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Migraine and obesity: moving beyond BMI

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> "The risk of migraine of all frequencies (episodic and chronic) is increased in those with obesity. In addition, the risk of migraine increases with increasing obesity status."

It has been over a decade since the publication of the first study evaluating the epidemiological association between obesity and headache [1]. Since Brown *et al.*'s study in 2000, multiple clinical and general population studies have followed [1–3]. Methodological differences in this early research generated some controversy. Some hypothesized that the disease risk between migraine and obesity was modified by age, being stronger in those of reproductive age compared with peri- or post-reproductive aged individuals; others hypothesized that this association was limited to only those with high-frequency or chronic migraine (CM). Notably, those general population studies evaluating only older individuals found no association between obesity and migraine. By contrast, all general population studies evaluating reproductive-age individuals reported significant associations between migraine and obesity, with the exception of studies that included individuals with other headache types, remitted migraine and chronic daily headaches in the control group [2,4].

Most recently, Peterlin *et al.* evaluated the episodic migraine (EM)–obesity relationship in a cross-sectional, general population analysis of over 3800 participants [4]. Controls included participants with no headache of any type and excluded remitted migraineurs. In general, obese individuals had an 81% increased risk of EM compared with those of normal weight (odds ratio: 1.81; 95% CI: 1.27–2.57; p = 0.001). In addition, subgroup analyses demonstrated that even the odds of low-frequency EM and very low-frequency EM were increased in those with obesity (low-frequency EM: odds ratio: 1.83;95% CI: 1.26–2.65; very low-frequency EM: odds ratio: 1.89; 95% CI: 1.29–2.78). Thus, this study extended the

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migraine–obesity relationship to include EM of all frequencies. These findings also substantiated previous data suggesting that the risk of EM increased with increasing obesity status from normal weight to overweight to obese [4].

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While the extension of the migraine–obesity association to include episodic migraineurs may appear to be only of theoretical interest, there are concrete implications for the design and development of clinical trials and treatment strategies. First, EM (12%) is much more prevalent than CM (<2%). Not addressing the potential impact of obesity when participants have EM excludes the greatest number of those in whom this relationship impacts. Second, it could also lead to a lost opportunity to modify an episodic migraineur's risk of progression to CM and leave clinicians with harder-to-treat patients. Third, given that CM patients are less responsive to treatments, exclusion of EM patients from studies evaluating weight-loss strategies could also lead to a greater likelihood of null findings and lost opportunities to identify effective weight-loss therapies for migraineurs. Finally, it is crucial to understand how these two disorders are related in humans in order to adequately design translational and basic science mechanistic studies.

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Given that multiple epidemiological studies have confirmed that obesity is comorbid with migraine, the question now is: where do we go from here? One of the most important epidemiological questions remaining is the direction of the migraine–obesity association. Vo *et al*. have shown that women with a history of pediatric migraine had higher weight gain as young adults [5]. In order to determine which comes first – obesity or migraine – prospective, longitudinal, general-population studies following children into adulthood are necessary. Second, in order to obtain a better understanding of how these two disorders interact, it may be time to move beyond reliance on BMI. Although anthropometric indices are inexpensive and useful surrogate estimates of obesity in general (especially in large-scale epidemiological research), ideally, obesity should be defined as an excess of adipose tissue, not an excess of weight (which includes lean, bone, organ and skin mass, as well as adipose tissue mass) [3]. Imaging measurements (e.g., MRI) of adipose tissue mass allows for more direct evaluations of adipose tissue, as well as the differentiation of the subcutaneous adipose tissue (SAT) and visceral adipose tissue masses. It has been hypothesized that differences in the volume and/or ratio of SAT and visceral adipose tissue in those with migraine as compared with those without could contribute to the migraine–obesity association [3,6–8]. Further-more, it is known that there is differential expression of several inflammatory-related proteins and receptors based on the depot location as SAT or visceral adipose tissue. Recent data support that one such protein, adiponectin, which is predominantly secreted from SAT, may be a marker of acute treatment response in migraineurs [9,10]. These possibilities are currently being further explored in ongoing research.

It may also be time for greater emphasis to be placed on how obesity modulates pain, and in particular, headache disorders. Rossi *et al.* have demonstrated that diet-induced obesity in mice 'primes' the trigeminal nociceptive pathway, rendering it responsive to an otherwise innocuous stimulus [11]. In this study, Rossi *et al.* used intradermal capsaicin in the skin, innervated by the trigeminal nerve, and found that a low dose of capsaicin that had no effect on mice fed a regular diet was sufficient to cause activation of second-order neurons in the trigeminal nucleus caudalis in obese mice [11]. Further research is needed to determine whether peripheral or central structures, or perhaps both, are implicated in this phenomenon. Interestingly, in another study, trigeminal thermal nociception in untreated obese mice appeared to be normal, suggesting that an underlying pain disorder may be necessary to unveil the effects of obesity on pain perception [12]. A better understanding of the pathophysiologic underpinnings of the migraine–obesity association is needed in order to truly understand this complex relationship and, more importantly, to allow the development of targeted therapeutic strategies for overweight migraineurs.

The initial steps evaluating weight-loss strategies in severe and morbidly obese migraineurs have already begun. Bond *et al.* conducted the first clinic-based study to evaluate changes in headache frequency after bariatric surgery in obese episodic migraineurs (BMI ≥35 kg/m^2) [13]. 3 months postoperatively, they found a reduction in monthly headache frequency from 3.7 to 2.2 headache days per month ($p = 0.01$) [13]. Subsequently, Novak *et al.* conducted a clinic-based study evaluating the impact of bariatric surgery in severe or morbidly obese migraineurs with similar findings, as well as additional improvement 6 months after surgery [14]. Most recently, Gunay *et al.* conducted a retrospective study of morbidly obese migraine patients who underwent Roux-en-Y gastric bypass [15]. Approximately 90% reported total or partial resolution of their migraines.

While these data are encouraging to suggest that bariatric surgery may have a role in the treatment of migraine in those with severe or morbid obesity, none of these studies included a control group. Thus, larger controlled studies evaluating bariatric surgery for migraine prevention are still needed. In addition, weight-loss strategies (e.g., diet and exercise studies) for those who do not qualify (e.g., BMI <35) or who do not choose to undergo bariatric surgery are warranted.

In addition to bariatric surgery, the impact of weight loss from behavioral weight loss strategies, such as diet and exercise, for migraine prevention, is not known. Although several randomized, clinical trials have consistently demonstrated reductions in migraine frequency with exercise, none of these studies were designed to determine if it was the exercise itself or the associated weight reduction that accounted for the improvement in headache frequency [16–18]. Similarly, although a variety of diets (e.g., high-fat, high-protein and low-carbohydrate diets) have been tried for headache prevention in migraineurs, all such studies have been either negative or methodologically flawed, preventing conclusions. Thus, we currently remain without definitive scientific evidence substantiating the efficacy of any particular diet or exercise regimen as a weight-loss therapy for migraine prevention. Encouragingly, several research teams are currently conducting prospective, randomized clinical trials that involve testing the efficacy of specific behavioral weight-loss therapies (diet and exercise) for migraine prevention.

Taken together, the current data supports that obesity is comorbid with migraine. The risk of migraine of all frequencies (episodic and chronic) is increased in those with obesity. In addition, the risk of migraine increases with increasing obesity status. Mechanisms for the migraine–obesity association have been hypothesized to be due to shared pathophysiological abnormalities (e.g., changes in hypothalamic activation and modulation of shared neurotransmitters and proteins [e.g., serotonin and adiponectin]; and/or to lifestyle choices [e.g., decreased exercise in migraineurs due to pain]). Limited, uncontrolled, research supports that bariatric surgery in severe or morbidly obese episodic migraineurs is associated with a reduction in headache frequency [13–15]. However, the role of weight loss from diet and exercise in overweight and obese migraineurs remains to be determined.

Future research evaluating potential mechanisms for the migraine–obesity association, as well as pharmacological and behavioral weight-loss treatment strategies for overweight and obese migraineurs, are needed. At present, pending further research, what we can say is that clinicians should actively provide migraine patients with education on the increased risk of migraine in those who are obese. In addition, we should appropriately tailor our choices of medications based on our patients' obesity status, given that many have the ability to both positively and negatively impact weight, and we should promote that our migraine patients maintain healthy lifestyle choices in both their diet and exercise routines.

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Biographies

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