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Expert Opinion

The Association of Obesity With Episodic and Chronic Migraine

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About 18% of adolescents and 33% of adults are obese in the United States. Recent studies demonstrating an association between migraine and obesity raise fascinating questions about the mechanism for this association and suggest new potential avenues of treatment for migraine.

CASE HISTORY

Case 1: This is a 33-year-old woman with a history of being overweight since childhood and episodic migraine since the age of 15. In the last 5 years, without medication overuse, her headaches have become chronic. Her family history is negative for migraine, but both parents are obese. Her current body mass index (BMI) is 36.

Case 2: This is a 38-year-old woman with a history of obesity since childhood and a history of episodic migraine since the age of 13 when her menses began. Last year, with a BMI of 39 and a headache frequency of 7 to 9 headaches per month, she underwent bariatric surgery. In the past 6 months, she notes some months with no headaches, and others with a maximum of 1 to 2 headache days. The migraines she does have now are easily treatable with triptans.

EXPERT OPINION

Excessive adipose tissue in relation to fat-free mass (FFM) results in obesity. Multiple demographic (eg, sex, age) and methodological (eg, self-reported vs measured indices) factors can impact the reported effect of obesity on various disease states.[1] Both women in the earlier cases are of reproductive age, which may be of particular relevance to the disease risk associated with obesity, including the risk of migraine.

Adipose tissue distribution substantially changes at puberty and with advanced age; and in several disease states, obesity increases the risk of disease in adults of reproductive age but is attenuated in older

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populations.[1] For example, obesity has been consistently associated with an increased risk of mortality and cardiovascular disease in reproductive-aged adults, while this association is less clear among the elderly.[2,3] Similar findings, discordant for reproductive-aged vs elderly populations, have been noted in the migraine literature, with multiple, large general population studies supporting increased odds of migraine and severe headaches with obesity among reproductive-aged participants,[4-7] but no such association was observed among older participants.[5,8,9] While these findings could truly be due to a change in the association between risk factors and disease state in aging populations, other explanations are also possible. One possibility is that the impact or implication of a given BMI differs between younger and older individuals.[1,10] Specifically, investigators have shown that with advancing age, the ratio of adipose tissue to FFM increases – *even in individuals who maintain the same BMI*. Thus, using the same definition of obesity (based on a BMI cut-point) in older and younger adults may not be appropriate. Another possibility may be that the BMI, in general, is not adequate in terms of indicating adiposity in older populations.[1,10]

In addition to demographic factors, how obesity is estimated in studies evaluating obesity can also impact the reported findings. Although most anthropometric measures of obesity conform reasonably well in predicting future disease status, differences may exist in evaluating short-term effects and effects on specific disease entities. Given that obesity is defined as excessive adipose tissue in relation to FFM, obesity is most accurately estimated by direct demonstration of an increase in adipose tissue to FFM, such as with computed tomography or magnetic resonance imaging.[10] However, direct measurements are not practical and are prohibitively expensive for large population-based epidemiological studies. Thus, indirect estimates of general or total body obesity (TBO), based on the BMI, and of regional or abdominal obesity, based on waist circumference measurements, are often used. Consequently, in the published studies evaluating migraine and obesity to date, obesity is defined as excess in relative body weight (which includes skin, organs, and muscle mass, in addition to adipose tissue mass) rather than just excessive adipose tissue mass.[1,10] Further, given that anthropometrics are estimates of obesity – even when height and weight are measured – the use of self-reported height and weight to calculate BMI may substantially underestimate potential obesity associations.[11] This underestimation may result from participants' tendency to overestimate their height and underestimate their weight when self-reported.[12] Hence, even in prospective cohort studies, when BMI is based on self-report, nondifferential misclassification of participants' obesity status (ie, TBO is ascertained before incident migraine) may result in spuriously low relative risk estimates.[10,11] Thus, it is important to recognize if BMI is estimated by self-report of height and weight (BMI-sr), or by measured height and weight (BMI-m) in studies evaluating the migraine-obesity association.[11] It is also important to note that as long as these potential limitations are kept in mind, the BMI can and has been a valuable and cost-efficient tool to evaluate disease associations, including migraine and obesity.

Is There an Association Between Episodic and Chronic Migraine and Obesity in Women, Men, and Adolescents?—In both cases earlier, the women were overweight or obese since childhood, with the onset of episodic migraine as adolescents. In one case, the pattern progressed to a chronic pattern. Obesity has been shown to be associated with both episodic and chronic headache among reproductive age subjects in multiple studies.[5-7,13,14] (See Tables 1 and 2.) However, all studies have consistently demonstrated no association between obesity and migraine in post-reproductive-aged individuals.[5,8,9] (See Table 3.)

The first study to identify an association between episodic headache and obesity was a longitudinal study by Scher and colleagues in 2003.[13] A total of 1932 participants between 18 and 65 years of age were evaluated, of whom 798 participants were episodic headache sufferers with 2-104 headache days per year (ie, <9 headache days/month) and 1134 were chronic daily headache (CDH) sufferers (ie, ≥15 headache days/month). Individuals with episodic headache who were obese (BMI-sr) had over a 5-fold increased odds of developing CDH at the second interview (odds ratio [OR] 5.53; 95%

Table 1.—Migraine and Obesity in Reproductive-Aged Participants

Reference	Study Design/Name	Sample Size	Sex	Age Range	Obesity DX	HA DX	Findings
Bigal et al (2006)[26]	CS/AMPP	Total: 30,215 EM: 3791	Combined and separate	18 to 89 years	Self-reported TBO	ICHD	The crude prevalence of migraine in men w/total body obesity (BMI-sr ≥ 35) (8.8%) was significantly greater than in those w/NL weight (7.2%), $P < .01$), but did not remain so after adjustments. The prevalence of those with episodic migraine with a frequency of 10-14 days per month was increased in participants w/total body obesity by BMI-sr (13.6%) as compared with those w/NL weight (4.4%). Note: Those with 15 or more headaches per month (ie, chronic daily headache) were excluded from these analyses.
Keith et al (2008)[11]	CS/Meta-analysis of 11 databases including WHS	Total: >200,000 EM:?	Women only	16 to 94 years	Mixed (self-reported and measured) TBO	Non-ICHD	Obese women (BMI-mixed) had increased risk for headache as compared with those with BMI 20.
Ford et al (2008)[4]	CS/NHANES	Total 7601 EM: 1649	Combined and separate	20 to 85 years	Measured TBO	Non-ICHD	Those with total body obesity (BMI-m) had a 37% increased odds for having migraine compared with those who were not obese or overweight (OR 1.37; CI 1.09, 172).
Peterlin et al (2010)[5]	CS/NHANES	Total 15,531 (≤55 years) EM: 3915	Sex stratified	20 to 55 years	Measured TBO and Ab-OB	Non-ICHD	The odds of migraine were increased by 38-39% in those with total body obesity (BMI-m) as compared with those without obesity (Women: OR 1.39;CI: 1.25, 1.56; Men: OR 1.38;CI 1.20, 1.59). The odds of migraine were increased in those with abdominal obesity (WC) as compared with those without abdominal obesity (Women OR 1.39;CI 1.25, 1.56; Men: 1.30; CI 1.13, 1.48).
Vo et al (2011)[6]	CS/OMEGA	3733 Premenopausal women only	Women	18-40 years	Self-reported TBO	Non-ICHD	Obese (BMI-sr) premenopausal women had a 48% increased odds of migraine as compared with non-obese (OR = 1.48; CI: 1.12-1.96). The odds of migraine increased with increasing obesity, with 2-fold (207%) increased odds of migraine in severely obese (OR 2.07 CI: 1.27-3.39) and almost 3-fold (275%) increased odds in morbidly obese (2.75 OR CI: 1.60-4.70).
Robberstad et al (2010)[7]	CS/HEAD-HUNT YOUTH	5588 Adolescents	Boys and girls together and separate	13-18 years	Measured TBO	Non-ICHD	Individually by each group, those with recurrent headache in general, recurrent migraine, or recurrent tension-type headache were more overweight or obese than those without headache. Those with migraine were more overweight or obese (BMI-m) than those without migraine (OR 1.6; CI: 1.4-2.2). Those with tension-type headache were more obese (BMI-m) than those without tension-type headache (OR 1.4; CI: 1.1.-1.6).

Ab-OB = abdominal obesity; AMPP = American Migraine Prevalence and Prevention; BMI-sr = body mass index based on self-report; BMI-m = body mass index based on measured height and weight; CDH = chronic daily headache; CS = cross-sectional; DX = diagnosis; EH = episodic headache; EM = episodic migraine; ICHD = International Classification of Headache Disorders; Long = longitudinal; NHANES = National Health and Nutrition Examination Survey; NL = normal; TBO = total body obesity; WC = waist circumference; WHR = waist to hip ratio.

Table 2.—Migraine and Obesity in Chronic Daily Headache

Reference	Study Design/Name	Sample Size	Sex	Age Range	Obesity DX	HA DX	Findings
Scher et al (2003)[13]	Longitudinal	Total: 1932 EH: 798 CDH: 1134	Both together	18-65 years	Self-reported TBO	Non-ICHD	The prevalence of CDH was higher in those with TBO (BMI-sr) as compared to those without (OR 1.34; CI: 1.0, 1.8). There was no difference in TBO (BMI-sr) prevalence in those with episodic headache as compared to chronic daily headache. Episodic headache sufferers with TBO (BMI-sr) had a 5-fold increased odds of transforming to chronic daily headache sufferers (OR 5.28;CI: 1.3-21.1) as compared to those episodic headache sufferers without obesity.
Bigal and Lipton (2006)[14]	CS/AMPP	Total: 30,849 CDH: 1243 – 401 TM – 863 CTTH	Both together	18-89 years	Self-reported TBO	Modified Silberstein-Lipton Criteria TM ICHD CTTH	The prevalence of CDH was higher in those with TBO (BMI-sr) (OR 1.3; CI: 1.1, 1.6). The prevalence of transformed migraine was associated with those with TBO (BMI-sr) that was ≥ grade II (ie, BMI ≥ 30), while the prevalence of CTTH was only associated with those with a BMI-sr ≥ 35.
Peterlin et al (2008)[17]	Clinic-based population (age and BMI matched)	Total: 37 CDH: 12 EM: 12	Women only	24-44 years	Measured TBO and Ab-OB	ICHD	Despite participants being matched by BMI (m), CDH sufferers (with CM or MOH) had a greater frequency of abdominal obesity (33%), as estimated by the WHR, than EM (8.3%) participants and controls (0%), $P = .049$.

Abd-OB = abdominal AMPP obesity; AMPP = American Migraine Prevalence and Prevention; BMI-sr = body mass index based on self-report; BMI-m = body mass index based on measured height and weight; CDH = chronic daily headache; CS = cross-sectional; DX = diagnosis; EH = episodic headache; EM = episodic migraine; ICHD = International Classification of Headache Disorders; Long = longitudinal; NHANES = National Health and Nutrition Examination Survey; NL = normal; TBO = total body obesity; WHR = waist to hip ratio; WHS = Women's Health Study.

Table 3.—Migraine and Obesity in Peri- and Post-Reproductive-Aged Participants

Reference	Study Design/Name	Sample Size	Sex	Age Range	Obesity DX	HA DX	Findings
Mattson (2007)[8]	CS	Total: 684 EM: 130	Women only	40-74 years	Measured TBO	ICHD	In older women, neither migraine prevalence or migraine attack frequency was associated w/total body obesity, using measured body mass indices (BMI-m).
Winter et al (2009)[9]	CS/WHS	Total: 63,467 EM: 9195	Women only	≥45 years	Self-reported TBO	Non-ICHD	In older women, there was no association between total body obesity (BMI-sr) and active migraine or prior history of migraine.
Peterlin et al (2010)[5]	CS/NHANES	Total: 6152 (>55 years) EM: 749	Both sexes separately	≥55 years	Measured TBO and Abd-OB	Non-ICHD	In older men, the odds of migraine were not associated with total body obesity (BMI-m) or abdominal obesity (WC). In older women, the odds of migraine were not associated with total body obesity (BMI-m). In older women, the odds of migraine were *decreased* in those with abdominal obesity (WC).

Abd-OB = abdominal obesity; AMPP = American Migraine Prevalence and Prevention; BMI-sr = body mass index based on self-report; BMI-m = body mass index based on measured height and weight; CDH = chronic daily headache; CS = cross-sectional; DX = diagnosis; EH = episodic headache; EM = episodic migraine; ICHD = International Classification of Headache Disorders; Long = longitudinal; NHANES = National Health and Nutrition Examination Survey; NL= normal; TBO = total body obesity; WC = waist circumference; WHR = waist to hip ratio; WHS = Women's Health Study.

confidence interval [CI]: 1.4-21.8) as compared with those episodic headache sufferers without obesity.[13]

Scher's study was subsequently followed by 2 small clinic-based studies,[15,16] as well as multiple large, general population cross-sectional studies.[10] Notably, studies that failed to document positive associations of episodic headache or migraine with obesity did not fully account for possible effect modification by participants' age (eg, different associations for reproductive age and older participants). Additionally, those studies relied on self-reported body mass indices to estimate obesity.[10] In contrast, studies that accounted for reproductive age or those that used objective measures of obesity confirmed significant associations of episodic headache and migraine with obesity in reproductive-aged adolescents and adults.[4-7] (See Table 1 for a detailed summary of relevant studies.)

In the first general population study evaluating the migraine–obesity association utilizing measured body mass indices (BMI-m), Ford et al evaluated 7601 participants in the National Health and Nutrition Examination Survey (NHANES), ranging from 20 to 85 years of age.[4] Migraine and severe headaches were self-reported. Those with obesity had a 37% increased odds for having migraine compared with those of normal weight (OR 1.37; 95% CI: 1.09, 1.72).

Following the Ford study, and also utilizing the NHANES database, Peterlin et al demonstrated that the migraine–adiposity association varies by age, sex, and adipose tissue distribution pattern (eg, TBO vs Abd-O). In their sample of over 15,500 participants, the authors reported that the prevalence of migraine was increased in both younger men and women (20-55 years old) with either TBO (women: OR 1.39; 95% CI: 1.24-1.55; men: OR 1.38; 95% CI: 1.20-1.59) or abdominal obesity (women: OR 1.39; 95% CI: 1.25-1.56; men OR 1.30; 95% CI: 1.13-1.48) – even after adjusting for demographic and cardiovascular confounders. Further, although the association of migraine with abdominal obesity did not remain significant in reproductive-aged men after adjusting for demographics, cardiovascular confounders AND TBO (BMI-m) (OR 1.03; 95% CI: 0.84-1.27), it did remain significant in reproductive-aged women (OR 1.26; 95% CI: 1.10-1.45). Peterlin et al's findings also supported previous studies that demonstrated that migraine was not associated with TBO in older men and women (>55 years of age), and additionally reported that while there was no association between migraine and abdominal obesity in older men, in post-reproductive-aged women, migraine prevalence was actually inversely associated with abdominal obesity. These data suggest that prior analyses that failed to account for possible effect modification by age group may have obscured important differences in migraine–obesity relations for adolescent and older individuals.

In a third general population study, Vo et al evaluated over 3700 adult premenopausal women in the OMEGA study to evaluate the odds of migraine in those with obesity (BMI-sr).[6] A 48% increased odds of migraine was found in those women with obesity (OR 1.48; 95% CI: 1.12-1.96).

Finally, Robberstad et al evaluated over 5500 adolescents (13-18 years of age) boys and girls in the HUNT Study.[7] Adolescents with recurrent headache in general demonstrated a 40% increased odds of being overweight or obese (BMI-m) (OR 1.4; 95% CI: 1.2-1.6). Similarly those adolescents with migraine demonstrated a 60% increased odds of being overweight or obese (BMI-m) (OR 1.6; 95% CI: 1.4-2.2).[7]

In addition to episodic headache, there is also an association between chronic headaches and obesity. The 2003 longitudinal study by Scher and colleagues demonstrated that the prevalence of CDH was increased in those who were obese (BMI-sr) (OR 1.34; CI: 1.0-1.8) or overweight (OR = 1.26; CI: 1.0-1.7).[13] This finding was later confirmed by Bigal and Lipton in a study of over 30,000 participants, of which 1243 individuals fulfilled criteria for CDH.[14] Of the CDH participants, approximately 401 fulfilled criteria for transformed migraine and 863 fulfilled criteria for chronic tension-type headache (CTTH). As in the Scher study, investigators noted a positive trend of increasing CDH prevalence with increasing categories of self-reported BMI. The prevalence for successive BMI-sr categories were as follows: 18.5-24.9 kg/m^2 (3.9%), 30-34.9 kg/m^2 (5.0%), and $\geq$35 kg/m^2 (6.8%). In addition, Bigal and Lipton showed that the association between CDH and obesity was stronger with transformed migraine than in CTTH, with the prevalence of transformed

migraine being associated with those with a BMI-sr ≥ 30, while the prevalence of CTTH was only associated with those with a BMI-sr ≥ 35.[14]

No large, general population studies have evaluated the association between CDH and abdominal obesity. However, a small clinic-based study of 27 women of reproductive age is of note as the first study to evaluate abdominal obesity in migraineurs and CDH sufferers with chronic migraine or medication overuse headache.[17] Although the primary aim of the study was to compare serum levels of adiponectin among healthy controls, episodic migraineurs, and CDH sufferers, body mass indices were measured, including waist and hip circumference. Despite participants having been matched based on BMI, the women with CDH had a greater frequency of abdominal obesity based on the waist to hip ratio (33%) as compared with episodic migraineurs (8.3%) and controls (0%), $P = .049$.[17]

What Might Be the Mechanism?—Adipose tissue is a functioning, active endocrine organ that influences energy homeostasis, reproduction, and inflammatory process, among other metabolic processes. Biological mechanisms underlying consistently observed associations of obesity and episodic and chronic migraine (particularly among reproductive aged population) are likely to be multifactorial, and to involve both peripheral and central pathophysiological processes. A detailed discussion on these biologically plausible mechanisms has recently been published.[10]

Peripherally, expansion of adipose tissue during weight gain leads to the recruitment of macrophages and T cells, as well as changes in the synthesis of cytokines and adipocytokines by adipocytes that favor chronic systemic inflammation and insulin resistance. Weight gain, which is known to lead to the induction of several pro-inflammatory cytokines (eg, tumor necrosis factor-α, interleukin [IL]-1 and IL-6),[10,18] may in turn contribute to local and systemic inflammation. Elevated plasma concentrations of pro-inflammatory cytokines and alterations in adipocytokines have been implicated in the pathogenesis of migraine.

Centrally, the regulation of feeding is controlled by the system involving the arcuate nucleus of the hypothalamus and its connections. Hypothalamic involvement in migraine was initially suggested based on the observations of premonitory symptoms in migraineurs, such as changes in thirst, food cravings, mood, and sleep disturbances.[10] More recently, functional imaging data have demonstrated hypothalamic activation during acute migraine attacks.[19] It has also been demonstrated that several hypothalamic peptides, proteins, and neurotransmitters involved in feeding have been implicated in migraine pathophysiology. Notably, these include serotonin, adiponectin, leptin, and orexin.[10]

Does Weight Gain or Loss Have an Effect on Migraine Frequency?—In the first case, the patient's headache pattern progressed from an episodic to a chronic pattern in association with a progression of obesity status from adolescence to adulthood. To date, no longitudinal studies have evaluated the effect of weight gain on migraine frequency. However, in a cross-sectional study, Vo et al demonstrated that the risk of migraine in reproductive-aged women substantially increased with increasing severity of obesity.[6] Specifically, while the overall odds of migraine in women with obesity of any level was 48% greater than women without obesity (OR 1.48; 95%CI: 1.12-1.96), those women with severe or class II obesity (BMI 35-39.9) had over a 200% increased risk (OR 2.07; 95%CI: 1.27-3.39), and those with morbid or class III obesity (BMI ≥ 40) had a 275% increased risk of migraine (OR 2.75; 95%CI: 1.60-4.70).[6] Further, Vo et al demonstrated that women with a history of pediatric migraine had a 67% increased odds of gaining ≥22 pounds above their weight at the age of 18 (OR 1.67; 95% CI: 1.13-2.47).[6] It is possible that a similar weight gain occurred in the first case. This weight gain may, thus, have resulted in a progression of her obesity classification from being overweight to obese and ultimately with her increasing headache frequency.

Finally, 2 small clinical studies that evaluated headache frequency in low-frequency episodic migraineurs following weight loss from bariatric surgery are worthy of note. In these studies, the monthly headache frequency declined from approximately 4 headache days per month at baseline to just 1 to 2 headache days per month 6

months following surgery. However, while these studies are suggestive that weight loss is associated with a decline in headache frequency in episodic migraineurs, larger, controlled studies will be needed to substantiate these findings and determine the true-effect size before bariatric surgery can be considered as part of treatment for migraine therapy.[20]

Should the Potential Effects of Medications on Weight Be Considered in Treating Obese Migraineurs?—Clinicians treating obese migraine patients should consider providing their patients with access to lifestyle education – particularly in terms of promoting healthy diet and exercise routines. Lack of physical activity has been demonstrated to be associated with a 21% increased risk of headache attacks in adult migraineurs (hazard ratio [HR] 1.209; $P < .01$),[21] and a 50% increased risk of migraine in adolescents (OR 1.5; 95%CI: 1.0-2.2).[7] In addition, aerobic activity may reduce headache frequency in episodic migraineurs.[22,23]

Particular care should also be taken by physicians in regard to their choices of medications prescribed to migraine patients, given that many migraine medications can affect weight either positively or negatively. Several medications that may be used for migraine prevention may also be associated with weight loss, and include topiramate, zonisamide, and protriptyline.[24,25] Other potential migraine preventive agents where weight loss is mild or neutral include duloxetine and venlafaxine. Verapamil, propranolol, and gabapentin, may be associated with mild to moderate weight gain or be weight neutral. In contrast, valproic acid, amitriptyline, and flunarizine may be associated with substantial weight gain.[24,25]

In summary, migraine is associated with obesity in those of reproductive age – the age when migraine is most prevalent.[26] Given that obesity is a modifiable risk factor, we should actively provide all migraine patients with education on the association of episodic and chronic migraine with obesity in general, as well as the increasing risk of migraine associated with increasing obesity, and the potential effect of weight gain and weight loss on headache frequency. Additionally, although longitudinal studies are needed to better characterize the influences migraine medications may have on energy balance and a patient's propensity to gain or lose weight, migraine patients should be made aware of the potential influence medications may have on their weight, and they should be encouraged to exercise, consume a healthy diet, and avoid excessive weight gain.

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