It is defined as one or more transient, fully reversible neurological deficits, of which at least one has to have a unilateral localization, that develop over 5 min or more and of which each deficit lasts between 5and 60 minutes.

The typical **headache phase** manifests in a unilateral frontotemporal (location), pulsating (quality), moderate or severe (intensity) head pain occurring in attacks lasting 4–72 hours, aggravated by routine physical activity and associated with nausea and/or photophobia and phonophobia. A subset of otherwise typical patients has facial location of pain. Migraine attacks associations can include cranial autonomic symptoms and symptoms of cutaneous allodynia. A minority (<10%) of women have attacks of migraine in association with the majority of their menstrual cycles; most such attacks arewithout aura. Attacks during menstruation tend to be longer and accompanied by more severe nausea than attacks outside the menstrual cycle. In children and adolescents (agedunder 18 years), attacks may last 2–72 hours. It is more often bilateral than is the case inadults; unilateral pain usually emerges in late adolescence or early adult life. Occipital headache in children is rare.

Very frequent migraine attacks are distinguished as chronic migraine. Because it is moreprone to accelerate with frequent use of symptomatic medications, it is usually associated with medication overuse, leading to co-occurrence of medication-overuse headache [1].

With regard to **migraine postdrome**, the symptoms can broadly be grouped into neuropsychiatric, gastrointestinal, sensory, and general systemic symptoms [18]. However, the most typically reported symptoms include tiredness, concentration difficulty, and neck stiffness [19]. The average duration of the postdrome ranges from 18to 25.2 hours. Postdrome symptoms also appear to be common, with 81% to 94% of patients reporting these symptoms in various studies [18].

Migraine with aura and severe pain are risk factors for experiencing prodromal and postdromal migraine symptoms, while preventive therapies were protective, especially for prodromal symptoms [20]. However, the severity of the migraine was not associatedwith the duration of the postdrome [19].

With regard to nutritional disorders, the clinical picture intensity is directly proportionalto severity; weather obesity or undernutrition. There are well established associated co- morbidities with obesity and overweight including hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, congestive heart failure, strokes, osteoarthritis, gallstones, sleep apnoea, cancers, reproductive issues in females and psychological aspects.

Among the less established associated comorbidities is chronic daily headache, under which the migraine headache in susceptible people would be tested in this study.

1.5. Treatment

The approach to migraine is directed by attack severity, associated nausea and vomiting, wether outpatient or medical care facility treatment, and patient-specific factors, such as the presence of vascular risk factors and drug preference.

Migraine treatments inculde abortive and prophylactic therapy.

1.5.1. Abortive (symptomatic) treatment:

The **abortive** (symptomatic) therapy of migraine ranges from the use of simple analgesics to triptans,

antiemetics, or the less commonly used dihydroergotamine. Abortive treatments are usually more effective if they are given early in the course of theheadache; a large single dose tends to work better than repetitive small doses. It should be kept in mind that many oral agents may be ineffective during acute migraine attacks because of poor absorption secondary to migraine-induced gastric stasis.

For **mild to moderate** migraine attacks not associated with vomiting or severe nausea, first choice would be simple analgesics (NSAIDs, acetaminophen) or combination analgesics because they are effective, more affordable, and having better adverse effect profile than migraine-specific agents such as triptans or ergots [21]. Antiemetic drugs (oral or rectal) should be added to simple analgesics when significant nausea or vomitingaccompany such attacks.

Oral triptans are reserved for moderate to severe migraine attacks not associated withvomiting or severe nausea. When such severe attacks are complicated by vomiting orsevere nausea, nonoral migraine-specific medications (including subcutaneous sumatriptan, nasal sumatriptan and zolmitriptan, nonoral antiemetic agents, and parenteral dihydroergotamine) are indicated.
Patients who present with migraine in **emergency** settings, the treatment follows the same principles as treatment in nonurgent settings outlined above, with the obvious difference that parenteral medications are more readily available. Reasonable options, with evidence of efficacy from randomized trials include: [22] subcutaneous sumatriptan, intravenous (IV) antiemetics (metoclopramide, prochlorperazine, chlorpromazine), IV dihydroergotamine combined with IV metoclopramide, and IV or intramuscular (IM) ketorolac.
Parenteral treatment with dexamethasone in the acute setting was found to reduce therate of early headache recurrence [23].
Opioids and barbiturates shouldn't be used for the treatment of migraine, except as afinal resort.

1.5.2. Preventive treatment:

Indications of preventive migraine treatment may include: frequent or long-lasting migraine headaches, migraine attacks that cause significant disability or diminished quality of life despite appropriate acute treatment, contraindication to acute therapies, failure of acute therapies, serious adverse effects of acute therapies, risk of medication overuse headache, and menstrual migraine [24, 25]. While the precise frequency or duration of migraine headaches that would prompt preventive therapy are not strictly defined, more than four headaches per month or headaches that last longer than 12 hoursare generally considered reasonable thresholds.

A number of drug classes are used for the prevention of migraine including beta-blokers(metoprolol, propranolol, and timolol), antidepressants (amitriptyline and venlafaxine) and anticonvulsants (valproate and topiramate).
Alternatives include calcium channel blockers including verapamil and flunarizine,which may be less effective but are generally safe and well tolerated.
The choice among preventive agents of comparable efficacy should be individualizedaccording to patient-specific characteristics, comorbid conditions, medication side effects, and patient preferences.
Regardless of the drug chosen, some general principles may improve the success rate ofpreventive migraine therapy and reduce complications. These include [26]:
starting the drug at a low dose, giving each treatment an adequate trial, avoidance ofinterfering,

overused, and contraindicated drugs, regular therapy re-evaluation, informing any woman of childbearing potential about any potential risks, involving patients in their care to maximize compliance.

Migraine headaches may improve independent of treatment. If the headaches are wellcontrolled, slow taper of the drug, if possible, is recommended. Many patients experience continued relief with either a lower dose or cessation of the medication.

Preventive migraine therapy requires a sustained commitment on the part of the patientand physician to achieve benefit.

In general, preventive drugs are started at a low dose and the dose is gradually increaseduntil therapeutic benefit develops, the maximum dose is reached, or side effects becomeintolerable. Benefit is often noted first at four weeks and can continue to increase for three months.

Nonpharmacologic measures that may be beneficial for migraine headache prevention include aerobic exercise, biofeedback, other forms of relaxation training, cognitive- behavioral therapies, acupuncture, and transcutaneous electrical nerve stimulation [27-31].

1.6. Literature review

In 2003, Scher and colleagues probably first identified an association between obesity and frequent headache in a 1932 participants' population-based study [5]. More specifiedto migraine, the study by Horev et al in 2005 found that morbidly obese women had unusually high incidence of migraine with aura; and attributed that to extraovarian production of estrogen and estradiol in the adipose tissue [32]. Later studies draw attention and focused on the potential relation between overweight and migraine headache characteristics such as severity, frequency, duration of attacks and disability related to migraine.

The population based study of Bigal et al. at 2006 concluded the above mentioned associations, (33) while his later works emphasized that the association was relatively specific only for chronic migraine (34,35). B. L. Peterlin et al added other factors to refine the association between migraine and obesity. they tested the effect of age, genderand fat distribution on migraine prevalence in 21,783 participants. Totally or abdominally obese men and women younger than 55 years found to have increased migraine prevalence. In older men, migraine is not associated with obesity but, strikingly; older abdominally obese women found to have lower prevalence of migraine independent of total body obesity [36].

Although the association between BMI and migraine was not confirmed by all studies, itbecame an accepted concept that many review articles had addressed it [37-44]. Other reviews crossed to the opposite bank and suggested weight reduction and life-style modifications as a possible remedy [45-47].

Finally, two meta-analyses and one systematic review came to an agreement that obesepatients had a higher risk of migraine in comparison to both normal weight and non- obese individuals. Moreover, the meta-analysis conducted by Ornello et al found that female patients in reproductive age have the strongest association between obesity andmigraine prevalence [48, 49, 40].

2. Aim of the study

The aim of this study is to determine how nutritional status (as measured by BMI) isassociated with migraine headache characteristics (severity, frequency, duration anddisability) in a random sample of female patients.

METHODS AND PATIENTS

3.1. Data collection

Among hundreds of female patients with headache attended the outpatient clinic at Neuroscience hospital, we collected one hundred patients who exclusively fulfilled theInternational Classification of Headache Disorders 3rd edition (ICHD-III) diagnostic criteria for migraine without aura.

Headache frequency was divided into chronic and episodic migraine using the ICHD-III definition of chronic migraine (headache occurring on 15 or more days/month for more than three months, which, on at least eight days/month, has the features of migraine headache) (1). Duration of headache attacks was categorized into 3 groups (4-24 hr, 24- 72 hr, and >72 hr). Headache severity was estimated using the verbal pain score between1 (no headache) and 10 (worst headache possible) and was categorized into 3 groups: mild (1-3), moderate (4-6) and severe (7-10). Migraine disability was estimated using the Migraine Disability Assessment (MIDAS) scale questionnaire (50).
MIDAS Grades defined as following: 0-5= grade I (Little or No Disability), 6-10 =grade II (Mild Disability), 11-20 = grade III (Moderate Disability), >21 = grade IV(Severe Disability).

We performed complete medical examination, including anthropometric measurements.

Height and weight were measured with standardized weight scales and metric bands. The patients wore no shoes. Height was measured to the nearest 1.0 cm, and weight tothe nearest 0.5 kg. BMI was defined as weight/height^2 and computed in kg/m^2.

BMI status in adults were categorized into four TBO (total body obesity) levels; underweight (BMI < 18.5), normal weight (18.5 to 25), overweight (25 ≤ BMI < 30) and obese (BMI ≥30) in accordance to World Health Organization (WHO) definitions
(4).

3.2. Statistical Analysis

Data were analyzed using IBM SPSS version 25 (SPSS Inc., Chicago, Illinois, USA). The descriptive data was reported in number and percentage form for categorical data, and mean and standard deviation for continuous data. Differences were evaluated using Student's t test (whenever there were two groups) of analysis of variance (whenever there were more than two groups) for continuous parametric data, and Pearson chi-squared test for categorical data. Univariate and multivariate logistic regression were performed to identify independent risk factors for duration and frequency of migraine and MIDAS score. From these analyses, the odds ratio (OR) and its corresponding 95% confidence interval (CI) were calculated. A P value of ≤ 0.05 was considered statistically significant.

Baseline Characteristics of the Patients at Presentation

4.1. Demographic Characteristics

The present study included 100 patients with migraine. The mean age of the patients at presentation was 35.74±10.82 years (range 19-58 years). About three-fourth of theincluded women were married. The mean BMI was 25.91±3.51 kg/m^2 (range 19-35 kg/m^2). The frequency of women with 0-1, 2-3 and ≤4 parities (defined as the number oftimes that the lady has given birth to a fetus with a gestational age of 24 weeks or more, regardless of whether the child was born alive or was stillborn) were 34%, 30% and 36%, respectively. Only 3% of the women were smokers (Table 4-1).

Table 4-1: Demographic Characteristics of the patients (n=100)

Variables	Value
Age, years	
Mean±SDRange	35.74±10.82 19-58
Marital status Single Married Divorced Widow	 22(22%) 74(74%) 2(2%) 2(2%)
Body mass index, kg/m^2	
Mean±SDRange	25.91±3.51 19-35
Parity (number of births)	
0-1 2-3 ≥4	34(34%) 30(30%) 36(36%)
Smoking	
NO YES	97(97%) 3(3%)

SD: standard deviation

4.2. Clinical Characteristics

Hypertension, diabetes and hormonal therapy was reported in 8%, 13% and 18%, of the patients respectively. In about two-third of the patients the duration of headache was 24-72 hrs, while the vast majority of patients (85%) had episodic frequency of the headache. The severity of headache was mostly moderate (53%) or severe (41%).

MIDAS grade was II or III in 39% and 36% of cases (Table 4-2).

Table 4-2: Clinical characteristics of patients (n=100)

Variables	Value
Hypertension	
No Yes	92(92%) 8(8%)
Diabetes	
No Yes	87(87%) 13(13%)
Hormonal therapy	
No Yes	82(82%) 18(18%)
Duration of headache	
4-24 hrs	22(22%)
24-72 hrs	63(63%)
>72 hr	15(15%)
Frequency	
EpisodicChronic	85(85%) 15(15%)
Severity Mild Moderate	
Severe	6(6%) 53(53%) 41(41%)
MIDAS grade	
I II IIIIV	17(17%) 39(39%) 36(36%) 8(8%)

SD: standard deviation, MIDAS: Migraine Disability Assessment

4.3. Categorization of Body Mass Index

According to WHO classification, 35 (35%) of the patients had normal body weight,54(54%) were overweight and 11(11%) were obese (Figure 4-1).

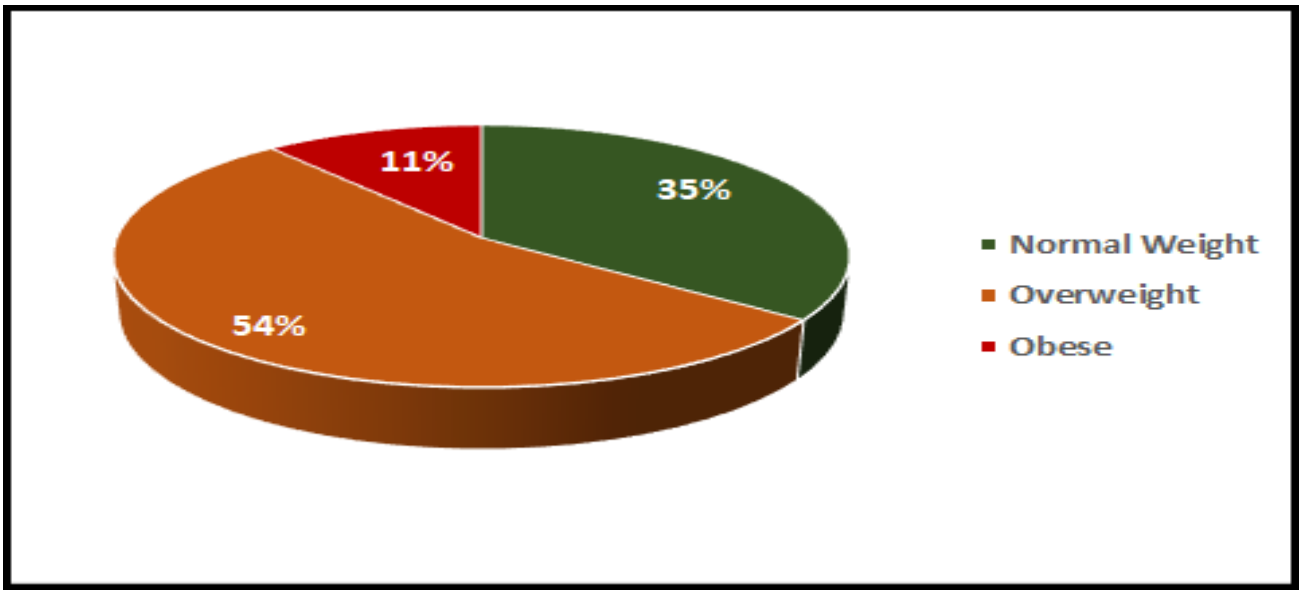

Figure 4-1: Categorization of BMI

4.3.1. Demographic Characteristics Of Subjects By BMI Grade

Normal weight patients showed lower mean age (29.31±8.83 years) than either overweight (38.28±10.77 years) or obese patients (43.73±5.44 years) with a highly significant differences. The frequency of married women was higher among obesepatients (100%) than overweight (77.78%) or normal weight patients (60%) with significant differences. Similarly, obese patients demonstrated higher frequency of women with ≥4 parities than other groups with highly significant differences (Table 4- 3).

Table 4-3: Demographic Characteristics Of Subjects By BMI Grade

Variables	Normal Weight (n=35)	Overweight (n= 54)	Obese(n=11)	p-value
Age, years	29.31±8.83[a]	38.28±10.77[b]	43.73±5.44[b]	**<0.001**
Marital status Single/ divorced/widow Married	 14(40%) 21(60%)	 12(22.22%) 42(77.78%)	 0(0%) 11(100%)	**0.020**
Number of births 0-1 2-3 ≥4	 19(54.29%) 13(37.14%) 3(8.57%)	 13(24.07%) 16(29.63%) 25(46.30%)	 2(18.18%) 1(9.09%) 8(72.72%)	**<0.001**
Smoking NO YES	 35(100%) 0(0%)	 51(94.44%) 3(7.40%)	 11(100%) 0(0%)	0.268

Different small letters indicate significant differences

4.3.2. Association of Clinical Characteristics with BMI

The incidence of diabetes and hormonal therapy use more common in obese patients (54.55%, 36.36%, respectively) than either overweight (9.26% and 22.22%, respectively) or normal weight patients (5.71% and 5.71%, respectively) with significantdifferences. Furthermore, parameter related to headache (duration, frequency, severity and MIDAS grade), in general, tend to be higher in obese patients than overweight or normal patients with significant differences (Table 4-4).

Table 4-4: Association of Clinical Characteristics with BMI

Variables	NormalWeight (n=35)	Overweight (n= 54)	Obese(n=11)	p-value
Hypertension No Yes	 34(97.14%) 1(2.86%)	 48(88.89%) 6(11.11%)	 10(90.90%) 1(9.09%)	0.371
Diabetes No Yes	 33(94.29%) 2(5.71%)	 49(90.74%) 5(9.26%)	 5(45.45%) 6(54.55%)	**<0.001**
Hormonal therapy No Yes	 33(94.29%) 2(5.71%)	 42(77.78%) 12(22.22%)	 7(63.63%) 4(36.36%)	**0.034**
Duration of headache 4-24 hrs 24-72 hrs >72 hr	 16(45.71%) 17(48.57) 2(5.71%)	 5(9.26%) 38(70.37%) 11(20.37%)	 1(9.09%) 8(72.72%) 2(18.18%)	**0.001**
Frequency **ofheadache** EpisodicChronic	 33(94.29%) 2(5.71%)	 45(83.88%) 9(16.67%)	 7(63.63%) 4(36.36%)	**0.04**
Severity of headache Mild ModerateSevere	 3(8.57%) 26(74.29%) 6(17.14%)	 3(5.55%) 22(40.74%) 29(53.70%)	 0(0%) 5(45.45%) 6(55.55%)	**0.01**
MIDAS score I II III IV	 10(28.57%) 19(54.29%) 5(14.29%) 1(2.86%)	 7(12.96%) 17(31.48%) 25(46.30%) 7(12.96%)	 0(0%) 3(27.27%) 8(72.72%) 0(0%)	**<0.001**

MIDAS: Migraine disability assessment score.

4.3.3.Association of Demographic Factors with the Duration of Headache

Mean age of patients in the longer duration of headache (>72) was 41.27±9.3 yearswhich was significantly higher than that of shorter durations. Likewise, longer durationheadache associated with higher frequency of married women, parity of ≥4 and obesityor overweight than those with shorter duration with significant differences (Table 4-5)

Table 4-5: Association of demographic factors with the duration of headache

Variables	4-24 hrs(n=22)	24-72 hrs (n=63)	>72 hrs (n=15)	p-value
Age, years	27.41±7.88	37.33±10.57[b]	41.27±9.3[b]	**<0.001**
Marital status				
Single/ divorced/widow	19(86.36%)	17(26.98%)	0(0%)	**<0.001**
Married	13(59.09)	46(73.02%)	15(100%)	
Number ofbirths				
0-1	13(59.09)	21(33.33%)	0(0%)	**<0.001**
2-3	4(18.18%)	23(36.51%)	3(20%)	
≥4	5(22.73%)	19(30.16%)	12(80%)	
Smoking				
NO	21(95.45)	61(96.83%)	15(100%)	0.722
YES	1(4.55%)	2(3.17%)	0(0%)	
BMI				
Normal weight	16(72.73%)	17(26.98%)	2(13.33%)	**0.001**
Overweight	5(22.73%)	38(60.32%)	11(73.33%)	
Obese	1(4.55%)	8(12.70%)	2(13.33%)	

Different small letters indicate significant differences. BMI: body mass index.

4.3.4.Association of Clinical Factors with the Duration of Headache

All diabetic women occurred within medium duration group with significant differences compared with long or short duration. On the other hand, the chronic frequency severe headache and grade IV MIDAS were more common among longer duration groups than other groups with highly significant differences (Table 4-6).

Table 4-6: Association of clinical factors with duration of headache

Variables	4-24 hrs (n=22)	24-72 hrs (n=63)	>72 hrs (n=15)	p-value
Hypertension				0.078
No	22(100%)	55(87.30%)	15(100%)	
Yes	0(0%)	8(12.70%)	0(0%)	
Diabetes				**0.012**
No	22(100%)	50(79.37%)	15(100%)	
Yes	0(0%)	13(20.63%)	0(0%)	
Hormonal therapy				0.167
No Yes	20(90.91%) 2(9.09%)	52(82.54%) 11(17.46%)	10(66.67%) 5(33.33%)	
Frequency of headache				**<0.001**
EpisodicChronic	22(100%) 0(0%)	58(92.06%) 5(7.94%)	5(33.33%) 10(66.67%)	
Severity of headache				**<0.001**
Mild Moderate	6(27.27%) 14(63.64%)	0 35(55.55%)	0(0%) 4(26.67%)	
Severe	2(9.09%)	28(44.44%)	11(73.33%)	
MIDAS score				**<0.001**
I II III	13(59.09%)	4(6.35%)	0(0%)	
IV	8(36.36%)	28(44.44%)	3(20%)	
	1(4.55%)	26(41.27%)	9(60%)	
	0	5(7.94%)	3(20%)	

MIDAS: migraine disability assessment score.

4.3.5.Association of Demographic Factors with Frequency of Headache

Nine patients (60%) of patients with chronic headache had ≥4 party compared with 31.76% in episodic group with a significant difference. Obesity and overweight were more common in chronic headache group than episodic group with a significant difference (Table 4-7)

Table 4-7: Association of demographic factors with frequency of headache

Variables	Episodic (n=85)	Chronic(n=15)	p- value
Age, years	35.4±11.0	37.67±9.9	0.457
Marital status Single/ divorced/widow Married	24(28.24%) 61(71.76%)	2(13.33%) 13(86.67%)	0.225
Number of births 0-1 2-3 ≥4	 29(34.12%) 29(34.12%) 27(31.76%)	 5(33.33%) 1(6.67%) 9(60%)	**0.049**
Smoking NO YES	 82(96.47%) 3(3.53%)	 15(100%) 0(0%)	0.460
BMI Normal weight Overweight Obese	 33(38.82%) 45(52.94%) 7(8.24%)	 2(13.33%) 9(60%) 4(26.67%)	**0.040**

BMI: body mass index.

4.3.6. Association of clinical factors with frequency of headache

The clinical factor with was significantly associated with the frequency of headache was the duration, in which two-third (66.67%) of patients with chronic headachedemonstrated longer duration compared with only 5.88% of patients with episodicheadache who had such duration (Table 4-8)

Table 4-8: Association of clinical factors with frequency of headache

Variables	Episodic (n=85)	Chronic (n=15)	p-value
Hypertension			
No Yes	77(90.59%) 8(9.41%)	15(100%) 0(0%)	0.215
Diabetes			
No Yes	74(87.09%) 11(12.94%)	13(86.67%) 2(13.33%)	0.967
Hormonal therapy			
No Yes	72(84.71%) 13(15.29%)	10(66.67%) 5(33.33%)	0.094
Duration of headache 4-24 hrs 24-72 hrs >72 hr	22(25.88%) 58(68.24%) 5(5.88%)	0(0%) 5(33.33%) 10(66.67%)	**<0.001**
Severity of headache			
Mild Moderate Severe	6(7.06%) 48(56.47%) 31(36.47%)	0(0%) 5(33.33%) 10(66.67%)	0.075
MIDAS score			
I II III IV	17(20%) 35(41.18%) 27(31.76%) 6(7.06%)	0(0%) 4(26.67%) 9(60%) 2(13.33%)	0.068

MIDAS: migraine disability assessment score.

4.3.7.Association of Demographic Factors with MIDAS Grade

Due to small number in some grades, MIDAS grade was categorized in to two grades: low I-II and high III-IV. Interestingly, patients in high grade group had significantly older age than those in low grade group (39.59±10.46 years versus 32.71±10.2). Likewise, the frequency of married women, and those with ≥ 4 party were higher in highgrade than low grade group with significant difference. Obesity and overweight were more common in high grade group than low grade group with a significant difference(Table 4-9).

Table 4-9: Association of demographic factors with MIDAS grade

Variables	I-II (n=56)	III-IV (n=44)	p-value
Age, years	32.71±10.2	39.59±10.46	**0.001**
Marital status Single/ divorced/widow Married	20(35.71%) 36(64.29%)	6(13.37%) 38(86.36%)	**0.012**
Number of births 0-1 2-3 ≥4	27(48.21%) 19(33.93%) 10(17.86%)	7(15.91%) 11(25%) 26(59.09%)	**<0.001**
Smoking NO YES	54(96.43%) 2(3.57%)	43(97.73%) 1(2.27%)	0.706
BMI Normal weight OverweightObese	29(51.79%) 24(42.86%) 3(5.36%)	6(13.37%) 30(68.18%) 8(18.18%)	**<0.001**

BMI: body mass index.

4.3.8.Association of Clinical Factors with the MIDAS Grade

Hypertension was encountered in 13.64% in high grade group compared with 3.57% inlow grade group with a highly significant difference (table 4-10).

Table 4-10: Association of clinical factors with the MIDAS grade

Variables	I-II (n=56	III-IV(n=44)	p-value
Hypertension			
No Yes	54(96.43%) 2(3.57%)	38(86.36%) 6(13.64%)	**0.001**
Diabetes			
No Yes	50(89.29%) 6(10.71%)	37(84.09%) 7(15.91%)	0.443
Hormonal therapy			
No Yes	48(85.71%) 8(14.29%)	34(77.27%) 10(22.73%)	0.275
Duration of headache			
4-24 hrs 24-72 hrs >72 hr	21(37.5%) 32(57.14%) 3(5.36%)	1(2.27%) 31(70.45%) 12(27.27%)	**<0.001**
Frequency of headache			
EpisodicChronic	52(92.86%) 4(7.14%)	33(75%) 11(25%)	**0.013**
Severity of headache			
Mild Moderate Severe	6(10.71%) 39(69.64%) 11(19.64%)	0(0%) 14(31.82%) 30(68.18%)	**<0.001**

4.3.9.Association of Demographic Factors with Severity of Headache

As there was a relatively low number of cases with mild headache this group was merged with a moderate group. Each of older age, married women, party ≥4 and higher BMI were significantly associated with severe headache (Table 4-11).

Table 4-11: Association of demographic factors with severity of headache

Variables	Mild/Moderate(n=59)	Severe(n=41)	p-value
Age, years	33.05±11.05	39.61±9.32	**0.002**
Marital status Single/ divorced/widow Married	22(37.29%) 37(62.71%)	4(9.76%) 37(90.24%)	**0.002**
Number of births 0-1 2-3 ≥4	 30(50.85%) 15(25.42%) 14(23.73%)	 4(9.76%) 15(36.59%) 22(53.66%)	**<0.001**
Smoking NO YES	 58(98.31%) 1(1.69%)	 39(95.12%) 2(4.88%)	0.359
BMI Normal weight Overweight Obese	 29(49.15%) 25(42.37%) 5(8.47%)	 6(14.63%) 29(70.73%) 6(14.63%)	**0.002**

BMI: body mass index.

4.3.10.Association of Demographic Factors with Severity of Headache

No significant difference in the frequency of HTN, DM or HRT between patients with mild/moderate of severe headache (Table 4-12).

4.4.Multivariate Analysis

In order to find if BMI is an independent risk factor for migraine severity, multivariate analysis was conducted. All variables that give a significant (or near significant association) with migraine severity were entered this analysis. Age was categorized in tocategories based on the general mean.

Table 4-12: Association of clinical factors with severity of headache

Variables	Mild/Moderate (n=59)	Severe(n=41)	p-value
Hypertension			
No Yes	56(94.92%) 3(5.08%)	36(87.8%) 5(12.2%)	0.197
Diabetes			
No Yes	49(83.05%) 10(16.95%)	38(92.68%) 3(7.32%)	0.159
Hormonal therapy			
No Yes	48(81.36%) 11(18.64%)	34(82.93%) 7(17.07%)	0.841
Frequency of headache			
EpisodicChronic	54(91.53%) 5(8.47%)	31(75.61%) 10(24.39%)	**0.028**
Duration of headache			
4-24 hrs 24-72 hrs >72 hr	20(33.7%) 35(59.32%) 4(6.78%)	2(4.88%) 28(68.29%) 11(26.83%)	**<0.001**
MIDAS score			
I II III IV	17(28.81%) 28(47.46%) 11(18.64%) 3(5.08%)	0(0%) 11(26.83%) 25(60.98%) 5(12.2%)	**<0.001**

MIDAS: migraine disability assessment score.

4.4.1.Multivariate analysis of association of demographic and clinical factors withthe duration of headache

For this analysis the duration of headache was categorized in to two groups: short (4-24hrs) and long (>24 hrs).

Most demographic factors (including age, marital status, parity and diabetes) were no longer had a significant association with the duration of headache. The only significant association was that the frequency of overweight in long duration group was 62.82%

compared with 22.73% among short duration group (OR= 8.09, 95%CI=2.15-30.51, p=0.002). Furthermore, 10.26% of patients with long duration had hypertension versus none among patients with short duration had this comorbidity (OR= 3.7, 95%CI=1.12- 24.5, p= 0.034) as shown in table 4-13.

Table 4-13: Multivariate analysis of association of demographic and clinical factors with the duration of headache

Variables	4-24hrs (n=22)	≥24 hrs (n=78)	p- value	OR(95%CI)
Age, years				
≤35	17(77.27%)	33(42.31%)	0.116	1.0
>35	5(22.73%)	45(57.69%)		1.89(0.41-8.86)
Marital status				
Single/ divorced/widow	9(40.91%)	17(21.79%)	0.112	1.0
Married	13(59.09%)	61(78.21%)		1.24(0.21-7.38)
Number of births				
0-1	13(59.09%)	21(26.92%)	0.240	1.0
2-3	4(18.18%)	26(33.33%)	0.979	3.13(0.47-21.04)
≥4	5(22.73%)	31(39.74%)	0.812	0.97(0.11-8.55)
BMI				
Normal weight	16(72.72%)	19(24.36%)	**0.008**	1.0
Overweight	5(22.73%)	49(62.82%)	**0.002**	**8.09(2.15-30.51)**
Obese	1(4.55%)	10(12.82%)	0.492	2.51(0.18-34.43)
Hypertension				
No Yes	22(100%)	70(89.74%)	**0.034**	**1.0**
	0(0%)	8(10.26%)		**3.7(1.12-24.5)**
Diabetes				
No Yes	22(100%)	65(83.33%)	0.109	1.0
	0(0%)	13(16.67%)		2.6(0.87-21.88)

BMI: body mass index.

4.4.2.Multivariate analysis of the association of demographic and clinical factorswith frequency of headache

All factors that showed a significant association with chronic headache in univariate analysis including BMI have lost their association in multivariate analysis (Table 4-14).

Table 4-14: Multivariate analysis of the association of demographic and clinicalfactors with frequency of headache

Variables	Episodic (n=85)	Chronic (n=15)	p- value	OR(95%CI)
Number of births				
0-1	29(34.12%)	5(33.33%)	0.269	1.0
2-3	29(34.12%)	1(6.67%)	0.193	1.0(0.25-4.06)
≥4	27(31.76%)	9(60%)	0.119	0.17(0.02-1.56)
BMI				
Normal weight	33(38.82%)	2(13.33%)	0.239	1.0
Overweight	45(52.94%)	9(60%)	0.240	2.85(0.49-16.45)
Obese	7(8.24%)	4(26.67%)	0.091	6.09(0.75-49.57)
Hormonal therapy			0.414	
No	72(84.71%)	10(66.67%)		1.0
Yes	13(15.29%)	5(33.33%)		2.51(0.15-2.17)

BMI: body mass index.

4.4.3.Multivariate analysis of association of demographic and clinical factors withseverity of headache

According to this analysis each of multi-parity and BMI are independent risk factors for the severity of headache. Multi-parity of 2-3 and ≥4 were more common in severe cases than mild/moderate cases (OR=9.89, 95%CI= 1.4-69.67, p=0.021 and OR=11.37, 95%CI=1.36-95.1, p= 0.025 respectively). Furthermore, 70.73% of patients with severe headache were overweight compared with 42.37% of patients with mild/moderate headache (OR= 4.32, 95%CI=1.34-13.96, p=0.014) as shown in table 4-15.

Table 4-15: Multivariate analysis of association of demographic and clinical factorswith severity of headache

Variables	Mild/Moderate(n=59)	Severe(n=41)	p- value	OR(95%CI)
Age, years				
≤35	34(57.63%)	16(39.02)	0.394	1.0
>35	25(42.37%)	25(60.98%)		1.63(0.53-5.01)
Marital status				
Single/ divorced/widow	22(37.29%)	4(9.76%)	0.129	1.0
Married	37(62.71%)	37(90.24%)		1.24(0.17-8.87)
Number of births				
0-1	30(50.85%)	4(9.76%)	0.060	1.0
2-3	15(25.42%)	15(36.59%)	**0.021**	**9.89(1.4-69.67)**
≥4	14(23.73%)	22(53.66%)	**0.025**	**11.37(1.36-95.1)**
BMI				
Normal weight	29(49.15%)	6(14.63%)	**0.047**	1.0
Overweight	25(42.37%)	29(70.73%)	**0.014**	**4.32(1.34-13.96)**
Obese	5(8.47%)	6(14.63%)	0.099	4.5(0.75-26.8)

BMI: body mass index.

4.4.4.Multivariate analysis of Association of demographic and clinical factors withMIDAS score

Multi-parity and BMI were also independent risk factor for high MIDAS grade. About 60% of patients with high MIDAS grade had ≥4 parity compared with 17.86% ofpatients with low grade who had such parity (OR=7.78, 95%CI=1.27-47.61, p=0.026). The frequency of overweight and obese patients among high grade group was 68.18% and 18.18%, respectively compared with 42.86% and 5.36%, respectively among low grade group with significant differences (OR= 3.56, 95%CI=1.15-11.03, p= 0.027 and OR=7.22, 95%CI=1.1-47.14, p=0.039, respectively) as shown in table 4-16.

Table 4-16: Multivariate analysis of Association of demographic and clinicalfactors with MIDAS score

Variables	I-II (n=56)	III-IV (n=44)	p-value	OR(95%CI)
Age, years				
≤35	34(60.71%)	16(26.36%)	0.311	1.0
>35	22(39.29%)	28(63.64%)		1.88(0.55-6.41)
Marital status				
Single/ divorced/widow	20(35.71%)	6(13.64%)	0.174	1.0
Married	36(64.29%)	38(86.36%)		1.03(0.18-5.76)
Number ofbirths	27(48.21%)	7(15.91%)	**0.031**	**1.0**
0-1	19(33.93%)	11(25%)	0.520	1.76(0.31-9.95)
2-3	10(17.86%)	26(59.09%)	**0.026**	**7.78(1.27-47.61)**
≥4				
BMI				
Normal weight	29(51.79%)	6(13.37%)	**0.046**	**1.0**
Overweight	24(42.86%)	30(68.18%)	**0.027**	**3.56(1.15-11.03)**
Obese	3(5.36%)	8(18.18%)	**0.039**	**7.22(1.1-47.14)**
Hypertension				
No Yes	54(96.43%)	38(86.36%)	0.140	1.0
	2(3.57%)	6(13.64%)		4.98(0.59-41.98)

BMI: body mass index.

5. Discussion

In this cross-sectional study that performed to address migraine headache characteristicsand disability, we found the following: higher BMI and parity are independent risk factors for both headache severity and higher MIDAS score. Such finding remained significant even after adjusting for other demographic and clinical factors. Although BMI did not affect the headache duration in univariate analysis, logistic multivariate analysis revealed that overweight is associated with a statistically significant longer headache duration as compared to obese patients. In addition, we found no statistical significance between BMI and headache frequency.

According to Ashkenazi et al., migraine exhibit a sexual dimorphism; and have been linked to estrogen and the hormonal life-cycle of women. So that, we included femalepatients and excluded male patients in an attempt to magnify the results [51].

Although waist circumference has been suggested as a better measure of abdominal fat than BMI, and may be better suited to predict future health risks; [52] TBO, rather than AO, may be a better measure of obesity in relation to migraine [53]. In addition to fulfillment of ICHD-III criteria, we included only those

who have active disease and notreceiving prophylactic migraine therapy in order to further clarify the results.

Some of our patients have other clinical comorbidities that could contribute indirectly totheir headache, namely: diabetes, hypertension, and hormonal therapy in addition to smoking. Of those, only hypertension was found to be a risk factor for higher MIDAS score in the univariate analysis. After multivariate analysis, hypertension was associatedwith longer headache duration.

Plenty of studies have addressed the relation between BMI and the severity, frequency,duration and disability of migraine headache without uniform conclusions. One population-based study that recruited 4290 migraineurs concluded that TBO and AO was associated with higher frequency of migraine headache attacks, although such conclusion was limited to women younger than 50 years old [53]. Another population survey in China (included 300 migraineurs out of 1327 primary headache patients) found significant effect of BMI on headache frequency, but not severity or duration [54]. A cross-sectional study by Winter et al., that recruited 9195 ladies with active migraine and reached to the same result [55]. In this study, such finding was not supported probably because of low number of chronic as compared to episodic migraine group thataffected the statistical power (however, lowest p value of 0.091 found in obese group).

In addition, the study by Kristoffersen classified the headache frequency into 5 differentgroups while we used the ICHD-III classification of episodic & chronic categories.

With regard to headache severity, which is significantly affected by BMI values in this study, many reports support this finding. Bigal and Lipton found that obesity is associated with increased headache severity in patients with episodic migraine [34]. Ford et al found non-linear association between higher BMI and the prevalence of severe headaches or migraines [56]. Similarly, Tiu and Das concluded the same association although they used MIDAS score as the severity indicator [57]. However, both Huang et al, and Mattsson found no significant association between BMI and severity of headache (54, 58).

The association of headache duration with BMI score remains vague. In this study, we find that overweight, rather than obese patients have longer headache episodes.

Although this relation is unique, it was not supported in previous reports [54, 58]. The underpinnings of such unique association may be due to the smaller sample size of obesepatients as compared to overweight patients.

The MIDAS Score was created by Stewart et al. in 2000 to determine level of disabilityin migraineurs [50]. In many research studies, it has been revealed that MIDAS score is directly proportional to BMI [35,57,59]. Tiu DN et al. found that MIDAS score was maximum in obese patients and lowest in normal subjects with statistically significant difference ($P< 0.05$). In this study, and consistent with the above mentioned reports, we found that MIDAS score is raised in higher BMI as compared to normal BMI subjects with statistically significant association. Similar significant associations were demonstrated between MIDAS score and parity as we found multi-parity to be independent risk factor for high MIDAS score in this study. About 60% of patients with high MIDAS grade had ≥4 parity compared with 17.86% of patients with low grade whohad such parity (OR=7.78, 95%CI=1.27-47.61, p=0.026).

The link between migraine headaches & BMI might be explained by the followingmechanisms:

1) calcitonin gene-related peptide (CGRP) (an important mediator of migraine) is elevated in obese people [60], (CGRP inhibitors are effective in migraine treatment);

2) obesity itself is a pro-inflammatory condition (through increasing circulatingcytokines levels [61-63];

3) furthermore, Adiponectin and leptin are adipokines that are mostly released from subcutaneous adipose tissue, and that may have nociceptive traits in themselves [64-67]. Both adiponectin and leptin are increased in migraineurs between attacks, although theymay be decreased during attacks [68]. Leptin levels are also increased in correlation withpro-inflammatory cytokines IL-6 and TNF-a [68], which have also been found to be elevated in people with migraine; [69]

4) migraines, like obesity, have been reported as a risk factor for cardiovasculardisorders, as well as for stroke [70-72];

5) migraine prevention medications, which were used in the preventive-treatment ofmigraine, may also be a possible contributing reason for the change of BMI [73,74]. The present study has several strengths, including face-to-face clinic interview. All measurements were recorded by interviewers to confirm the right body height and
weight. In addition, we collected information about many migraine features, including migraine frequency, severity, and duration. Furthermore, information about a number ofpotential confounders was available, allowing us to adjust the association between BMI and migraine. In addition, the homogenous nature of patients further reduced potentialconfounding.

The following limitations might be considered when interpreting the results. First, it is aclinic-based study with limited study sample derived from relatively small region of Iraq. Thus, the findings of the study may not be extrapolated to other populations.

Second, despite our ability to control for a number of potential confounders, we cannotexclude the possibility of residual and immeasurable confounding factors. Further, ourdata was cross-sectional which prevents the determination of time sequence of the association between BMI and migraine.

6. Conclusion

In conclusion, BMI does have significant effects on migraine headache severity and the resulting disability but its effects on headache frequency and duration do not supportedand need to be studied further in the future.

7. Recommendations

We recommend to perform a larger study sample with more representation of all agegroups and BMI grades to refine results more. In addition, we recommend perform aprospective study on the effect of intended weight loss on migraine characteristics.

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