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Metabolic syndrome and migraine

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Migraine and metabolic syndrome are highly prevalent and costly conditions. The two conditions coexist, but it is unclear what relationship may exist between the two processes. Metabolic syndrome involves a number of findings, including insulin resistance, systemic hypertension, obesity, a proinflammatory state, and a prothrombotic state. Only one study addresses migraine in metabolic syndrome, finding significant differences in the presentation of metabolic syndrome in migraineurs. However, controversy exists regarding the contribution of each individual risk factor to migraine pathogenesis and prevalence. It is unclear what treatment implications, if any, exist as a result of the concomitant diagnosis of migraine and metabolic syndrome. The cornerstone of migraine and metabolic syndrome treatments is prevention, relying heavily on diet modification, sleep hygiene, medication use, and exercise.

Keywords: migraine, metabolic syndrome, obesity, hypertension, hyperlipidemia, insulin resistance, prothrombotic state, inflammatory state

INTRODUCTION

Migraine is a condition that is usually characterized by a moderate or severe throbbing headache, unilateral pain, nausea or vomiting, light and sound sensitivity, and disability. Neurologic, gastrointestinal (Aurora et al., 2007), and autonomic symptoms (Blau, 1992) may be present. Experts believe that some individuals have a genetic predisposition for migraine (Van Den Maagdenberg et al., 2010) and defective pain control mechanisms (Aderjan et al., 2010). Vascular dilation and inflammation (Viola et al., 2010) occur in acute migraine, but migraine is now felt to be a neuronal disorder (Ba’albaki and Rapoport, 2008). Migraine pathogenesis involves the release of inflammatory neuropeptides [such as calcitonin gene-related peptide (CGRP)], trigeminal activation (Buzzi and Tassorelli, 2010), and cortical spreading depression (Milner, 1958; Ayata, 2010; Viola et al., 2010). Migraine is associated with many comorbid central and peripheral disorders, such as ischemic stroke, Raynaud phenomenon, depression, anxiety, obesity, and possibly metabolic syndrome (Guldiken et al., 2009; Buse et al., 2010). The interplay and causality of migraine and its comorbid disorders is not well understood (Marmura, 2009), particularly in regard to migraine’s association with obesity and metabolic syndrome.

Metabolic syndrome includes a number of abnormalities, including hypertension, insulin resistance, atherogenic dyslipidemia, a proinflammatory state, a prothrombotic state, and increased waist circumference or obesity (Alberti et al., 2006). Several organizations have proposed diagnostic criteria for metabolic syndrome (Alberti et al., 2006), contributing to confusion concerning the most useful definition in any given patient population. Some have questioned if diagnosing metabolic syndrome is useful to patient care (Kahn et al., 2005; Ansilver et al., 2006). The presence of metabolic syndrome has been associated with a significant risk of cardiovascular disease (Mottillo et al., 2010), stroke (Gupta et al., 2010), and type 2 diabetes (Aschner, 2010). Obesity may also be a risk factor for migraine, especially chronic migraine.

METABOLIC SYNDROME, INSULIN RESISTANCE, AND MIGRAINE

Although studies of metabolic syndrome components (hypertension, hyperlipidemia, insulin resistance, adiposity) and migraine exist, only one study characterized metabolic syndrome patients with migraine. Guldiken et al. (2009) surveyed 210 patients who met Adult Treatment Panel 3 (ATP III) criteria for metabolic syndrome. They assessed headache symptoms lasting more than a year and meeting International Classification of Headache Disorders-II (ICHD-II) criteria for migraine. Patients with migraine and metabolic syndrome (n = 41, 19.5%) were significantly more likely to have diabetes, increased waist circumference, and elevated body mass index than patients with metabolic syndrome without migraine. These findings indicate that insulin resistance may be associated with migraine pathogenesis. Several lines of evidence support this theory. Studies of migraine triggers indicate that 46.3% (Yadav et al., 2010) – 57.3% (Hauge et al., 2010) of migraineurs associate fasting with migraine onset. Additionally, two clinic-based population studies of ICHD-II–defined adult migraineurs found that insulin resistance is significantly altered in (1) young, non-obese, non-diabetic, normotensive migraine patients as opposed to healthy control subjects (Rainero et al., 2005), and (2) migraine patients compared with non-migraine headache patients (Cavestro et al., 2007). One group reported a link between insulin receptor gene polymorphism at locus 19p13.3/2 and migraine with aura (McCarthy et al., 2001; Kaunisto et al., 2005; Curtin, 2006; Netzer et al., 2008), although it is unclear if this polymorphism confers a loss or gain of function. While insulin receptors are found in many regions of the brain, the signals that these receptors propagate and the effect of resistance on their activity remains unclear. The clinical characteristics of migraine...
itself may lead to metabolic syndrome. Physical activity usually worsens migraine symptoms during acute attacks, which could lead patients to avoid exercise (ICHD-2 criteria for migraine). Affective disorders or medications used to treat migraine, such as antidepressants, commonly cause weight gain (Young and Rozen, 2005; Table 1). Even topiramate, which tends to decrease weight, may worsen or cause dyslipidemia (Franzoni et al., 2007).

**SYSTEMIC BLOOD PRESSURE AND MIGRAINE**

A few studies have reported the presence of blood pressure abnormalities (systolic or diastolic) in migraine. Hypertension is clearly linked to cerebrovascular disease (Netzer et al., 2008) and has been associated with self-reported headache (subtype unspecified; Cirillo et al., 1999). Severe headache is a common symptom of a hypertensive emergency. Blood pressure abnormalities have been associated with migraine in pregnancy (Adeney and Williams, 2006), migraine with aura, and chronic migraine (Granella et al., 1987). Migraine is a risk factor for pre-eclampsia and gestational hypertension (Allais et al., 2010). Studies of hypertension in non-pregnant adults with migraine are conflicting. A large demographic study positively associated migraine with systolic hypertension (Gudmundsson et al., 2006) but diastolic hypertension has been associated with increased frequency of episodic migraine in one study (Gudmundsson et al., 2006), but diastolic hypotension was non-significantly associated with migraine in another study (Seçil et al., 2010). Some have suggested that autonomic dysfunction is an important part of migraine; many migraineurs exhibit symptoms, such as diarrhea or sweating, tied to sympathetic over-activity (Mélek et al., 2007). Further study will be required to assess the role of blood pressure abnormalities in migraine.

**MIGRAINE AND OBESITY**

Obesity is a major public health problem (Friedman, 2009). Obesity has been associated with numerous pain syndromes, including chronic pain (Ray et al., 2010), fibromyalgia (Okifuji et al., 2010), low back pain (Heuch et al., 2010), and neck pain (Mäntyselkä et al., 2010). Migraine patients may have multiple metabolic abnormalities associated with obesity, including cerebrospinal fluid (CSF) neuropeptide Y elevation (Valenzuela et al., 2000), CSF tumor necrosis factor alpha (TNF) elevation (Rozen and Swidan, 2007), and systemic adiponectin depression (Peterlin et al., 2007). Given the recently characterized metabolic activity of adipose tissue (Bigal et al., 2007a), the interaction between obesity and migraine is particularly complex and has been the subject of multiple large and conflicting studies.

Population-based studies suggest that obesity is not associated with migraine prevalence (Bigal et al., 2006b) but may be a risk factor for the transformation of episodic migraine to chronic migraine (Scher et al., 2003; Bigal and Lipton, 2006). Bigal et al. studied 30,215 subjects, 3,791 of whom reported migraine symptoms. In age-, education-, and race-adjusted models, migraine prevalence was not significantly associated with elevated body-mass index (BMI). However, increasing weight was associated with increasing headache frequency, severity, and disability (Bigal et al., 2006a). Bigal et al. (2007b) further identified 18,968 migraine patients from a validated, mailed survey and compared them to patients with probable migraine and severe episodic tension-type headache. Bigal et al. (2007b) found that BMI and headache frequency and disability were positively correlated in the migraine patient population but not in other headache groups. Winter et al. (2009) confirmed these findings in a survey of 63,467 women age 45 years, wherein they found that women with a high BMI (morbid obesity) and current (as opposed to historical) migraine attacks were more likely to suffer from more frequent migraine (OR 3.11 for daily migraine vs. lower BMI groups) and migraineurs with photophobia and photophobia but not with aura. Finally, Tietjen et al. (2007) studied 721 migraine patients recruited from eight study centers and found that patients with migraine, obesity, depression, and anxiety had greater migraine frequency and migraine-related disability.

Several studies failed to find any association between migraine and obesity. Keith et al. (2008) surveyed 11 independent datasets totaling 220,370 females with headache, reporting no association between diagnosed migraine and BMI. Molarius et al. (2008) found no association between obesity and self-reported migraine in a survey of 43,770 patients. Mattsson (2007) studied 684 females age 40–74 and did not find any association between obesity and migraine prevalence, frequency, severity, or disability. Tellez-Zenteno et al. (2010) surveyed 1,371 migraine patients and 612 age- and gender-matched controls. They found that migraine patients were more likely to be overweight but less likely to be obese or morbidly obese (Tellez-Zenteno et al., 2010). They additionally did not find any association between weight and headache severity or frequency (Tellez-Zenteno et al., 2010). Unfortunately, many patients with migraine are unaware of their diagnosis, often labeling frequent headaches as “sinus” or “stress” headaches (Eross et al., 2007).

A number of smaller studies found an association between BMI and migraine prevalence. Peterlin et al. (2010) proposed that differences in visceral as opposed to subcutaneous adipose tissue may help explain sex differences in migraine prevalence. Women
after menopause and men both tend to have more abdominal obesity stored in visceral tissue, placing them at increased risk for hypertension, hyperlipidemia, and cardiovascular events. Subcutaneous fat, often in the gluteo-femoral region in women, appears to increase leptin and adiponectin levels, which may impair insulin sensitivity and modulation of inflammatory processes contributing to migraine risk. In a 7,601 patient sub-population of the National Health and Nutrition Examination Survey, Ford et al. (2008) reported that overweight and underweight patients were more likely to suffer from migraine. Horev et al. (2005) interviewed 27 morbidly obese women patients, reporting migraine symptoms in 13 patients (10 with aura) and tension-type headache in an additional 4 patients. In the adolescent population, Pinhas-Hamiel et al. (2008) surveyed 273 individuals and uncovered 39 children with headache and 15 with migraine. Increasing weight was associated with increased headache prevalence (Pinhas-Hamiel et al., 2008). Of note, migraine patients tend to significantly underestimate self-reported weight and BMI when compared with actual measurements (Katsnelson et al., 2009).

THE METABOLIC ACTIVITY OF EXCESS ADIPOSE TISSUE LIKELY CONTRIBUTES TO A PROINFLAMMATORY STATE, CONTRIBUTING TO MIGRAINE PATHOGENESIS

While the relationship between migraine and obesity is controversial, most large studies suggest that obesity is not associated with migraine prevalence, but may be associated with increased headache frequency.

Multiple neurotransmitters and hormones, including CGRP, substance P, neuropeptide Y (Valenzuela et al., 2000), adiponectin (Peterlin et al., 2007), leptin (Guldiken et al., 2008), orexin-A (Ray and Kumar, 2010), interleukin (IL)-1 (Yilmaz et al., 2010), IL-6, and TNF-α have been implicated in migraine pathogenesis (Rozen and Swidan, 2007; Yilmaz et al., 2010). Adipocytes and associated macrophages are known to be metabolically active (Bigal et al., 2007a), producing many mediators of migraine. Adiponectin and leptin, hormones involved in the regulation of appetite and metabolism, play a central role in adipose tissue development and subsequent aberrations in the metabolic milieu of obesity (Arita et al., 1999; Stofkova, 2009). Serum adiponectin levels have been inversely correlated with BMI (Arita et al., 1999) and adiponectin may mediate many of the inflammatory metabolites associated with migraine (Peterlin et al., 2007). Leptin is an adipose-derived hormone that helps regulate appetite and metabolism, produced by adipose tissue and increased in obese patients. Leptin acts on receptors in the hypothalamus combating the effect of feeding stimulants, such as neuropeptide Y, reducing appetite (Peterlin, 2009). Elevated serum leptin is also known to enhance both innate and adaptive immune system activity (Stofkova, 2009). In one study of episodic migraine subjects, Leptin was decreased compared to controls with similar BMI (Guldiken et al., 2008), but the duration of disease may be an overlooked factor. In patients with acute inflammation, levels are increased, but they decrease with chronic exposure to inflammation, suggesting that patients with a long history or frequent migraine would be at greatest risk of weight gain (Peterlin, 2009).

Vascular dilation and inflammation are thought to contribute to migraine pathogenesis and pain symptoms. Inflammatory and immune mediators, including TNF-α, IL-1, CGRP, orexin, and IL-6, are involved in migraine pathogenesis, and substance P, CGRP, and IL-6 are elevated during acute migraine attacks (Jang et al., 2010). TNF-α is a proinflammatory molecule produced by excess adipose tissue (Rönnemaa et al., 2000) and serum TNF-α levels are elevated in menstrual migraine (Mueller et al., 2001). The gain of function TNF-α-308 A and IL-1β + 3953 T allele gene polymorphisms are elevated in patients with migraine without aura (Yilmaz et al., 2010), although the implications are unclear. CGRP is a neurotransmitter that mediates nociceptive transmission from the trigeminal nerve complex to the thalamus (Summ et al., 2010). Elevated CGRP levels have been detected in obese patients, conferring further risk of migraine in susceptible patients (Recober and Goadsby, 2010). Similarly, IL-6 is elevated in migraine patients regardless of current treatment protocol and is thought to lower the pain thresholds. Orexin-A and B receptors have been studied in migraine. Orexin-A is thought to depress CGRP release (Holland et al., 2005), and orexin activation is thought to confer resistance to dietary related features of metabolic syndrome (Funato et al., 2009). Migraine and obesity independently give rise to an altered inflammatory and immune marker milieu, and further research will be required to elucidate how these two diseases interact.

IT IS UNCLEAR IF OBESITY CAUSES MIGRAINE OR IF MIGRAINE CAUSES OBESITY

Obesity, like other comorbid states in migraine, is a result of genetic and environmental susceptibility to disease. It is unclear if migraine, or its treatment, is a cause of obesity, or if obesity causes increased migraine frequency. Exercise increases endorphin levels and pain tolerance and in rats decreases opioid usage (Hoseini et al., 2009) and increases insulin sensitivity (Su et al., 2005). Physical activity tends to exacerbate symptoms of migraine, so it is likely that patients with frequent migraine would avoid strenuous activity. In most studies, obesity does not predispose to increased migraine prevalence, but it could be a risk factor for more frequent or severe attacks.

MIGRAINE AND PROTHROMBOTIC STATE

Metabolic syndrome is associated with an acquired prothrombotic state. Thrombosis is a leading cause of multiple cardiovascular and cerebrovascular disease processes. Migraine, particularly migraine with aura, is associated with an increased risk of cardiovascular and cerebrovascular disease in epidemiological studies (Kurth et al., 2006; Allais et al., 2008); however, objective ultrasound-based measures of atherosclerosis do not support a greater atherosclerotic burden in migraineurs when compared with headache-free controls (Moschiano et al., 2007). Migraine without aura is not associated with an increased burden of vascular disease (Kurth et al., 2006). Certain migraine syndromes, particularly in migraine with aura, are associated with computed tomography and magnetic resonance imaging findings, including infarct-like white matter changes (Moschiano et al., 2007). These infarcts may accumulate over time as seen on follow-up studies (Kruit et al., 2010). The cause of these findings are unclear, but seem to correlate with attack frequency. One possibility is that spreading oligemia during migraine aura may lead to subclinical ischemia. There is no evidence to support anticoagulation in migraine and it is
unclear whether an acquired prothrombotic state would increase the prevalence of migraine.

Gain of function platelet glycoprotein polymorphisms have been associated with a minor increase in risk of migraine; however, these polymorphisms have been more strongly associated with multiple neurologic phenomena and a putative mechanism for the association with migraine requires further study (Herak et al., 2009). In the pediatric migraine population, factor V Leiden, factor II G20210A, methylenetetrahydrofolate reductase (MTHFR) C677T, and A1298C mutation frequency are not significantly associated with migraine; however elevated homocysteine and depressed folate levels may be (Bottini et al., 2006). Except in cases with antiphospholipid antibody syndrome (Asherson et al., 2007) and patient foramen ovale (PFO; Wilmhurst et al., 2005), anticoagulation or antithrombotic agents do not appear to prevent migraine.

Adult and pediatric patients with migraine with aura are significantly more likely to have PFO than those in the general population. PFO-associated microembolization of cortical vasculature may contribute to the initiation of cortical spreading depression in migraine with aura (Rigatelli et al., 2010). An observational, prospective study reports that 89% of migraine patients with PFO improved following closure, with 46% reporting cure at 12 months (Trabattoni et al., 2011). However, a randomized, double-blind, sham-controlled trial did not find a significant association from PFO closure and improved migraine symptoms (Dowson et al., 2008).

**Clinical Implications**

Migraine treatment may be acute or preventive, and patients with severe, frequent attacks may require both. Because patients with chronic migraine have frequent or even daily headaches, preventive treatments are key, and preventive treatments, such as weight loss and behavior modification, are critical to avoiding the development of metabolic syndrome and managing and avoiding the cardiovascular implications of the disease (Bond et al., 2010). However, significant controversy exists regarding the relationship between metabolic syndrome and migraine and the effect that treating one has on abating the other. Further, the subcomponents of metabolic syndrome, including insulin resistance, elevated blood pressure, obesity, proinflammatory state, and prothrombotic state, have an unclear association with migraine prevalence, frequency, and characteristics (Table 2). It is unknown if treating metabolic syndrome risk factors results in a decrease in migraine attack rates or duration, or susceptibility to migraine development. Finally, the prevalence of metabolic syndrome in the migraine population has not been assessed.

**Migraine Diets, Food Avoidance, and Supplements May Be Useful in Migraine, But These Treatments Are Not Specific to Migraineurs With Metabolic Syndrome**

While food related headache triggers are well documented (Alpay et al., 2010), the use of so-called “migraine diets,” designed to minimize migraine frequency and food sensitization, has been controversial (Damen et al., 2006). One small trial of 30 patients with migraine without aura does support food avoidance based on detection of circulating serum immunoglobulins against specific foods; however, larger studies are required to determine the efficacy of this technique (Alpay et al., 2010). Four non-prescription supplements, including magnesium, *Petasites hybridus*, coenzyme Q10, and riboflavin, have been found to be effective migraine preventive agents based on double-blind placebo-controlled trials (Sun-Edelstein and Mauskop, 2009). However, supplementation is not intended exclusively for the obese population.

**Sleep Disturbance Is Associated With Increased Headache Severity But Not Specifically Migraine in Patients With Metabolic Syndrome**

Obesity can cause sleep abnormalities (Kopelman, 2000), which may worsen headaches and general health (Rains, 2008). In particular, obstructive sleep apnea and sleep disturbance are associated with chronic migraine and chronic daily headache (Rains and Poceta, 2006). Obstructive sleep apnea is also associated with metabolic syndrome (Bhushan et al., 2010). Weight loss is frequently curative in obese patients with obstructive sleep apnea. In patients who do not lose weight, continuous positive airway pressure therapy appears to reduce apnea-associated headache frequency (Rains and Poceta, 2010). Further, good sleep hygiene may reduce migraine frequency (Gilman et al., 2007).

**Medication Choice in Migraine Prevention May Have Implications for Weight Gain and Concomitant Metabolic Syndrome Management**

Numerous medications used in the treatment of migraine, including tricyclic antidepressants (i.e., amitriptyline; Taylor, 2010), do not appear to prevent migraine, and their use may contribute to weight gain, dyslipidemia, and other metabolic effects that may exacerbate migraine.

### Table 2 | Select metabolic derangements found in migraine by migraine type.

| Drug class                  | Medication         | Metabolic effect                                      | Reference                           |
|-----------------------------|--------------------|-------------------------------------------------------|-------------------------------------|
| Antiepileptic               | Topiramate         | Weight loss, dyslipidemia                              | Franzoni et al. (2007)              |
| Tricyclic antidepressant    | Amitriptyline      | Reduction in serum orexin-A and orexin-B levels.      | Caproni et al. (2011), Berlingen et al. (2005) |
|                             |                    | Increase in serum neuropeptide Y. Weight gain.         |                                     |
|                             |                    | Increased serum leptin, C-peptide, and insulin insulin | Sharma et al. (2001), Forsee (2009) |
| Beta-adrenergic receptor blocker | Propranolol        | Weight gain, worsening of glycermic and lipidic control (non-vasodilating beta-blockers as a drug class) | Harrison et al. (2004) |
| SSRI/SNRI                   | Venlafaxine        | Weight gain, hypertension at high dose                | Tokgoz et al. (2012), Pylwanen et al. (2002) |
| Antiepileptic               | Valproic acid and derivatives | Increased BMI, serum insulin, leptin, neuropeptide Y |                                     |

*NOS = Not otherwise specified.*
PHYSICAL ACTIVITY IS EFFECTIVE IN REDUCING RISK OF METABOLIC SYNDROME AND INACTIVITY MAY BE ASSOCIATED WITH MIGRAINE

Several large population studies suggest that reduced physical activity is associated with migraine. Milde-Busch et al. (2010) surveyed 1,260 10th and 11th grade adolescents for ICHD-II–criteria migraine and tension-type headache and found a 3.4× risk of self-reported migraine symptoms in subjects with physical inactivity. In the HUNT study, Robberstad et al. (2010) reported that, among a subset of 3,847 adolescents assessed for recurrent headache symptoms (migraine or tension-type), physical activity, smoking status, and weight, overweight subjects were 1.4× more likely to report recurrent headache and those with low physical activity were 1.2× more likely to report recurrent headache. In a broader cross sectional survey of 46,648 individuals, also performed by the HUNT study group, low physical activity (sweating or exercising during leisure time to the point of being out of breath less than 1 h per week) was associated with a higher incidence of self-reported migraine and non-migraine headache (Varkey et al., 2008). A single patient case report suggests that intense running may abort an evolving migraine, though this has yet to be reproduced (Strelniuk, 2009). Similarly, a high level of physical activity may confar a reduced risk of metabolic syndrome (Dai et al., 2010).

Several studies have evaluated aerobic exercise programs in migraine patients (Köseoglu et al., 2003; Dittrich et al., 2008; Varkey et al., 2009). These programs have focused on increasing oxygen uptake and have been well tolerated except for rare post-exercise migraines (Varkey et al., 2009). Aerobic programs have demonstrated improved depression (Dittrich et al., 2008) and pain severity (Lockett and Campbell, 1992) scores. It is hypothesized that aerobic exercise programs are associated with basal beta endorphin levels, potentially modifying pain sensation threshold (Köseoglu et al., 2003). For patients with metabolic syndrome, exercise is more complicated. Studies reviewing exercise protocols for obese patients and in rats indicate that a mix of resistance and endurance training may be indicated to improve cardiovascular disease risk endpoints (Hansen et al., 2010; Touati et al., 2010).

CONCLUSION

Metabolic syndrome and migraine are highly complex biochemical processes. It is likely that the two interact; however, it is unclear how they do. Further research will be required to elucidate the best clinical practices in patients who present with both diseases. Weight loss, good sleep hygiene, increased physical activity, and management of life stressors are the cornerstone of preventive healthcare in the adult population. These should be encouraged in all patients, although the exact benefits in patients with migraine and metabolic syndrome are unclear. Preventive treatments, including nutraceuticals, pharmaceuticals, and avoidance of triggers, are commonly accepted migraine treatments. The choice of pharmaceutical may have implications for the management of metabolic syndrome; however, much has yet to be learned about the long-term use of all preventive medications. Consultation with the patient regarding pharmacologic side effects is necessary.

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Headache Medicine and Facial Pain

November 2012 | Volume 3 | Article 161 | 6
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