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## Migraine and Obesity: Epidemiology, Mechanisms, and Implications

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### Abstract

Adipose tissue is a dynamic neuroendocrine organ that is involved in multiple physiological and pathological processes, and when excessive, results in obesity. Clinical and population-based data suggest that migraine and chronic daily headache are associated with obesity, as estimated by anthropometric indices. In addition, translational and basic science research shows multiple areas of overlap between migraine pathophysiology and the central and peripheral pathways regulating feeding. Specifically, neurotransmitters such as serotonin, peptides such as orexin, and adipocytokines such as adiponectin and leptin have been suggested to have roles in both feeding and migraine. In this article, we first review the definition and ascertainment of obesity. This is followed by a review of the clinical and population-based studies evaluating the associations between obesity and chronic daily headache and migraine. We then discuss the central and peripheral pathways involved in the regulation of feeding, where it overlaps with migraine pathophysiology, and where future research may be headed in light of these data.

### Keywords

migraine; obesity; BMI; abdominal obesity; adipocytokines; adiponectin

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Obesity affects more than a billion adults worldwide.<sup>1</sup> In the United States alone it has been estimated that 31% of men and 33% of women fulfill criteria for general/total body obesity, while 42% of men and 61% of women fulfill criteria for abdominal obesity.<sup>2</sup> Both general and abdominal obesity have been shown to be associated with an increased risk of morbidity and mortality.<sup>3–6</sup> Obesity has also been shown to be associated with a reduced quality of life and pain disorders, such as low-back pain and more recently headache.<sup>7,8</sup> While in the past, the pain associated with obesity had been largely attributed to structural changes,<sup>9</sup> it is difficult to attribute headache to structural changes. In order to improve our understanding as to how a non-structurally related pain disorder may be associated with obesity, it is

necessary to understand the nature of obesity as well as usefulness and limitation of different obesity measurements.

## Normal Adipose Tissue Distribution

The human body contains lipids that are stored in the form of triglycerides in adipose tissue cells called adipocytes. Adipose tissue and adipocytes exhibit a sexual dimorphism which first becomes evident after puberty.<sup>10-12</sup> During puberty, men begin depositing adipose tissue centrally (in abdominal depots), a pattern which persists throughout adulthood.<sup>10</sup> In contrast, during puberty women preferentially deposit adipose tissue in the subcutaneous depots in the gluteo-femoral region, but changes to an abdominal pattern postmenopausally.<sup>10-12</sup>

Differences in adipocyte function and expression of proteins have been shown to exist based on depot locations, as either gluteo-femoral or abdominal, and based on the depth as either subcutaneous adipose tissue (SAT) or visceral adipose tissue (VAT) (Table 1).<sup>10-12</sup> Adult men have less SAT and more VAT than adult women, with VAT representing approximately 20% of total body fat in men as compared with 6% in women.<sup>11</sup> Although women demonstrate an increase in VAT deposition peri- and postmenopausally, the total volume never reaches the levels seen in men of similar age.<sup>13,14</sup>

## Obesity

Excessive adipose tissue in relation to fat-free mass results in obesity. Multiple factors can impact the effect of obesity on various disease states.<sup>15,16</sup> Age is one such factor.<sup>16</sup> In several disease states, obesity increases the risk of disease in reproductive aged adults, but is attenuated in older populations.<sup>17,18</sup> For example, in adults of reproductive age, obesity has been consistently associated with an increased risk of mortality and cardiovascular disease, regardless of the anthropometric index evaluated. In contrast, in elderly populations this association is less clear, with several studies reporting that obesity is not associated, or even inversely associated, with mortality and cardiovascular disease.<sup>17,18</sup> Recently it has been suggested that abdominal obesity in female migraineurs may show a similar age variation in disease risk, with an increased odds of migraine and severe headaches in younger women with abdominal obesity, and a decreased odds of migraine and severe headaches in older women with abdominal obesity.<sup>14</sup> Several reasons may account for this finding, including change in the association between risk factors and disease state in aging populations, selective survival, or the lack of change in the definitions used to estimate obesity based on the body mass index (BMI) and waist circumference (WC) in aging populations.<sup>19</sup>

In addition to gender and age, the distribution of adipose tissue can impact the effect of obesity on disease risk as well.<sup>14</sup> Specifically, although both total body obesity (TBO) and abdominal obesity (Ab-O) have been shown to be associated with an increased risk of several disease states, Ab-O has frequently been shown to be a better predictor of disease than TBO as estimated by the BMI (eg, diabetes, cardiovascular disease).<sup>1,4,5</sup> Furthermore, how obesity is estimated can also impact obesity-related findings.

Obesity is most accurately estimated by direct demonstration of an increase in adipose tissue to fat-free mass, such as with CT or MRI imaging.<sup>10,15,16</sup> However, direct measurements are not practical and are substantially more expensive than indirect measurements. Thus, indirect estimates of general or TBO, based on the BMI, and of regional or abdominal obesity, based on WC measurements, are often used (see Table 2). Consequently, obesity is often “*de facto*” 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.<sup>15,16</sup>

Several methodological issues have been discussed in evaluating TBO with indirect measures such as BMI. While most anthropometric measures of TBO perform reasonably well in predicting future diseases, differences may exist in evaluating short-term effects and effects on specific disease entities.<sup>1,4,5</sup> First, individuals tend to overestimate their height and underestimate their weight when self-reporting, including migraineurs.<sup>20,21</sup> This can lead to non-differential misclassification in prospectively collected data (ie, TBO is ascertained before disease occurs) but may lead to a differential bias in cross-sectional or case-control studies. Second, the implications of the BMI changes with advancing age, as the ratio of adipose tissue to fat-free mass increases with age – even in individuals who maintain the same BMI.<sup>16,22</sup> Thus, using the same definition of obesity (based on a BMI cut-point) in older and younger adults may not be appropriate and may be one explanation for changing associations of obesity on outcomes in the elderly. Finally, BMI does not take into consideration gender-specific differences in adipose tissue distribution.<sup>16</sup>

Despite their limitations, BMI and WC can be valuable tools to estimate and track gross population changes in obesity in a cost-efficient manner. The World Health Organization criteria and grades for general/TBO and abdominal obesity are noted in Table 2.<sup>23,24</sup> In the following section, we review the current research evaluating the relationship between obesity and chronic daily headache or migraine using these indirect estimates of TBO and Ab-O. We will then discuss the central and peripheral pathways involved in the regulation of feeding, where it overlaps with migraine pathophysiology, and then briefly touch on where future research may be headed.

## THE EPIDEMIOLOGY OF OBESITY AND HEADACHE

### Obesity and Chronic Daily Headache

The first study to identify an association between frequent headache and obesity was a study by Scher and colleagues in 2003 (Table 3).<sup>8</sup> A total of 1932 participants between 18 and 65 years of age were evaluated, of whom 1134 participants were chronic daily headache (CDH) sufferers, and 798 participants were episodic headache sufferers. Data, including self-reported height and weight, were collected at 2 time points, 11 months apart. Two important findings were reported from this study. First, the prevalence of CDH was associated with those who self-reported having TBO (OR 1.34; CI: 1.0–1.8) or being overweight (OR 1.26; 1.0–1.7). Second, compared with those of normal weight, individuals with episodic headache who also had TBO at baseline were at increased odds of having CDH at follow-up (OR 5.28; CI: 1.3–21.1). Specifically, 30% (7/23) of newly identified cases of CDH fulfilled criteria for TBO, as compared with only 13% (94/726) of those who remained episodic.

These results were later confirmed by Bigal and Lipton (Table 3).<sup>25</sup> Of the 1243 individuals who fulfilled criteria for CDH, approximately 401 fulfilled criteria for transformed migraine and 863 fulfilled criteria for chronic tension-type headache (CTTH). As in the study by Scher, the prevalence of CDH was higher in those with self-reported TBO as compared with the normal-weight group. Specifically, 6.8% of those with a BMI  $\geq$  35 (OR 1.8; CI: 1.4–2.2) and 5% of those with a BMI  $\geq$  30 (OR 1.3; CI: 1.1–1.6) had CDH, as compared with 3.9% of those with a BMI between 18.5 and 24.9. In addition Bigal and Lipton showed that the association between CDH and TBO was stronger in transformed migraine than in CTTH.

Finally, a small clinic-based study of 27 women of reproductive age evaluated abdominal obesity in CDH sufferers and migraineurs (Table 3).<sup>26</sup> Although the primary aim of the study was to compare serum levels of adiponectin, a protein secreted from adipocytes, between healthy controls and migraine or CDH sufferers, body mass indices were measured, including height, weight and waist and hip circumference. Headache diagnoses were based on international classification of headache disorders (ICHD)-II criteria. Despite participants

having been matched based on BMI, results showed that the women with CDH had a greater frequency of abdominal obesity (based on the waist to hip ratio) as compared with controls and those with episodic migraine.

General population studies evaluating association between CDH and Ab-O are warranted.

1. The prevalence of CDH is increased in those with TBO.
2. TBO is associated with an increased risk of transforming from episodic to chronic daily headache.
3. Ab-O may be associated with CDH.

### Obesity and Episodic Headache and Migraine

**CDH & obesity conclusions**—Migraine and adipose tissue both exhibit a sexual dimorphism; and both have been linked to estrogen and the hormonal life-cycle of women. The prevalence of migraine occurs more commonly in adult women of reproductive age than men, (being 2–3 times greater in women than men) with increases in migraine prevalence first being seen in women during puberty and decreases after menopause.<sup>27</sup>

Similarly, a sexual dimorphism is found with adipose tissue distribution.<sup>11–14</sup> Following puberty, an increase in the total volume of SAT and a decrease in the volume of VAT is seen in girls as compared with boys. This pattern persists throughout the life span of men and throughout the reproductive ages of women.<sup>11,13</sup> Postmenopausal women have an increase in both total adipose tissue volume and VAT volume, as compared with premenopausal women. The increase in VAT in older women has been demonstrated to first occur around the ages of 40–50 years and again from 50 to 60 years of age.<sup>11,13</sup>

Given that adipose tissue distribution varies by age and reproductive status, we distinguish between 2 categories: (1) studies that specifically recruited periand postmenopausal women or whose mean age of participants was over 50 (predominantly peri- & post-reproductive age); and (2) studies whose mean age was under 50 years of age or whose methods did not specifically recruit peri- and postmenopausal women (predominantly reproductive age).

### Obesity and Migraine in Reproductive-Age Participants

In 2005, 2 small clinic-based studies reported an increased frequency of migraine attacks in those with TBO (Table 4).<sup>28,29</sup> In the first, Peres et al compared 74 patients with TBO (mean age of 39 years) who presented to an obesity surgery clinic to 70 age-matched controls.<sup>28</sup> A total of 75% of those with TBO had a life-time headache diagnosis as compared with 42% of the controls,  $P < .001$ . Furthermore, ICHD migraine was reported by 66% of those with TBO as compared with 18.5% of the non-obese controls,  $P < .0001$ . Similarly, in the second clinic-based study by Horev et al, 63% of 27 patients with TBO reported episodic headache and 48% fulfilled migraine criteria.<sup>29</sup>

These 2 studies were subsequently followed by 4 cross-sectional, general population-based studies evaluating obesity in those of reproductive age with varying results.<sup>14,30–32</sup> One of these studies found no association between migraine prevalence and TBO;<sup>30</sup> another found no association between migraine prevalence and TBO, but did find an association between headache prevalence and obesity.<sup>31</sup> The other 2 studies reported a positive association between the prevalence of migraine or severe headaches and obesity.<sup>14,32</sup>

In the first of the general population studies, Bigal et al evaluated 30,215 participants, of whom 3791 fulfilled ICHD migraine criteria and 25,150 were controls (Table 3).<sup>30</sup> The age of participants ranged from 18 to 89 years with a mean of 39 years. TBO was estimated

using self-reported height and weight. Several findings from this study are of note. First, the crude and adjusted prevalence of migraine was increased in women who were underweight. In addition the crude prevalence of migraine was increased in men with a BMI  $\geq 35$  (8.8%) as compared with men of normal weight (7.2%),  $P < .01$ ; however, this finding did not remain significant after adjusting for demographics. Finally, although migraine prevalence was not found to be associated with self-reported BMI, the prevalence of high-frequency episodic migraine was associated with TBO. Specifically, while only 4.4% of those with a BMI between 18.5 and 24.9 reported migraine attacks occurring 10–14 days per month, 13.6% (OR 2.9; CI: 1.9–4.4) of those with a BMI  $\geq 30$  reported attacks between 10 and 14 days per month.<sup>30</sup>

In the second general population study, Keith et al conducted a meta-analysis of data from women in 11 different general population databases (Table 4).<sup>31</sup> Demographics, self-report of headache or migraine and TBO was obtained from over 200,000 women, ranging in age from 16 to 94 years. TBO was estimated in all but one of the 11 datasets using self-reported height and weight. Although migraine prevalence was not able to be shown to be associated with TBO, obese women had an increase risk for headache as compared with those with a BMI of 20.

The above studies were subsequently followed by 2 studies which evaluated the prevalence of migraine or severe headaches in those with obesity using measured body mass indices.<sup>14,32</sup> In the first of these studies, Ford et al evaluated 7601 participants ranging in age from 20 to 85 years of age.<sup>32</sup> Migraine or severe headaches was self-reported by participants. TBO was estimated using measured height and weight to calculate the BMI. Similar to the study by Bigal, migraine prevalence was increased in those who were underweight. In addition those with TBO had a 37% increased odds for having migraine or severe headaches compared with those of normal weight, (OR 1.37; CI: 1.09–1.72).<sup>32</sup>

In the second general population study, Peterlin et al evaluated the prevalence of migraine in those with TBO using measured body mass indices.<sup>14</sup> A total of 15,531 reproductive-age participants, ranging from 20 to 55 years of age, who self-reported migraine or severe headaches were evaluated. TBO was estimated using measured height and weight to calculate the BMI. In addition Ab-O was evaluated based on a WC. As in the Ford study,<sup>32</sup> the odds of migraine or severe headache was increased by approximately 39% in woman of reproductive age with TBO (OR 1.39; CI: 1.24–1.56), with a similar result in men of the same age group (OR 1.38; CI: 1.20–1.59). These associations were independent of abdominal obesity for both genders. In addition a very similar association was found between abdominal obesity and migraine or severe headaches in women. In those women of reproductive-age with abdominal obesity, the odds of migraine or severe headache was increased by approximately 39%, (OR 1.39; CI: 1.25–1.56); and this association was independent of TBO. In contrast, while the odds of migraine or severe headache were also increased in men with abdominal obesity, (OR 1.30; CI: 1.13–1.48), it was not independent of TBO.<sup>14</sup>

Confirmatory studies using ICHD criteria and measured body mass indices are needed.

Migraine prevalence and obesity in those of reproductive age conclusions

1. The prevalence of migraine may be increased in those who are underweight as estimated by TBO.
2. The prevalence of migraine may be increased in those with TBO, Confirmatory studies using ICHD criteria and measured body mass indices are needed.
3. The prevalence of migraine may be increased in those with Ab-O.

## Obesity and Migraine in Peri- and Postmenopausal Age

Three general population studies have evaluated the migraine and obesity relationship in peri- and postmenopausal aged participants<sup>14,33,34</sup>. All 3 studies reported no association between migraine prevalence and TBO in women, and one of the studies found a decreased prevalence of migraine in women with abdominal obesity.

In the first of these studies, Mattsson evaluated 684 peri- and postmenopausal women between 40 and 74 years of age, with a mean age of 54 (Table 5).<sup>33</sup> Importantly, this was the first general population study to use both ICHD criteria for the diagnosis of migraine and to estimate TBO using measured body mass indices. Neither migraine prevalence nor migraine attack frequency was associated with TBO.<sup>33</sup>

In the second study of peri- and postmenopausal women, Winter et al evaluated over 63,000 women 45 years of age or older, with a mean age of 54, (Table 5).<sup>34</sup> The diagnosis of migraine was evaluated using self-reported information in a manner previously shown to correlate well with ICHD criteria.<sup>35</sup> TBO was evaluated using self-reported height and weight. Two important findings were noted. First, although an age-adjusted increased relative risk for the prevalence of migraine was found in those with a BMI  $\geq 35$ , adjustment for major cardiovascular risk factors and postmenopausal status completely attenuated this association. This finding supports results from Mattsson et al that there is no association between migraine prevalence and obesity in peri- and postmenopausal women. Second, the Winter et al data support the findings from Bigal et al suggesting that the association between BMI and migraine frequency may be J-shaped. Compared with women with a BMI of 27 and 29, the relative odds of having daily migraine attacks was over 3-fold increased for women with active migraine and a BMI of  $\geq 35$ ; in addition there was an over 2-fold increase for women with active migraine and a BMI of  $<23$ .<sup>34</sup>

The third general population study evaluating the association between migraine and TBO also evaluated older men and evaluated the prevalence of migraine and severe headaches in those older individuals with abdominal obesity.<sup>14</sup> As in the previous studies, Peterlin et al found that TBO was not associated with migraine prevalence in older women and extended this finding to older men (Table 5). However, abdominal obesity was associated with a 26% *decreased* odds of migraine or severe headache in women (OR 0.74; CI: 0.58–0.94), a finding independent of TBO. These results may suggest that the sexual dimorphism and aging-related changes in the metabolic function of adipose tissue, such as seen with cardiovascular disease or all cause mortality or a survivorship bias may play a role in the obesity–migraine relationship.<sup>14</sup>

Further studies using ICHD criteria and measured body mass indices are needed.

Migraine prevalence and obesity in those of peri- and postmenopausal age conclusions

1. Migraine prevalence is not associated with TBO in older women and men.
2. The odds of migraine or severe headache are not increased in older women and men with abdominal obesity.

## THE OVERLAP BETWEEN THE CENTRAL AND PERIPHERAL REGULATION OF FEEDING AND MIGRAINE PATHOPHYSIOLOGY

The reason population-based data suggest an association between obesity with high-frequency episodic migraine and chronic daily headache (and possibly migraine prevalence) is likely multifactorial and may involve more complex mechanisms than just similar peripheral proinflammatory states. Below, we discuss these potential mechanisms that could,

at least in part, explain this association. Specifically, the central and peripheral pathways regulating feeding and adipose tissue function share extensive overlap with pathways implicated in migraine pathophysiology. In the following section we will describe a broad overview of the central and peripheral regulation of feeding and then focus on some of the protein and peptides which play a role in both feeding and migraine pathophysiology.

### The Hypothalamic Regulation of Feeding

Adipose tissue is an active endocrine organ with roles in energy homeostasis, reproduction, as well as immune and inflammatory process among others (Fig. 2).<sup>36</sup> Centrally, the regulation of feeding is controlled by the system involving the arcuate nucleus (ARC) of the hypothalamus and its connections (Fig. 1).<sup>37</sup>

The ARC neurons and its connections are also defined as “the melanocortin system” for their target, the melanocortin receptor. The ARC, or “first order neurons” of the melanocortin system, contains orexigenic and anorexigenic neuropeptides that are the main regulators of energy expenditure and appetite. The primary orexigenic peptides of the ARC consist of the agouti-gene-related protein (AgRP) and neuropeptide Y (NPY) containing neurons which stimulate feeding. The primary anorexigenic peptides consist of the pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) expressing neurons, which inhibit feeding (Fig. 1).<sup>38,39</sup>

There is feedback regulation of the central and peripheral signals involved in feeding and energy balance. For example, signals from adiponectin, leptin, and ghrelin act on the ARC to produce reciprocal activation or inhibition of the POMC/CART neurons while inhibiting or activating the NPY/AGRP neurons.<sup>37</sup> Signals from the ARC neurons are then transmitted to “second order neurons” in several other hypothalamic nuclei which also play a role in energy regulation, including the paraventricular (PVN) nucleus, which express adiponectin and leptin receptors, as well as the ventromedial (VM) and lateral hypothalamus (LH) nuclei.<sup>36–39</sup>

In the LH, there are 2 groups of neurons, the orexin neurons, which stimulate feeding, and the melanin-concentrating hormone (MCH) neurons, which inhibit food intake. In addition the LH, VM, and PVN modulate the activity of the autonomic nervous system. Neurons project from these second order neurons to the brainstem nuclei, the nucleus tractus solitarius (NTS), and the dorsomotor nucleus of the vagus (DMV), where the descending hypothalamic inputs are integrated with the peripheral inputs from the liver and gastrointestinal tract (Fig. 1).<sup>37–39</sup>

### The Hypothalamus and Its Role in Migraine

Hypothalamic involvement has been well described in several headache disorders, including migraine.<sup>40,41</sup> Its role 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.<sup>40</sup> More recently, functional imaging data support these observations, with hypothalamic activation being demonstrated during acute migraine attacks.<sup>41</sup> 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, orexin, adiponectin, and leptin.

**Serotonin**—Serotonin is a neurotransmitter synthesized from the essential amino acid tryptophan. It is hydroxylated by tryptophan hydroxylase to 5-hydroxytryptamine (5-HT) and then decarboxylated to produce serotonin. After release, synaptic serotonin continues to

stimulate pre and post synaptic receptors until it is converted to 5-hydroxyindole acetic acid (5-HIAA) or reabsorbed into the presynaptic neuron.<sup>42</sup>

The serotonin receptors currently thought to be most directly implicated in feeding control mechanisms are 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors, with the postsynaptic 5-HT<sub>1B</sub> and 5-HT<sub>2C</sub> receptors being directly involved in satiety. Activation of either 5-HT<sub>1B</sub> or 5-HT<sub>2C</sub> produces hypophagia.<sup>43</sup> Mice with a disruption of the 5-HT<sub>2C</sub> receptor exhibit increase feeding and develop late-onset obesity and diabetes.<sup>44</sup>

Serotonin has also been linked to several neuronal cell bodies and neuropeptides involved in feeding, including POMC, NPY, and orexin. Serotonergic compounds directly activate the anorexigenic POMC neurons and cause the release of  $\alpha$ -melanocyte-stimulating hormone (MSH) in the hypothalamus.<sup>43</sup> In addition, fenfluramine, a 5-HT<sub>1B</sub> and 5-HT<sub>2C</sub> agonist, has been shown to block NPY induced hyperphagia. And NPY levels have been shown to decrease after treatment with serotonin receptor agonists and to increase after administration of serotonin receptor antagonists. Finally, serotonergic neurons in the dorsal raphe nucleus express orexin receptors and are excited by orexin A.<sup>43</sup>

A full review of the connection between serotonin and migraine is beyond the scope of this article; however, we will briefly summarize key points. Specifically low brain serotonergic activity has been implicated as one of the components in the cascade ultimately resulting in migraine. Inter-ictal levels of plasma serotonin have been shown to be low in migraineurs, along with a 60% increase in 5-HT plasma levels during attacks.<sup>42</sup> Thus, it has been hypothesized that migraine may be a syndrome of chronically low serotonin, which would promote an increased drive to feed but with migraine attacks triggered by a sudden raise in 5-HT release, which would coincide with a decreased feeding drive.<sup>45</sup> Not surprisingly, several drugs that modulate serotonin and its receptors, including those receptors most directly implicated in satiety, the 5-HT<sub>1B</sub> and 5-HT<sub>2C</sub> receptors, are also used in the management of migraine.<sup>42,43</sup>

**Orexin**—As with serotonin, orexin has been linked to migraine and feeding. Specifically, orexin (OX) A and OXB are peptides with neuronal cell bodies primarily localized in the LH (Fig. 1). However, orexin containing neurons have been shown to project to the cortex, thalamus, hypothalamus, brainstem (including the locus coeruleus and the raphe nucleus), as well to the gastrointestinal tract.<sup>46</sup> Orexin acts on 2 G-protein coupled receptors, OXR1 and OXR2, which have been shown to contribute to the regulation of food intake as well as arousal and pain.<sup>47–49</sup>

In animal studies, centrally administered orexin increases food intake and has also been shown to reverse the cholecystokinin-induced loss of appetite. In addition in VAT orexin has been shown to decrease the expression of hormone-sensitive lipase, which suggests that orexin might also modulate adipose tissue metabolism by inhibiting lipolysis.<sup>49</sup>

In addition to their role in feeding, the orexins also participate in inflammatory processes. Several animal studies have demonstrated anti-nociceptive properties of the orexins. In mouse and rat models of nociception and hyperalgesia, intravenous OXA has been shown to be analgesic with an efficacy similar to that of morphine in both the hotplate test and carrageenan-induced thermal hyperalgesia tests.<sup>48</sup> Similarly, intrathecally administered OXA in rats has been shown to inhibit heat-evoked hyperalgesia as well as to reduce mechanical allodynia.<sup>50</sup> Finally, OXA has also been shown to inhibit neurogenic vasodilation as well as TNC neuronal nociceptive responses to electrical stimulation of the dura mater in rats.<sup>51,52</sup>



However, the orexins may also have a pro-nociceptive role. The orexins have been shown to excite the histaminergic neurons in the tuberomammillary nucleus (which terminates in the dorsal raphe nucleus and periaqueductal grey region), which can attenuate the antinociceptive effects of OXA. Specifically OXA activates histamine receptors, H1 and H2; and intra-cerebro-ventricular (ICV) injections of a histamine receptor antagonist along with OXA in mice has shown greater antinociceptive effects than ICV OXA alone.<sup>47</sup> Furthermore, OXA levels have been shown to be elevated in the cerebrospinal fluid of chronic daily headache sufferers.<sup>53</sup> This would suggest that the orexin receptor antagonists, such as ACT-078573 or SB649868, which have been reported to be under development by Actelion and GSK for sleep disorders, could also have a role in migraine therapy.<sup>54,55</sup>

Thus, although the full role of the orexins and their receptors in migraine is still being determined, the current data suggest that the OXA can modulate neurogenic vasodilation, TNC activation, and pain. In addition, the existing data linking OXA and migraine further support the importance of the regulation of the hypothalamus, in not just feeding, but also pain. Further research evaluating orexin levels during or between migraine attacks is warranted.

**Adipocytokines**—In addition to peptides and neurotransmitters, adipocytokines participate in energy homeostasis and the regulation of feeding (Fig. 2).<sup>56</sup> Adiponectin and leptin are 2 such adipocytokines that have been shown to have central and peripheral roles in the regulation of feeding and have been suggested to be altered in migraineurs.<sup>26,57,58</sup>

### Adiponectin

Adiponectin (ADP) is a protein primarily secreted from adipocytes, with receptors expressed in the brain (notably in POMC and NPY neurons of the hypothalamus), the endothelium of blood vessels, as well as in liver and muscle.<sup>56,59</sup> Human plasma ADP can exist as one of several characteristic oligomers or multimers, including high molecular weight (HMW), middle molecular weight (MMW), or low molecular weight (LMW)-ADP.<sup>56,60</sup> It has been noted that women have higher ADP levels than men by puberty.<sup>60,61</sup>

The ADP is most often reported as having anti-inflammatory properties based on the observations that total-ADP (T-ADP) levels are reduced in obesity and type II diabetes. However, elevated levels have been noted in type I diabetes, preeclampsia, and arthritis.<sup>26</sup> Furthermore, several lines of evidence now support adiponectin as exerting either pro- or anti-inflammatory properties depending on the form or multimer involved. For example, the globular head of ADP (gADP) can induce self-tolerance to re-exposure of gADP, as well as tolerance to other pro-inflammatory stimuli,<sup>62</sup> suggesting that a pattern similar to what is seen with serotonin in migraineurs, could exist with gADP, ie, low levels of gADP interictally and increases during acute attacks.<sup>56</sup> In addition the LMW, multimer of ADP has been shown to have anti-inflammatory properties through reduction of interleukin (IL)-6 secretion, while HMW-ADP has been shown to activate nuclear factor kappa- $\beta$  (NFk $\beta$ ) pathways and to induce IL-6 secretion in humans.<sup>63</sup>

The first study to evaluate adiponectin and its multimers in headache sufferers found elevated levels of T-ADP in chronic daily headache sufferers, predominantly due to an elevation in the HMW multimer.<sup>26</sup> And although episodic migraineurs showed a similar trend with higher levels of both T-ADP and HMW-ADP as compared with controls, it did not reach significance. Further and larger studies evaluating adiponectin levels both inside and outside an acute migraine attack are needed to evaluate this relationship more fully.

## Leptin

Leptin is an adipocytokine with roles in appetite suppression and modulation of inflammatory processes. Like adiponectin, leptin is primarily produced by adipocytes, but also by several other tissues including the brain. In addition, leptin receptors are abundantly expressed in the ARC and DM hypothalamus.<sup>64</sup> Leptin is inhibited by testosterone and increased by ovarian sex steroids, with women exhibiting levels that are 2–3 times higher than men even when matched for age and BMI.<sup>65,66</sup>

Mice with a mutation in the gene encoding leptin (ob/ob mice) or the leptin receptor (db/db mice) express an obese phenotype and have defects in immune function.<sup>36</sup> Although elevated leptin levels are associated with an increase in the expression of anorexigenic POMC expression and a decrease in orexigenic NPY and AGRP expression, serum leptin levels are increased in obesity due to leptin resistance. Thus, both leptin deficiency and leptin resistance result in obesity.<sup>38</sup>

Leptin has also been shown to modulate inflammation. Leptin can induce eicosanoid synthesis and the production of nitric oxide and several cytokines including tumor necrosis factor (TNF)- $\alpha$  and IL-6. Similarly, it has been shown that leptin increases IL-6 production in microglia via several pathways, which include leptin receptors and the pro-inflammatory NF $\kappa$ B pathways.<sup>67,68</sup> In models of acute inflammation circulating leptin levels are promptly and greatly increased. Acute infection, sepsis, and rheumatoid arthritis have all been shown to be associated with increased leptin synthesis.<sup>67</sup> Finally, intraperitoneal injections of leptin in mice have also been shown to be associated with an increase in pain sensitivity.<sup>69</sup> However, there are some data suggesting an anti-inflammatory role for leptin. In human adipocytes, chronic stimulation with proinflammatory cytokines for 24 hours has been shown to cause a suppression of leptin production.<sup>70,71</sup>

The first study to evaluate leptin levels in migraineurs evaluated serum leptin levels pre- and post treatment of amitriptyline in 19 patients and of flunarazine in 20 patients.<sup>57</sup> BMI and serum leptin levels were found to be increased at both 4 weeks and 12 weeks post treatment as compared with baseline levels. This suggests that serum leptin levels may have been low at baseline in these patients. However, response to therapy was not evaluated and it is unclear if the changes in leptin levels were entirely due to weight gain or a therapeutic response. In addition, disease duration, abdominal obesity, and sex hormones were not evaluated, all of which could affect leptin levels.<sup>57</sup>

More recently, Guldiken et al evaluated interictal serum leptin levels in migraineurs as compared with age- and gender-matched controls.<sup>58</sup> Lower leptin levels and lower fat mass was found in episodic migraineurs. However, after adjusting for fat mass, there was no significant difference in leptin levels between the groups.<sup>58</sup> It should also be noted that neither sex hormones nor the phase of the menstrual cycle were controlled for in this study. Thus, no firm conclusion as to the change in level of leptin levels in migraineurs can currently be drawn. However, one could speculate that leptin levels may be low in migraineurs who have had the disease for longer durations since the data suggest that chronic exposure to inflammation may be associated with decreased leptin levels.<sup>70,71</sup> Additionally, it is possible that serum leptin levels in migraineurs are elevated, as has been found in other acute inflammatory conditions. Thus, future studies evaluating serum leptin levels in migraineurs with special attention given to disease duration, sex hormones, and the menstrual and life cycle stage in women are warranted.

## The Peripheral Regulation

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 adipocytokine by adipocytes.<sup>36</sup>

Specifically, weight gain leads to the induction of adipocytokines and several pro-inflammatory cytokines, including TNF- $\alpha$ , IL-1, and IL-6; all of which can contribute to local and systemic inflammation (Fig. 2).<sup>36,72</sup> In the next section we will briefly review the role of cytokines in feeding and their link to migraine.

**Cytokines**—Pro-inflammatory cytokines, such as IL-1, IL-6, and TNF- $\alpha$ , are proteins that are predominantly produced by activated immune cells and are involved in amplification of the inflammatory response. Interleukin-6, IL-10, and TNF- $\alpha$  are also expressed or modulated by adipocytes.<sup>37</sup> The extent to which adipocytes modulates their activity varies based on body fat. For example TNF- $\alpha$  is mainly produced by macrophages; and with the increase in resident adipose tissue macrophages with obesity, this results in the main source of TNF- $\alpha$  coming from adipose tissue macrophages. TNF- $\alpha$  has also been shown to induce insulin resistance and inhibit adipocyte differentiation.<sup>56</sup> Similarly one-third of the IL-6 concentration in the circulation of obese individuals comes from adipocytes.<sup>37,60</sup>

Several alterations in cytokines have been reported in patients with migraine. Specifically, serum TNF- $\alpha$  and IL-6 have been shown to be increased in episodic migraineurs, while increased cerebrospinal fluid TNF- $\alpha$  has been demonstrated in chronic daily headache sufferers.<sup>73,74</sup> In addition, serum levels of the anti-inflammatory cytokine, IL-10 have also been shown to be lower following treatment of acute attacks with sumatriptan, suggesting elevated levels of IL-10 during acute attacks.<sup>75</sup> Adiponectin and leptin have been shown to be modulated and to modulate several of these cytokines. Thus, future studies evaluating the effect of cytokines on adipocytokines and of adipocytokines on cytokines in migraineurs would be of interest.

## CONCLUSION

Adipose tissue is a dynamic neuroendocrine organ that participates in multiple physiological and pathological processes, including inflammation.<sup>48</sup> Clinical, population-based, translational, and basic science research show multiple areas of overlap between the central and peripheral pathways regulating feeding and migraine pathophysiology. The current epidemiological research suggests that chronic daily headache prevalence is increased in adults with obesity and that the prevalence of episodic headaches may be increased in reproductive-aged adults with obesity as well. In order to define this relationship more fully, future studies should use standardized methods to estimate obesity and migraine. Further, the gender- and age-related changes of both obesity and migraine should be taken into account.

In addition to the epidemiological associations, basic and translational research has suggested that several proteins and neurotransmitters, which modulate the pathways regulating feeding and energy homeostasis, may also play a role in migraine pathophysiology, including serotonin, orexin, and adipocytokines. Further research into the role of obesity-related neuroendocrine peptides and neurotransmitters, their receptors and biochemical-signaling pathways may help elucidate migraine disease mechanisms and may initiate new preventive strategies.

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## Abbreviations

<b>5-HT</b>	5-hydroxytryptamine/serotonin
<b>Ab-O</b>	abdominal obesity
<b>ADP</b>	adiponectin
<b>AgRP</b>	agouti-gene related protein
<b>ARC</b>	arcuate nucleus of the hypothalamus
<b>BMI</b>	body mass index
<b>CART</b>	cocaine and amphetamine-regulated transcript
<b>CDH</b>	chronic daily headache
<b>DMV</b>	dorsomotor nucleus of the vagus
<b>HMW</b>	high molecular weight
<b>ICHD</b>	international classification of headache disorders
<b>ICV</b>	intra-cerebro-ventricular
<b>IL</b>	interleukins
<b>LH</b>	lateral hypothalamus
<b>LMW</b>	low molecular weight
<b>MCH</b>	melanin-concentrating hormone
<b>MMW</b>	middle molecular weight
<b>MSH</b>	melanocyte-stimulating hormone
<b>NFκ-β</b>	nuclear factor kappa-β
<b>NPY</b>	neuropeptide-Y
<b>NTS</b>	nucleus tractus solitarius
<b>OX</b>	orexin
<b>OXR</b>	orexin receptor
<b>POMC</b>	pro-opiomelanocortin
<b>SAT</b>	subcutaneous adipose tissue
<b>TBO</b>	total body obesity
<b>TNC</b>	trigeminal nucleus caudalis
<b>VAT</b>	visceral adipose tissue
<b>VM</b>	ventromedial hypothalamus
<b>WC</b>	waist circumference

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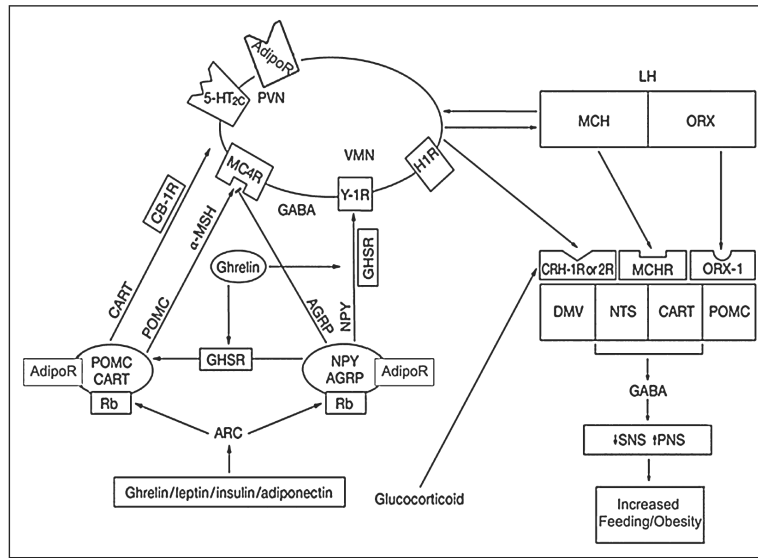
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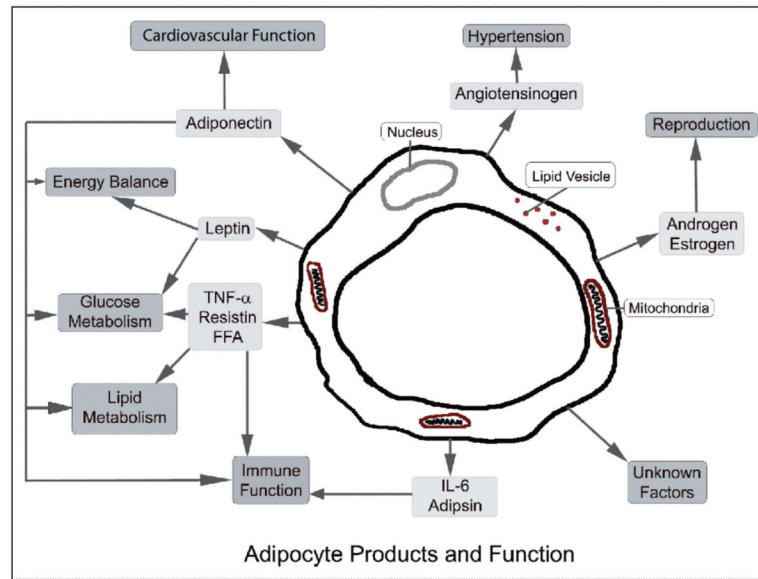
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**Fig 1.**

The Hypothalamic Regulation of Feeding and Adipose Tissue (Modified with permission from Macmillian Publishers LTD: Nature Clinical Practice Gastroenterology & Hepatology, copyright 2005.) One of the most important hypothalamic nuclei involved in regulating feeding is the arcuate nucleus (ARC). The ARC consists of orexigenic peptides that stimulate feeding (the agouti-gene-related protein [AgRP] and neuropeptide Y [NPY] containing neurons,) and anorexigenic peptides that inhibit feeding (the pro-opiomelanocortin [POMC] and cocaine and amphetamine-regulated transcript [CART] expressing neurons). There is feedback regulation of the central and peripheral signals involved in feeding and energy balance. For example, signals from adiponectin and leptin act on the ARC to produce reciprocal activation or inhibition of the POMC/CART neurons while inhibiting or activating the NPY/AGRP neurons (AdipoR, adiponectin receptor; Rb, leptin receptor). The ARC neurons or “first order neurons” are also defined as “the melanocortin system” for their target, the melanocortin receptor 4. POMC activation from peripheral signals triggers the release of  $\alpha$ -melanocyte stimulating hormone (MSH) from axon terminals, which then activates melanocortin-4-receptors (MC4R), resulting in suppression of food intake. Signals from the ARC neurons are then transmitted to “second order neurons” in several other hypothalamic nuclei that also play a role in energy regulation, including the paraventricular (PVN), ventromedial (VM), and lateral hypothalamus (LH). Specifically in the LH are 2 groups of neurons, the orexin neurons, which stimulate feeding, and the melanin-concentrating hormone (MCH) neurons, which inhibit feeding. These second order neurons (the LH, VM, and PVN) modulate the activity of the autonomic nervous system (ANS) and project to the brainstem nuclei, the tractus solitarius (NTS), and the dorsomotor nucleus of the vagus (DMV), where the hypothalamic signals are integrated with peripheral inputs from the gastrointestinal system and liver.



**Fig 2.** Adipocyte Products and Function (Modified with permission from Macmillan Publishers Ltd: Nature Reviews Immunology, Adipocytokines: mediators linking adipose tissue, inflammation and immunity, copyright 2006.)

**Table 1**

Major Characteristics of Adipose Cells From Subcutaneous Adipose Tissue (SAT) Depots and Visceral Adipose Tissue (VAT) Depots<sup>10-12</sup>

Biochemical factor	Regional difference	Physiological effect
Adiponectin secretion	SAT > VAT	Increased insulin sensitivity
Leptin	SAT > VAT	Decreased insulin sensitivity
Secretion		Decreased CNS regulation of VAT
Estrogen receptor- $\beta$	SAT > VAT	
Insulin anti-lipolytic effect	SAT > VAT	Increased free fatty acids and triglyceride turnover
Interleukin-6	VAT > SAT	Cardiovascular risk Inflammation
Catecholamine lipolytic response	VAT > SAT	
Angiotensinogen	VAT > SAT	Increased blood pressure
Plasminogen activator inhibitor-1	VAT > SAT	Cardiovascular risk
Glucocorticoid receptors	VAT > SAT	Increased lipoprotein lipase and triglyceride storage

SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.

**Table 2**

WHO Criteria for Total Body Obesity as Estimated Based on Body Mass Index and Abdominal Obesity as Estimated Based on Waist Circumference

WHO criteria for total body obesity for men and women		
BMI < 18.5	Underweight	
BMI 18.5–24.9	Normal weight	
BMI 25–29.9	Grade I obesity	Overweight
BMI 30–39.9	Grade II obesity	Severe overweight
BMI ≥ 40	Grade III obesity	Morbid obesity
WHO criteria for abdominal obesity		
Men		
WC < 94	Normal weight	
WC 94–102	Action level 1	Overweight
WC > 102 cm	Action level 2	Abdominal obesity
Women		
WC < 80	Normal weight	
WC 80–88 cm	Action level 1	Overweight
WC > 88 cm	Action level 2	Abdominal obesity

BMI = body mass index; WC = waist circumference.

**Table 3**

Migraine and Obesity in Chronic Daily Headache

Reference	Study Design	Sample Size	Gender	Mean age (range)	Obesity diagnosis	HA diagnosis	Findings
Scher et al (2003) <sup>8</sup>	Long-Gen Pop	Total: 1,932 EH: 798 CDH: 1,134	Both together	EH: 41 years CDH: 40 years (18–65)	Self-reported TBO	Non-ICHD	No difference in TBO prevalence in those with EH as compared with those with CDH.  The prevalence of CDH was higher in those with TBO grade II (OR 1.34; CI: 1.0–1.8).  Transformation of EM to CDH (or incident CDH) at 11 months was associated with TBO (OR 5.28; CI: 1.3–21.1)  The prevalence of CDH was higher in those with TBO grade II (OR 1.3; CI: 1.1–1.6).  The prevalence of transformed migraine was associated with those with TBO grade II (BMI <math>\geq 30</math>), while the prevalence of CTTH was only associated with those with a BMI <math>\geq 35</math>.
Bigal and Lipton (2006) <sup>25</sup>	CS-Gen Pop	Total: 30,849 CDH: 1,243 – 401 TM – 863 CTTH	Both together	39 years (18–89)	Self-reported TBO	Modified Silberstein-Lipton Criteria TM/ICHD CTTH	
Peterlin et al (2008) <sup>26</sup>	Clinic-based Pop (age and BMI matched)	Total: 37 CDH: 12 EM: 12	Women only	34 years	Measured TBO and Ab-OB	ICHD	Despite participants being BMI matched, CDH sufferers had greater frequency of abdominal obesity, as estimated by the WHR, than EM and controls, $P = .049$ .

Ab-OB = abdominal obesity; BMI = body mass index; CDH = chronic daily headache; CS = cross-sectional; EH = episodic headache; EM = episodic migraine; ICHD = International Classification of Headache Disorders; Long = longitudinal; NL = normal; TBO = total body obesity; WC = waist circumference; WHR = waist to hip ratio.

Table 4

## Migraine and Obesity in Reproductive-Aged Participants

Reference	Study design	Sample size	Gender	Mean age (range)	Obesity diagnosis	HA diagnosis	Findings
Peres et al (2005) <sup>28</sup>	Clinic-based Pop	Total: 144 (74 pts TBO vs 70 age-matched controls)	Both together	39 years (14–69)	?	ICHD	75% of those w/TBO had life-time HA diagnosis as compared with 42% of controls, $P < .001$ . Migraine reported by 66% those w/TBO as compared with 18.5% of non-obese controls, $P < .0001$ . 63% of those w/TBO had EH 48% of those w/TBO had migraine
Horev et al (2005) <sup>29</sup>	Clinic-based Pop	Total: 27 (27 TBO pts)	Women only	40 years (21–61)	?	ICHD	The crude prevalence of migraine in both men and women together was higher in those underweight (15.8%) vs those w/NL weight (13.1 %) and remained significant in women after adjustments.
Bigal et al (2006) <sup>30</sup>	CS-Gen Pop	Total: 30,215 EM: 3,791	Combined and Separate	39 years (18–89)	Self-reported TBO	ICHD	The crude prevalence of migraine in men w/TBO as estimated by BMI 35 (8.8%) was greater than in those w/NL weight, (7.2%), $P < .01$ , but did not remain significant after adjustments. The prevalence of HFEM was increased in participants w/TBO (13.6%) as compared with those w/NL weight (4.4%).
Keith et al (2008) <sup>31</sup>	CS-Gen Pop Metaanalysis of 11 databases	Total: >200,000 EM: ?	Women only	? (16 to 94)	Mixed self-reported and measured TBO	Non-ICHD	Obese women had increased risk for headache as compared with those with BMI 20. Those who were underweight (OR 2.01; CI: 1.34, 3.02) or with TBO (OR 1.37; CI: 1.09, 1.72) had increased odds for having migraine or severe headaches compared with those with BMI of 18.5 to 24.9.
Ford et al (2008) <sup>32</sup>	CS-Gen Pop	Total 7,601 EM: 1,649	Combined and Separate	46 years (20–85)	Measured TBO	Non-ICHD	Migraine prevalence was increased in those with TBO, using measured height & weight. (Women: OR 1.39; CI: 1.25, 1.56; Men: 1.30; CI: 1.13, 1.48)
Peterlin et al (2009) <sup>14</sup>	CS-Gen Pop	Total 15,531 ( 55 years) EM: 3,915	Genders separate	38 years (20–55)	Measured TBO and Ab-OB	Non-ICHD	Migraine prevalence was increased in those with abdominal obesity (WC). (Women OR 1.39; CI: 1.25, 1.56; Men: 1.30; CI: 1.13, 1.48)

Ab-OB = abdominal obesity; BMI = body mass index; CDH = chronic daily headache; CS = cross-sectional; EH = episodic headache; EM = episodic migraine; ICHD = International Classification of Headache Disorders; Long = longitudinal; NL = normal; TBO = total body obesity; WC = waist circumference; WHR = waist to hip ratio.

**Table 5**

Migraine and Obesity in Peri- and Postmenopausal-Aged Participants

Reference	Study design	Sample size	Gender	Mean age (range)	Obesity diagnosis	HA diagnosis	Findings
Mattsson (2007) <sup>33</sup>	CS-Gen Pop	Total: 684 EM: 130	Women only	54 years (40–74 years)	Measured TBO	ICHHD	Neither migraine prevalence or migraine attack frequency was assoc w/TBO, using measured body mass indices in older women.
Winter et al (2009) <sup>34</sup>	CS-Gen Pop	Total: 63,467 EM: 9,195	Women only	54 years ( 45 years)	Self-reported TBO	Based on ICHHD	There was no association between TBO, by self-reported BMI, and active migraine or prior history of migraine in older women.
Peterlin et al (2009) <sup>14</sup>	CS-Gen Pop	Total: 6,152 (>55 years) EM: 749	Both genders separately	68 years ( 55 years)	Measured TBO and Ab-OB	Non-ICHHD	Migraine prevalence was not associated with measured total body or abdominal obesity in older men.  Migraine prevalence was not associated with measured TBO in older women.  Migraine prevalence was <i>decreased</i> in older women with abdominal obesity (WC).

Ab-OB = abdominal obesity; BMI = body mass index; CDH = chronic daily headache; CS = cross-sectional; EH = episodic headache; EM = episodic migraine; ICHHD = International Classification of Headache Disorders; Long = longitudinal; NL = normal; TBO = total body obesity; WC = waist circumference; WHR = waist to hip ratio.