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# 26 Migraine Headaches

## *Food Triggers and Nutrient Therapies*

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### **I. INTRODUCTION**

Migraine is a common and disabling disorder that affects millions of Americans. It is also one of the most common ailments with which patients present to their primary care providers. Though a wide range of acute and preventive headache medications are now available, most patients will not have a significant improvement in their headaches unless lifestyle modifications are made. These include sleep hygiene, stress management, aerobic exercise, and dietary modification. In this chapter the role of food and nutrients in the treatment and prevention of migraine headaches will be discussed.

### **II. EPIDEMIOLOGY**

Migraine is a common neurological disorder that affects 18% of women and 6% of men in the United States [1], and has an estimated worldwide prevalence of about 10% [2]. The prevalence of migraine rises throughout early adult life and falls after midlife. Population-based studies have reported that migraine is inherited, with a relative risk of migraine headache in a first-degree family member ranging from 1.4 to 1.9 [3, 4]. In monozygotic twins the concordance rates for migraine range from 37% to 52%, and 15% to 21% for dizygotic twins [5, 6]. These figures indicate that environmental factors play a significant role in the migraine.

Of the migraine sufferers who consult a physician, about two-thirds visit primary care physicians. Only 16% consult neurologists or headache specialists. These observations emphasize the importance of continuously improving the ability of primary care physicians to accurately diagnose migraine in their patients [7].

### **III. PATHOPHYSIOLOGY**

Though the understanding of migraine pathophysiology has increased dramatically in recent years, the exact etiology remains to be defined. The current prevailing theory is based on a hyperexcitable “trigeminovascular complex” in patients who are genetically predisposed to migraine. In these people, there is a lowered threshold for migraine attacks and a vulnerability to environmental triggers. The theory proposes that in susceptible individuals, the trigeminovascular neurons release neurotransmitters, such as calcitonin gene-related peptide (CGRP) and substance P, when headache triggers are encountered. This leads to vasodilation, mast cell degranulation, increased vascular

permeability, and meningeal edema, resulting in neurogenic inflammation. This nociceptive information is transmitted from the trigeminal nerve to brainstem nuclei, thalamic nuclei, and the cortex, where migraine pain is ultimately perceived [8]. The locus coeruleus, which comprises noradrenergic neurons, the dorsal raphe, which consists of serotonergic neurons, and the periaqueductal gray also play modulatory roles in the transmission of pain [9].

Mitochondrial dysfunction, which leads to impaired oxygen metabolism, has been speculated to play a role in migraine pathophysiology [10–12], as migraineurs have been shown to have a reduction in mitochondrial phosphorylation potential in intervals between headaches [13, 14]. This theory is the basis for the use of supplements that enhance mitochondrial function in the treatment of migraine, such as riboflavin, coenzyme Q10 (CoQ10), and alpha lipoic acid.

## IV. THE ROLE OF FOOD AND NUTRIENTS IN MIGRAINE

### GLUCOSE DYSREGULATION

The importance of eating regularly cannot be overemphasized, as skipping meals can trigger headaches [15]. Skipped meals and fasting were reported migraine triggers in up to 57% of subjects in clinic and population-based studies [16–19]. While the mechanism by which fasting and skipping meals triggers headaches is unknown, several theories have been proposed. Alterations in serotonin and norepinephrine in brainstem pathways could precipitate headache onset [20], as could the release of stress hormones such as cortisol. Hypoglycemia could potentially bring on a headache [9]. In one study [21] three-quarters of participants with migraine headaches demonstrated 5-hour glucose tolerance tests consistent with reactive hypoglycemia. Micronutrients involved in glucose regulation include chromium, biotin, magnesium, zinc, copper, vitamin E, and L-carnitine [22].

### FOOD TRIGGERS

The recognition of dietary migraine triggers is important because it helps not only in reducing the frequency of migraine, but also in giving migraineurs a sense of control over a condition that can render them helpless and debilitated [9]. Although the scientific basis for many of these triggers remains controversial, it appears that subsets of migraineurs may be sensitive to them [9]. Patients should therefore be aware that the foods and substances listed in Table 26.1 [9, 17, 23–38] are potential migraine triggers. Caffeine and alcohol are discussed in detail because of their complex relationship to headache. Not all of the foods listed will trigger a migraine in any one individual. Headaches are generally triggered by a combination of substances, during a time of particular vulnerability such as menses or emotional stress. Food diaries are helpful in sorting out which substances or circumstances are problematic for each patient.

### Alcohol

Alcohol, in particular red wine, is frequently cited as a migraine trigger. Wine contains tyramine, sulfites, histamine, and the phenolic flavonoids, all of which can theoretically precipitate migraines [9]. Histamine may trigger headache via the release of nitric oxide from the vascular endothelium, resulting in vasodilation [35]. Phenolic flavonoids in red wine have been shown to cause the release of serotonin from platelets, which may occur in parallel with the release of serotonin in the central nervous system, potentially leading to headache [36].

Alcohol hangover headache (AHH) is a common occurrence that generally occurs after ingesting large amounts of alcohol. In addition to headache, AHH comprises a constellation of physical, cognitive, and psychological symptoms including anorexia, tremulousness, dizziness, nausea, tachycardia, and irritability [39]. The headache usually occurs the morning after alcohol consumption, when the blood alcohol concentration is falling [40], and can continue for 24 hours after the blood alcohol concentration reaches zero. AHH is not always dose-related and in fact occurs more commonly in

**TABLE 26.1**  
**Potential Food Triggers in Migraine**

Trigger	Food	Mechanism	Prevalence	Reference(s)
Phenylethylamine	Chocolate, cacao.	Releases vasoactive amines such as serotonin and catecholamines in migraineurs with MAO-B deficiency.	19–50%	17, 23–26
Tyramine	Aged cheese, smoked fish, cured meats, yeast extract, beer, fermented foods.	May trigger migraines via the release of norepinephrine and its agonist effect at $\alpha$ -adrenergic receptors.	9–18%	9, 17, 25
Aspartame	NutraSweet.	Possibly via an alteration of serotonergic metabolism in the brain.	—	27–29
Monosodium glutamate (MSG). Also known as hydrolyzed vegetable protein (HVP), autolyzed yeast, sodium caseinate, yeast extract, hydrolyzed oat flour, texturized protein, and calcium caseinate	Chinese food, meat tenderizer, many canned and prepared foods.	Possibly via a direct vasoconstrictor effect or by activation of a neurotransmission pathway in which nitric oxide is released in endothelial cells, inducing vasodilation.	13%	17, 25, 30–31
Nitrates and Nitrites	Sausages, cured meats and fish such as hot dogs, bacon, ham, salami, pepperoni, corned beef, pastrami, lox.	Probably via the release of nitric oxide and subsequent vasodilation, although the interaction of nitrites with blood pigment to produce methemoglobin may also play a role.	—	9, 26, 32–34
Alcohol	Red and white wine, beer, darker colored beverages such as bourbon and whiskey.	Tyramine, histamine, phenolic flavonoids and sulfites in wine may precipitate migraines (see discussion in text).	29–35%	9, 17, 25, 35–36
Caffeine	Coffee, tea, soda, medications such as Excedrin, Fiorinal, and Fioricet.	Via the blockade of inhibitory and excitatory adenosine receptors in the brain and vasculature, resulting in vasoconstriction and the release of excitatory neurotransmitters.	14%	17, 25, 37–38

light or moderate drinkers than regular heavy drinkers [41–42]. In migraineurs, a migraine can be triggered the day after moderate alcohol ingestion, while nonmigraineurs usually need to consume large amounts in order to develop AHH.

Darker colored alcoholic beverages, such as red wine, bourbon, and beer contain congeners, which are natural byproducts of alcohol fermentation. These drinks are more likely to induce AHH as compared to clear alcoholic beverages such as gin or vodka. The pathophysiology of AHH may involve a vasodilatory effect in the intracranial vasculature, alteration of sleep patterns, or an inflammatory mechanism via an alteration of cytokine pathways and prostaglandin release [43–45]. Magnesium depletion may also play a role. Patients who are prone to AHH should be advised to drink in moderation, and stay well-hydrated. Eating greasy food prior to alcohol consumption may help to slow or delay alcohol absorption, and consuming foods naturally rich in fructose, such as honey and tomato juice, allows for more effective alcohol metabolism.

### Caffeine

Caffeine is a common dietary substance found in coffee, tea, soda, and chocolate. It is also included in various prescription (Fioricet®, Fiorinal®, Esgic®) and over-the-counter headache medications (Excedrin®). Caffeine works via the blockade of inhibitory and excitatory adenosine receptors in the brain and vasculature, resulting in vasoconstriction and the release of excitatory neurotransmitters. Some of the involved pathways are important in pain perception [37–38].

Caffeine's effect on the central nervous system varies with the dose and frequency of use. In general, one serving of brewed coffee has 115 mg caffeine, while a serving of Pepsi has 38 mg. Excedrin contains 65 mg caffeine per tablet. At low to moderate doses (50 to 300 mg), caffeine causes increased alertness, concentration, and energy. At doses greater than 300 mg, anxiety, insomnia, and irritability can occur [9, 46]. Caffeine's effect on headaches is paradoxical in that it can worsen or alleviate headaches, depending on dosage and frequency. When used infrequently, caffeine is effective in headache treatment because it has a mild, direct analgesic effect [47] and also assists in the absorption of other analgesics. It also crosses the blood-brain barrier quickly, and reaches therapeutic levels in the brain within 20 minutes. These characteristics make caffeine a useful component of combination analgesics (i.e., Fiorinal, Fioricet). High doses (>300 mg/day) consumed on a regular basis are associated with headache. Regular use of caffeine-containing analgesics is associated with medication-overuse headaches [48–50].

Headaches also occur with abrupt withdrawal of caffeine. The higher the level of baseline caffeine ingestion, the greater the likelihood of caffeine withdrawal headache, although these headaches can occur in patients consuming moderate amounts of caffeine [51], and when patients consuming 100 mg caffeine daily stop abruptly [52]. Caffeine withdrawal is also associated with depression, drowsiness, and impaired concentration. Patients with headaches who wish to continue drinking caffeinated beverages should limit their daily intake to less than 200 mg. Patients who use caffeine-containing analgesics should limit intake to 2 to 3 days per week to avoid medication-overuse headache. Those who wish to cease caffeine consumption should gradually taper their intake over several weeks [9]. Patients should also be aware that drinking grapefruit juice increases the time for caffeine metabolism, since it occupies the same enzyme. This may modify the effects of caffeine during periods of consumption and withdrawal.

### NUTRIENTS

For many migraine sufferers, traditional acute and preventative medications such as triptans, anti-inflammatories, antiepileptics, blood pressure medications, and antidepressants are contraindicated, or have side effects that limit their use. Over-the-counter medications such as acetaminophen or ibuprofen tend to become less effective in alleviating headaches over time, and can lead to medication-overuse headache. For these reasons, migraineurs often seek alternative treatment options. In recent years there has been an increasing demand for natural therapies for common ailments such as headache.

### **Magnesium**

Magnesium is an essential cation that plays a vital role in multiple physiological processes, regulating tissue and cell functions. Deficits in magnesium can be seen in any chronic medical illness, including cardiovascular disease, diabetes, pre-eclampsia, eclampsia, sickle cell disease, and chronic alcoholism [53]. Symptoms of magnesium deficiency include premenstrual syndrome, leg muscle cramps, coldness of extremities, weakness, anorexia, nausea, digestive disorders, lack of coordination, and confusion. Magnesium may be involved in migraine pathogenesis by counteracting vasospasm, inhibiting platelet aggregation, and the stabilization of cell membranes [54]. Its concentration influences serotonin receptors, nitric oxide synthesis and release, inflammatory mediators, and various other migraine-related receptors and neurotransmitters [55]. Magnesium also plays a role in the control of vascular tone and reactivity to endogenous hormones and neurotransmitters, via its relationship with the NMDA receptor [56–57]. In the brain, a deficiency of magnesium results in contraction and potentiation of vasoconstrictors [58].

Studies have shown that migraineurs have low brain magnesium during migraine attacks [59] and may also have a systemic magnesium deficiency [60, 61]. Furthermore, a deficiency of magnesium may play a particularly important role in menstrual migraine [62]. There have been two double-blind, placebo-controlled trials that have shown that oral magnesium supplementation is effective in headache prevention [63–64]. A third study [65] was negative, but this result has been attributed to the use of a poorly absorbed magnesium salt, since diarrhea occurred in almost half of patients in the treatment group. Intravenous magnesium has been shown to be an effective migraine abortive agent in patients with low ionized magnesium levels, but not in those with normal levels [66]. The most commonly reported adverse effect of magnesium supplementation is diarrhea.

A potential nutrient-nutrient interaction occurs between magnesium and calcium supplements. Women of childbearing age are advised to take calcium supplements for bone health. Calcium supplements that do not also contain magnesium can reduce the absorption of magnesium since the two minerals compete for absorption. Often women who take calcium without magnesium experience constipation, which should alert physicians to the presence of supplement-induced low magnesium.

### **Riboflavin**

Riboflavin, also known as vitamin B2, is a precursor for flavin mononucleotides that are cofactors in the Krebs cycle. It is essential for membrane stability and the maintenance of energy-related cellular functions [67]. A randomized controlled trial evaluating the use of riboflavin (400 mg) as a migraine prophylactic agent, with a total of 128 subjects was positive [68]. Minor adverse reactions included diarrhea and polyuria.

### **CoQ10**

CoQ10 is an endogenous enzyme cofactor made by all cells in the body, functioning to promote mitochondrial proton-electron translocation. It has been used in the treatment of mitochondriopathies and mitochondrial encephalomyopathies such as Kearns-Sayre syndrome, and is being investigated for use in neurodegenerative disorders, cancer, and blood pressure management.

In an open label study [69] in which 31 patients with migraine, with and without aura, used 150 mg daily of CoQ10 for 3 months, 61% had at least a 50% reduction in migraine days without significant adverse events. Supplementation was effective within the first month of therapy. Later, a small randomized controlled trial [70] was conducted over 3 months with 42 patients. CoQ10, in a dose of 100 mg three times daily, significantly decreased attack frequency, headache days, and days with nausea. Nausea, anorexia, dyspepsia, diarrhea, and cutaneous allergy were reported, but at a low rate [69–70].

### **Alpha Lipoic Acid**

Like riboflavin and CoQ10, alpha lipoic acid, also known as thioctic acid, is a nutrient that enhances mitochondrial oxygen metabolism and adenosine triphosphate (ATP) production [71], with very few adverse effects. Supplementation has resulted in clinical and biochemical improvement in several

mitochondriopathies [71–73]. Its use in migraine prevention has been evaluated in one open pilot study [unpublished data, discussed in reference 74] and one randomized placebo-controlled trial (RCT) [74] to date.

Although there was a clear trend for reduction of migraine frequency after treatment with 600 mg alpha lipoic acid in the RCT, the result was not significant. The authors attributed the equivocal result to the fact that the study was underpowered. Within-group analyses did show a significant reduction in attack frequency, headache days, and headache severity in patients in the treatment group.

## HERBAL SUPPLEMENTS

### **Feverfew (*Tanacetum parthenium*)**

Feverfew is an herbal preparation that is available as the dried leaves of the weed plant *Tanacetum parthenium*. It was used to treat headache, inflammation, and fever several centuries ago, and was rediscovered in the late 20th century. The mechanism by which it works in migraine prophylaxis may be related to the parthenolides within the leaves. These may inhibit serotonin release from platelets and white blood cells, and inhibit platelet aggregation. Feverfew may also have anti-inflammatory action through the inhibition of prostaglandin synthesis and phospholipase A [75–78].

Randomized controlled studies conducted over the past few decades have yielded conflicting results [79–83]. Inconsistencies in these results were possibly related to the fact that different preparations have been found to vary more than 400% in the strength of the active ingredient, parthenolide [84], and different methods of feverfew extraction have resulted in differences in extract stability [85]. Taking into account these variables, a new, more stable feverfew extract (MIG-99) was evaluated in a three-arm randomized controlled trial (2.08 mg, 6.25 mg, 18.75 mg TID versus placebo) [86]. Although none of the doses were significant for the primary endpoint, a subset of patients with high frequency of migraine attacks did seem to benefit. In a follow-up study, investigators evaluated 6.25 mg TID of MIG-99 versus placebo, and reported a statistically significant and clinically relevant reduction in migraine frequency in the MIG-99 group. While MIG-99 may be mildly effective, there are no known commercially available preparations [67]. Side effects reported in the RCTs include gastrointestinal disturbances, mouth ulcers, and a “post-feverfew syndrome” of joint aches.

### **Butterbur (*Petasites hybridus*)**

In recent years, *Petasites hybridus* root extract, also known as butterbur, has emerged as a potential new treatment in the prevention of migraine. The butterbur plant is a perennial shrub that was used in ancient times for its medicinal properties. It was rediscovered in the middle of the 20th century and used as an analgesic and antispasmodic agent for migraine, asthma, urinary tract spasm, and back pain [87–91]. *Petasites* is thought to act through calcium channel regulation and inhibition of peptide-leukotriene biosynthesis. Leukotrienes and other inflammatory mediators may have a role in the inflammatory cascade associated with migraine [92–94]. *Petasites* is also used to ameliorate allergic rhinitis, which has a similar pathophysiology. In the United States, the *Petasites* extract is marketed as a food supplement called Petadolex, which contains 50 mg of petasites per capsule.

Several studies have been conducted to evaluate the efficacy of *Petasites hybridus* in migraine prevention. A randomized, double-blind, placebo-controlled trial [87] using 50 mg of Petadolex twice daily showed a significantly reduced number of migraine attacks and migraine days per month. Lipton and colleagues [95] compared *Petasites* extract 75 mg twice daily, *Petasites* extract 50 mg twice daily, and placebo twice daily in a randomized trial of 245 patients and found that the higher dose of *Petasites* extract was more effective than placebo in decreasing the number of monthly migraine attacks. A multicenter prospective open-label study [96] of Petadolex in 109 children and adolescents with migraine resulted in 77% of all patients reporting a reduction in migraine frequency of at least 50%. In all three studies, Petadolex was well-tolerated and no serious adverse events occurred. The most frequently reported adverse reactions were mild gastrointestinal symptoms, predominantly eructation (burping).

### Other

Ginger has been used for its medicinal qualities in China for centuries, in the treatment of pain, inflammation, and musculoskeletal symptoms. It has anti-inflammatory qualities that could be related to the reduction of platelet aggregation and the inhibition of prostaglandin and leukotriene biosynthesis [97]. There are anecdotal and folkloric descriptions of its efficacy in relieving headache.

Valerian root is a perennial herb that is used for its sedative and hypnotic qualities, especially in insomniacs [98]. The effective dose for insomnia is 300 to 600 mg, which is equivalent to 2 to 3 g of dried herbal valerian root soaked in one cup of hot water for 10 to 15 minutes [99]. In migraine patients with anxiety, it may be preferable to benzodiazepines as it is not associated with sleepiness on awakening. At high doses, it is associated with headaches and muscle spasm.

### Dietary Fat Composition

Eicosapentaenoic acid (EPA), an unsaturated fatty acid that is one of the body's natural omega-3 fatty acids, may also be useful in headache prevention. Small studies [100] have suggested that headache severity and frequency can be reduced by adding EPA to the diet, possibly by lowering prostaglandin levels and serotonin activity. A dose of 600 mg/day in three divided doses has been suggested for headache prevention [101–102]. Foods richest in EPA are fish that inhabit cold deep water, such as salmon, tuna, mackerel, and herring. A high disproportion of dietary omega-6 fats, consumption of trans fats, and an impairment in the conversion of dietary omega-3 fats into EPA all suggest a deficit in EPA. Dietary changes can reduce or obviate the need for EPA supplementation long-term.

## V. MIGRAINE AND COMORBID CONDITIONS

### GENERAL INFORMATION

Migraine is comorbid with numerous medical conditions, some of which are well-defined medical disorders (stroke, hypertension, hypothyroidism, asthma, allergies, and endometriosis), and others of which are idiopathic symptomatic medical conditions (irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, interstitial cystitis, and pelvic pain) [103–111]. Psychiatric comorbidities have been described as well [112–113]. A putative neurobiological link has been suggested [114] because of the bidirectional link between migraine and many of these disorders.

A recent retrospective chart review of 223 patients seen at a university headache clinic [115] showed that among patients presenting for evaluation at a specialty headache center, there are two groups of migraine comorbid conditions, in addition to a group characterized by a lack of comorbidities. One of the groups had a strong association with metabolic disorders such as diabetes mellitus (DM), hypertension (HTN), and hypercholesterolemia, while the other group was defined by a link with fibromyalgia, depression, and anxiety.

### MOOD DISORDERS, MIGRAINE, AND OBESITY

Migraine has been linked to mood disorders in both community and clinic-based studies [116]. While the association between migraine and depression has been most widely reported, migraine is also linked to anxiety disorders and bipolar disorder [116]. Large-scale population studies [117–120] have shown that migraineurs are 2.2 to 4.0 times more likely to have depression, and other studies have reported that the relationship between the two disorders is bidirectional, with each disorder increasing the risk for the other [112, 121–122].

Depression and anxiety are also strongly associated with obesity [123–129], and obesity is associated with migraine. Longitudinal population-based studies have shown that obesity is a risk factor for developing chronic daily headache [130], and, in people with episodic migraine, body mass index (BMI) is associated with migraine attack frequency and severity [131]. A recent cross-sectional multicenter study [132] on comorbid conditions in headache clinic patients showed that both depression

and anxiety were more common in obese subjects, and both depression and anxiety modified the strength of the relationship of obesity with migraine frequency and disability.

The above relationships between obesity, depression, anxiety, and chronic, disabling migraine are suggestive of a common pathogenetic pathway among the disorders [132]. A proinflammatory mechanism has been proposed to explain the relationship between obesity and migraine [130–133], and a neurobiological link mediated by common brain monoamines and peptides has been proposed as the connection between mood disorders, migraine, and the regulation of body weight [132, 134–135]. Alterations in the hypothalamic-pituitary-adrenal system may also be involved [132, 136–139].

### **MIGRAINE, VASCULAR AND RELATED METABOLIC DISORDERS**

Migraine has been associated with a constellation of metabolic disorders (DM, HTN, hypercholesterolemia) [115], all of which are risk factors for cardiac and cerebrovascular disease. While migraine with aura had not been associated with early-onset coronary heart disease in large cohort studies [140–143], two recent large-scale prospective cohort studies [144–145] found positive relationships between migraine and ischemic heart disease. Women who reported a history of migraine without aura did not have an increased risk for any ischemic vascular events.

The link between migraine and ischemic stroke has been well-described in both clinic and population-based studies. Recently, two large-scale prospective cohort studies [146–147] were published. The Women's Health Study [146], with over 39,000 participants, found a 1.7-fold increased risk for ischemic stroke in women with migraine with aura as compared to women without migraine, with the risk being strongest in women ages 45 to 55 years. This risk was not seen in older women or those with migraine without aura. The Atherosclerosis Risk in Communities Study [147] with over 12,000 subjects over age 55 found that migraineurs with aura had a 1.8-fold increased risk of ischemic stroke compared to those without migraine or other headache. This result did not reach statistical significance, which may be explained by vague diagnostic terminology used in the study. The evidence is most convincing for younger women with migraine with aura, although the migraine and stroke relationship may also apply to older individuals. Stroke risk is significantly increased by smoking and the use of oral contraceptives [148–150].

### **MIGRAINE, IRRITABLE BOWEL SYNDROME, AND CELIAC DISEASE**

Irritable bowel syndrome (IBS) is a chronic, functional gastrointestinal disorder in which episodic attacks are marked by abdominal discomfort, and alterations in bowel movements (constipation, diarrhea, or alternating periods of both) [151]. IBS patients tend to have a higher likelihood of comorbid "affective spectrum disorders" or "functional somatic syndromes," which include migraine, fibromyalgia, and depression [152–153] and a familial association among patients with IBS, migraine, depression, and fibromyalgia, has also been noted [154]. More recently, a prevalence study [155] of migraine, fibromyalgia and depression in people with IBS showed that for migraine, subjects in the IBS cohort had a 60% higher odds compared to non-IBS subjects.

Celiac disease is a gluten-sensitive enteropathy characterized by malabsorption and weight loss, which can be reversed with a gluten-free diet. Gluten is a component of foods with wheat, barley, and rye [156]. While there have been several studies [157–159] evaluating the association between migraine and celiac disease, the evidence is inconclusive. However, in migraine patients with prominent gastrointestinal features, IBS and celiac disease should be considered.

### **MIGRAINE AND RESTLESS LEG SYNDROME**

Restless Leg Syndrome (RLS) is a disorder characterized by sensory symptoms and motor disturbances of the limbs, usually when at rest. These features include: a desire to move the limbs, often associated with paresthesia or dysesthesia, exacerbation of symptoms at rest and relief with activity,

motor restlessness, and nocturnal worsening of symptoms [160]. While most cases are idiopathic, RLS may be secondary to iron deficiency, peripheral neuropathy and renal disease, especially in patients with later onset of symptoms [161–163]. Iron deficiency should therefore be ruled out with serum ferritin levels in patients presenting with RLS.

A recent case-control study [164] showed that RLS occurs more frequently in patients with migraine than those without, and older age and longer duration of migraine may raise the risk of RLS. Age and duration of migraine merit special consideration when evaluating those patients because the RLS may be secondary to iron deficiency, as noted above, or renal insufficiency resulting from long-time use of headache medications.

A dysfunctional dopaminergic system might explain the relationship between migraine and RLS, and a common genetic factor for both disorders may be established with future studies.

## VI. TREATMENT RECOMMENDATIONS

Reactive hypoglycemia should be suspected in migraineurs who crave sweets, or develop headaches after fasting. Those patients should be advised to avoid refined sugar and eat frequent meals. Increasing protein, complex carbohydrates, and fiber in the diet may also be beneficial in preventing hypoglycemia [22].

Given the data discussed above, the most effective supplements for headache prevention are magnesium and *Petasites hybridus*. Second-line supplements in migraine prevention include feverfew, CoQ10, riboflavin, and alpha lipoic acid. Though gastrointestinal side effects have been reported with these supplements, they are generally well-tolerated and appeal to patients who prefer natural therapies to traditional prescription medications. In addition, some of the supplements may be especially beneficial in patients who have relevant comorbid conditions. For example, riboflavin may provide an added benefit in patients with cheilosis.

Oral magnesium supplementation may be beneficial for many migraineurs with frequent headaches, especially those with menstrual migraine. Magnesium oxide, chelated magnesium, and slow-release magnesium are the recommended formulations as they are likely to be the best absorbed. Daily supplementation with 400 mg should be used for at least 3 months. Diarrhea may be a limiting adverse effect in some patients.

Intravenous magnesium (1 g magnesium sulfate in 10 ml normal saline), given within 1 week of menstruation, is an option for women with menstrual migraines who do not respond to oral supplementation. Patients with nonmenstrual migraines can also be given magnesium infusions on an as-needed or monthly basis if they do not respond to oral magnesium or have gastrointestinal side effects from oral dosing.

The relationship between migraine, vascular, and metabolic disorders emphasizes the importance of addressing and treating modifiable risk factors such as obesity, hypertension, high cholesterol, and diabetes mellitus early, and with a multidisciplinary approach that includes nutritional recommendations. RLS, irritable bowel syndrome, and celiac disease are other potential comorbid conditions with nutritional implications.

## VII. SPECIAL CONSIDERATIONS

### PEDIATRIC MIGRAINE

Migraine headaches are not limited to the adult population. Childhood migraine can be severe and debilitating, and is associated with missed days of school, anxiety, and depression [165–166]. Among children, the prevalence of migraine has been increasing over the past few decades, much more so than that in adults [167–168]. Although the cause of this increase is not known, dietary trends of increased caffeine consumption, aspartame in diet drinks, and underage drinking are likely to play a role [169].

Pediatric migraine differs from adult migraine in that attacks tend to be shorter in duration [170]. Anorexia, abdominal pain, and vomiting are prominent features, occurring in 90% of patients [171–172]. These features affect treatment options in that gastroparesis from nausea and vomiting may limit the use of oral analgesics, and the shorter headache duration means that symptoms may resolve even before oral analgesics reach therapeutic levels. Furthermore, the cognitive side effects of migraine preventive drugs are particularly problematic in children. For these reasons dietary modification in this population cannot be overemphasized.

As with adult migraineurs, pediatric migraineurs and their parents should be counseled regarding potential food triggers. In addition to the triggers described earlier in this chapter, food dyes and frozen foods or snacks may be particularly relevant to the pediatric population. Food diaries should be kept for these patients, and a well-balanced diet without fasting or skipping meals is strongly advised [169]. Other nonpharmacologic therapies such as biofeedback are also indicated in the treatment of pediatric migraine. For those children who continue to have frequent debilitating headaches, the supplements described above may be a more palatable option than prescription medications. Even more significantly supplemental nutrients may be correcting an underlying deficiency brought on by eating “junk foods,” diet patterns known to lower magnesium.

## PREGNANCY

Pregnancy also warrants special consideration in the treatment of the migraineur. While migraines generally improve during pregnancy, headaches may worsen or remain the same in some women [173]. In particular, women may experience an increase in headaches during the first trimester, triggered by wide fluctuations in estrogen levels. After the first trimester, headaches generally improve due to a stabilization in estrogen levels.

## VIII. SUMMARY

Reactive hypoglycemia is a poorly recognized but important migraine trigger. This is a challenge since excess weight predisposes to migraines and losing the weight often involves eating less to the point that blood glucose dips. Patients are advised to eat smaller, more frequent meals, with more protein, complex carbohydrates, and fiber. Glucose tolerance testing may be warranted in those who continue to have symptoms.

Food allergies are addressed as per the protocol outlined in Chapter 15, “Food Reactivities.” Migraineurs should be aware of potential food triggers, and advised to avoid the foods and food components listed in Table 26.1.

Of the herbal supplements, we most commonly use magnesium oxide, chelated or slow-release magnesium in a dose of 400 mg daily, and butterbur in a dose of 50 mg three times daily for migraine prevention. Feverfew, CoQ10, and riboflavin are other options for migraine prophylaxis. While we do use magnesium during pregnancy, butterbur and most other herbal preparations should be avoided in pregnant women.

Nonpharmacologic measures are particularly important in pediatric migraine, given the shorter headache duration in children and prominent nausea and vomiting. We emphasize the avoidance of food triggers and skipped meals, and recommend magnesium CoQ10, feverfew, as well as biofeedback in these patients.

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