Diet and Headache: Part 2

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Background.—Comprehensive diets do not require the exclusion of a specific provocative food or ingredient, but regulate the quantities of core components of foods such as vitamins, ions, proteins, carbohydrates, and fats.

Objectives.—To review the evidence supporting the use of comprehensive diets in the prevention of migraine and other headache disorders and to discuss the mechanisms through which food, and ingredients within foods and beverages might trigger attacks of headache

Methods.—This represents Part 2 of a narrative review of the role of diet in the prevention of migraine and other headache disorders. A PubMed search was performed with the following search terms: "folate," "vitamin D," "low fat diet," "omega-3 and omega-6 fatty acid diet," "ketogenic diet," "Atkins diet," and "sodium." Each of these search terms was then crossreferenced with "headache" and "migraine" to identify relevant studies. Only studies that were written in English were included in this review.

Results.—Low fat and high omega-3/low omega-6 fatty diets decrease the frequency of attacks of migraine and/or other headache disorders as demonstrated in two separate randomized controlled trials. A ketogenic diet was more effective than a standard diet in reducing the frequency of migraine in a single nonrandomized clinical study. An observation study found that dietary consumption of folate was inversely associated with the frequency of migraine attacks in persons with migraine with aura that have the C variant of the methylene tetrahydrofolate reductase gene. The mechanisms though which diets may precipitate headache include their effects on neuropeptides, neuro-receptors and ion channels, inflammation, sympathetic nervous system, release of nitric oxide, vasodilation, and cerebral glucose metabolism.

Conclusions.—Evidence exists to support the use of comprehensive diets in the prevention of migraine and other headache disorders. However, the results of these studies should be considered preliminary until replicated in larger randomized controlled clinical trials.

INTRODUCTION

Comprehensive diets do not require the exclusion of a specific provocative food or ingredient, but regulate the quantities of core components of foods such as vitamins, ions, proteins, carbohydrates, and fats. An assumption is made that these core components may either be preventive or provocative for headache. They are so ubiquitous in foods that it would be impractical to try to identify them through use of a food diary. Examples of these comprehensive diets include high folate, low fat, ketogenic, modified Atkins, and high omega-3/low omega-6 diets. This narrative review will present the evidence supporting the use of comprehensive diets in the prevention of migraine and other headache disorders. We will also discuss the possible mechanisms through which foods might trigger headache and propose a rational approach to diet in the headache patient.

METHODS

This monograph represents Part 2 of a narrative review of the role of diet in the prevention of migraine and other headache disorders. A PubMed search was performed to identify relevant studies with the following key words: "folate," "vitamin D," "low fat diet," "omega-3 and omega-6 fatty acid diet," "ketogenic diet," "Atkins diet," and "sodium." Each of these search terms was then crossreferenced with "headache" and "migraine" to identify relevant studies. Studies were eligible if they were published in the English language.

HIGH FOLATE DIETS

Folate and vitamin B12 are important cofactors for enzymes involved in the metabolism of homocysteine. One such enzyme is methylene tetrahydrofolate reductase (MTHFR), which converts a less active form of folate to its more active form. Specific mutations in the MTHFR gene have been associated with an increased prevalence of migraine. A 2011 meta-

analysis reported that the homozygous pattern of the T allele of the MTHFR gene increased homocysteine levels and conferred a greater risk for migraine with aura (odds ratio [OR] 1.42; 95% CI 1.2, 1.82) and overall migraine (OR 1.37; 95% CI: 1.07, 1.76).[1] Another study found that total homocysteine levels were significantly higher in the cerebrospinal fluid (CSF) of migraineurs compared with controls particularly in those with aura.[2] Therefore, both homocysteine and folate may be important in the pathogenesis of migraine headache.

Persons with migraine have a lower consumption of folate in their diet as compared to those without migraine.[3] Another study found that folate consumption in the diet was inversely correlated with the frequency of migraine in those with the CC variant of the MTHFR gene.[4] Diets and/or supplements that are high in folate and vitamins B6/B12 may prevent attacks of migraine particularly in persons with certain gene variants of enzymes involved in homocysteine metabolism.[5]

Two randomized controlled trials (RCTs) reported that vitamin B supplementation (2 mg folate, 25 mg B6, 400 mcg B12) significantly reduced the severity and disability of headache in persons with migraine with aura.[6,7] This effect was most pronounced in the C allele carriers of the MTHFR gene variant. Another study found that supplementation with a 1 mg dosage of folate and other B vitamins did not reduce headache outcome measures, which could indicate that high doses of folate acid are needed to see a clinical effect.[8] Therefore, there may be certain subgroups of persons with migraine that might benefit from a high folate diet and/or supplements that contain moderate to high amounts of folate and vitamins B12 and B6.

VITAMIN D AND DIET

The majority of past studies have not demonstrated any difference in the serum levels of vitamin D in patients with migraine as compared to controls, but one study[9] did show certain vitamin D polymorphisms to be associated with migraine without aura.[10–12] The largest study published to date found an increased prevalence of persons with "non-migraine" headache in the lowest quartile of serum vitamin D levels as opposed to the highest quartile (OR 1.2; 95% CI: 1.04, 1.29).[10] Another study noted that headache was more common in those with low vitamin D levels (eg, < 50 nmol/mL).[13] Two other case studies in pediatric patients reported that severe vitamin D deficiency produced headaches that resembled tension-type headaches that significantly improved with treatment with vitamin D.[14,15] Therefore, there may be a slight increased risk for "non-migraine" headaches in those with vitamin D deficiency.

There have been three RCTs of vitamin D3 supplementation in the prevention of migraine and/or headache. Knutsen

and colleagues reported that scores on the Headache Impact Test (HIT-6), a headache disability measure, did not differ in 251 participants randomized to supplementation with either vitamin D3 group or placebo.[16]

Mottaghi and colleagues randomized 77 persons with migraine to either 50,000 U of vitamin D3 or matching placebo administered one day per week during a 10 week treatment period.[17] There was no difference in the intensity or duration of migraine, but the headache index (duration × frequency of headache) was significantly lower in the vitamin D3 treated group.

Buettner and colleagues performed a study in which 57 persons with episodic migraine were randomized to combined therapy with simvastatin and vitamin D3 or matching placebo.[18] There was a reduced frequency of migraine days in the treatment groups as compared to placebo over the 12 week treatment period (-8.0 days from baseline vs $+1.0$, respectively; $P < .001$). In summary, there is scant evidence that supplementation of vitamin D3 by itself reduces the frequency of migraine or headache based on results of randomized controlled trials. However, the use of vitamin D3 as an adjunctive agent to a statin therapy shows promise, but must be confirmed in future RCTs.

LOW FAT DIETS

There have been two studies that investigated the role of low fat diets in the prevention of migraine headache. Ferrara and colleagues performed a cross-over study in which 83 persons with episodic or chronic migraine were randomized to a low or normal lipid diets and then crossed over to the opposite diet.[19] The low lipid diet restricted lipids to <20% of their total daily energy intake, while the normal lipid diet had lipid contents of 25–30%. Those receiving the low lipid diet had lower attack frequency (2.9 vs 6.8; $P < .05$) and intensity (1.2 vs 1.7; $P < .05$) than those receiving the normal fat diet. Another noncontrolled open study reported that migraine frequency decreased from a median of 6 days per month at baseline to 1 day per month after institution of a low fat diet with <20 grams (g) of lipids.[20] Thus there is one RCT and one open trial that support the use of a low lipid diet for the treatment of migraine.

HIGH OMEGA-3 and LOW OMEGA-6 FATTY ACID DIETS

There has been conflicting evidence on the role of omega-3 fatty acids (FAs) in the prevention of migraine headaches. Sadeghi and colleagues reported that lower intake of omega 3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was associated with a higher frequency of migraine attacks.[21] The largest RCT did not show a

statistically significant difference in the number of migraine attacks during the last four weeks of the treatment period in the omega-3 supplemented group as compared to the placebo group, which was the primary outcome measure.[22] However, there was a reduction in attacks during the entire four month treatment period in the omega-3 administered group.

A randomized single-blind study found that persons receiving valproate supplemented with omega-3 FAs had a reduced frequency and severity of headache as compared to those receiving valproate alone.[23] Another study randomized adolescents with migraine to either fish oil or olive oil during a 2 month treatment period.[24] Both therapies reduced the frequency and severity of headache, compared to baseline. Therefore, there is conflicting evidence on the role of omega-3 FA supplementation "by itself" in the prevention of headache.

Others have postulated that it is not just the quantities of high omega-3 FAs in the diet that are important, but that a certain ratio of omega-3 to omega-6 FAs must be attained to prevent migraine. This hypothesis is based on the fact that omega-3 FAs have been shown to be anti-nociceptive while omega-6 FAs have been found to be pro-nociceptive.[25] Ramsden and colleagues conducted the only RCT of omega-3 and omega-6 FAs in the prevention of headache in persons with chronic daily headache.[26] They hypothesized that a diet high in the anti-inflammatory omega-3 FAs and low in the pro-inflammatory omega-6 FA (↑O3/↓O6) diet would be superior to one that was low only in omega-6 FAs (↓O6) diet. Those randomized to the ↑O3/↓O6 diet ($n = 33$) experienced greater reductions in headache days (-8.8 vs -4.0 days per month; $P < .02$) and the HIT-6 (-7.5 vs -2.1 days per month; $P < .001$) as compared to those on the ↓O6 diet ($n = 34$). They also measured metabolites of omega-3 FAs in the platelets of these participants and found them to be elevated during treatment with the ↑O3/↓O6 diet. A post hoc analysis of the data revealed that these omega-3 metabolites (eg, 2-docosahexaenoylglycerol and cosahexaenoylethanolamine) were inversely correlated with the headache outcome measures.[27] This study provides the strongest published evidence to date that a ↑O3/↓O6 diet is preventive for chronic daily headache.

KETOGENIC DIETS

Very low carbohydrate diets or a ketogenic diet (KD) typically restrict the amount of carbohydrates to < 20 g per day.[28] The ratios of fat to the combined amounts of protein and carbohydrate range from 2:1 to 4:1 in most KDs.[29] After several days of a very low carbohydrate diet, the reserves of glycogen are depleted and ketone bodies are produced to maintain energy production within the mitochondria. These diets have been primarily used to achieve weight loss in obese individuals and to treat epilepsy.[30,31]

Ketogenic diets have been used in the preventative treatment of migraine headache. Di Lorenzo and colleagues conducted a prospective observational study in which patients with migraine were allowed to choose a ketogenic or standardized low calorie diet.[32] Those given the KD ($n = 45$) were asked to follow a strict ketogenic diet for the first month followed by a gradual reintroduction of carbohydrates over the following five months. There were ≥ 75% reductions in headache attack frequency (2.91 attacks per month at baseline vs .5 during the KD; $P < .0001$), days with headache (5.11 days/month at baseline vs .9 during the KD; $P < .0001$) and quantity of abortive meds administered during the first month with institution of the KD (4.91 tablets/month at baseline vs .5 during KD; $P < .001$). The headaches outcome measures worsened with each subsequent month on reinstitution of carbohydrates despite the fact that their weight continued to decline. This would support the contention that it is not the weight loss, but the KD itself that was responsible for the improvement. Persons receiving the standardized low carbohydrate diet ($n = 51$) did not significantly improve their headache outcome measures. This study provides the best evidence to date that a strict ketogenic diet improves migraine during a short lasting ketosis.

A more relaxed form of a KD has been termed a "modified Atkins" diet. Such diets restrict carbohydrates to a lesser degree than the ketogenic diets and some allow carbohydrates with a low glycemic index.[29] There has only been one case series of a modified Atkins diet in the treatment of migraine.[33] This study found no reduction in the frequency of headache with institution of a modified Atkins diet in three adolescents with chronic daily headache that completed the study, but there was extremely poor compliance with the diet in this group of patients.

HIGH AND LOW SODIUM DIETS

Sodium intake may also influence the frequency of headache. Amer and colleagues performed a retrospective analysis of a multicenter study that examined the effects of dietary sodium intake on hypertension in person enrolled in the DASH-Sodium clinical trial.[34] The purpose of the study was to determine if the frequency of self-reported headache was different during time periods with high, intermediate, or low sodium intake. The study population included those with pre-hypertension (eg, systolic blood pressures between 120–159 and diastolic pressures between 80–95 mm Hg). They were randomized to receive one of two different diets – either a dietary approaches to stop hypertension (DASH) or control diet. The DASH diet is one that includes high amounts of fruits, vegetables, and low-fat dairy products. Once randomized, each participant received each of three different levels of

sodium in their diet (high [150 mmol], intermediate (100 mmol], and low [50 mmol]) during three separate treatment periods (eg, three way cross-over trial). During the last week of each treatment period participants were asked if they had experienced headache. The odds of experiencing a headache was significantly lower during the low sodium diet as compared to the high sodium diet for both the DASH and control diets (ORs of .69 [95% CI; .49, .98] and .69 [.49, .99], respectively). This study found that a low sodium diet was associated with a lower frequency of headache as compared to a high sodium diet in persons with prehypertension.

Another dietary study examined the association between dietary sodium intake and severe headache or migraine. This study was part of the National Health and Nutrition Examination Survey (NHANES), which is a survey of medical conditions and health habits within a representative group of persons from the United States. During the 2003–2004 survey, investigators conducted a one day dietary interview of foods consumed during the prior 24 hour time period. They also asked patients if they had experienced severe headache or migraine during the past three months. An inverse association was observed between dietary sodium intake and severe headache or migraine when comparing the fourth quartile to the first quartile of dietary sodium intake (adjusted OR .81 [95% CI .66, .99]). A further subgroup analysis found that the relationship was only significant in women with lower body mass index. The investigators reported an OR of .66 (95% CI; .49, .88) for women with a lower body mass index (BMI < 50 percentile). Thus, high sodium intake led to a lower frequency of severe/headache or migraine in this study.

The two studies have contradictory results with lower salt intake being associated with less frequent headaches in the first study and higher salt intake being associated with fewer migraines/severe headaches in the second study. These opposite results might be explained by differences in study design. There were differences in outcome measures, with the first study using the frequency of "headache" within the prior week as their primary endpoint and the second using the frequency of "migraine/severe headache" within the prior three months. The second study did not control for blood pressure or medications used to treat high blood pressure in their analyses, which might have confounded their results.[35] High salt intake might lead to hypertension and the subsequent use of anti-hypertensive medications (eg, beta blockers, calcium blockers, or others) that might prevent attacks of migraine. In addition, the first study included patients with prehypertension, while the second study included a population-based sample. The results of the second study were only significant in women with a lower BMI, which is a group that would be less likely to have prehypertension or hypertension. Therefore, it is possible that the high salt intake is provocative in those with prehypertension or hypertension while preventive in those with low BMI.

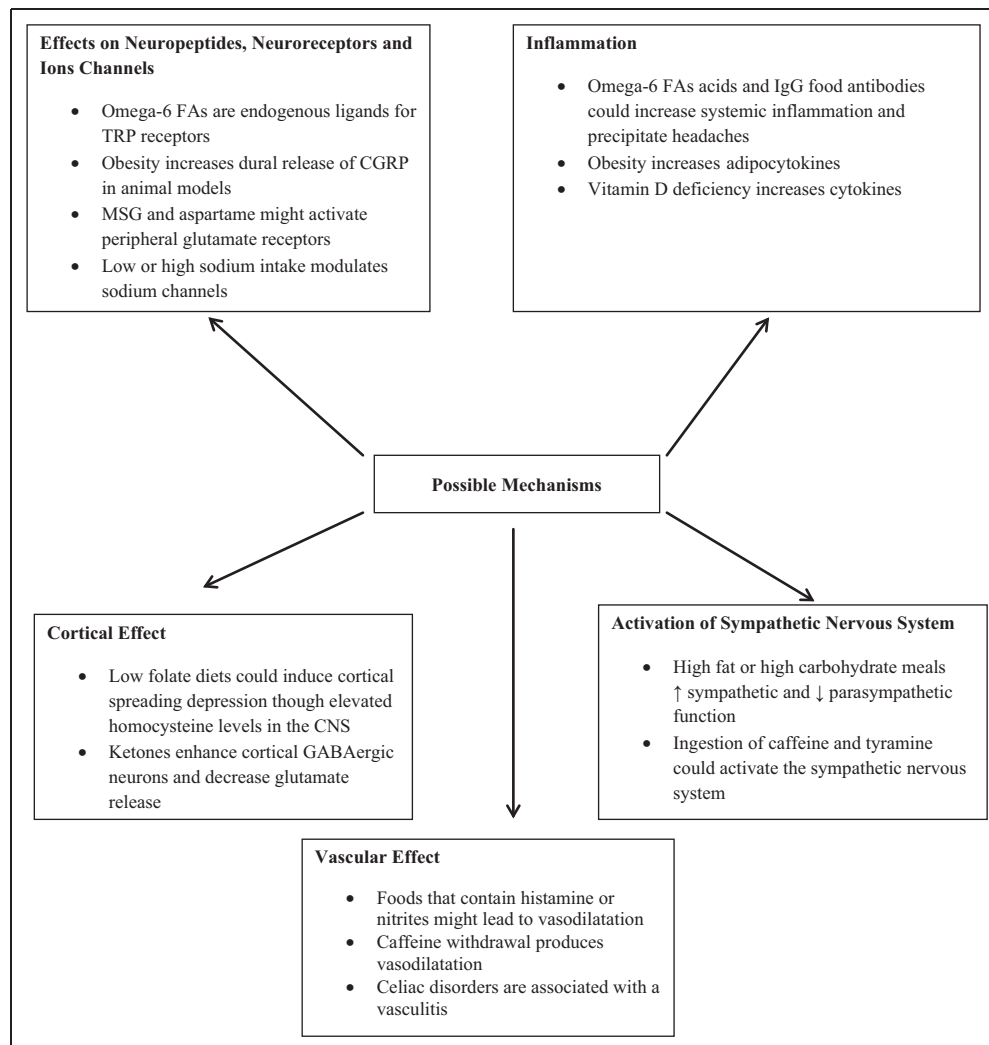## POSSIBLE MECHANISMS OF DIETARY TRIGGERS

There are a number of possible mechanisms through which diets could trigger headaches. These include their effects on neuropeptides, neuroreceptors and ion channels, inflammation, sympathetic nervous system, release of nitric oxide, vasodilation, and cerebral glucose metabolism (Fig. 1).

The fat composition of the diet may be important in modulating pain through its effects on inflammation, neuroreceptors, and ion channels. Omega-6 FAs are pro-inflammatory and are metabolized to derivatives that are sources for production of arachidonic acid and prostanoids.[36] These derivatives are endogenous ligands for transient receptor potential (TRP) receptors that on activation increase sensitization of trigeminal afferents.[37] It may be the ratio of omega-3/omega-6 FAs that is most important in modulating nociception rather than their absolute serum levels.[38] Rats kept on a diet with a low ratio of omega-3/omega 6 FAs were noted to have more pronounced mechanical allodynia after ligation of the infraorbital nerve.[37] Another animal study found that omega-3 and omega-6 FAs produced hyperpolarization and decreased excitability of neuronal sodium channels.[39]

Administration of monosodium glutamate (MSG) could alter headache through its effects on glutamatergic neurotransmission. Baad-Hansen and colleagues found a decrease in the pressure pain threshold (PPT) in the left masseter muscle after a single dosage of liquid MSG at low dosages (eg, 75 mg/kg of body weight), but no difference was found in PPTs in the right masseter or either temporalis muscle.[40] Shimada and colleagues gave MSG (150 mg/kg of body weight) dissolved in lemon soda daily for five consecutive days to 14 healthy adults and reported decreased mean PPTs in the masseter muscle as compared to baseline on days 2 and 3 of administration.[41] No change in mean masseter PPTs was noted in the same group of participants when they received normal saline (24 mg per kg of body weight) added to lemon soda. Salivary glutamate levels were higher in the MSG group than the normal saline group averaged over the five day time period. The authors postulated that high interstitial glutamate levels in the masseter muscle attained after MSG administration might activate peripheral N-methyl D-aspartate (NMDA) receptors and sensitize peripheral nociceptors to mechanical stimuli. Aspartame might also produce headache through similar mechanisms as it is metabolized to aspartic acid, which is an NMDA receptor agonist.

Certain foods might precipitate migraine through modulation of the sympathetic nervous system. Diets high in fats or

Fig. 1.—Possible mechanisms of food triggers.

carbohydrates can cause sympathetic activation or parasympathetic withdrawal within 120 minutes of meal ingestion in healthy men.[42] Acute caffeine consumption increases blood pressure and heart rate by activation of the sympathetic nervous system.[43] This activation is more pronounced in nonhabitual coffee drinkers as opposed to habitual drinkers. Tyramine stimulates the release of norepinephrine from sympathetic nerve terminals. In persons receiving a tyramine infusion the probability of headache was reduced by pretreatment with a α-adrenergic agonist.[44]

Other foods (eg, citrus fruits, vanillin, alcohol, and decaffeinated coffee) inhibit sulfotransferases in the gut that metabolize dopamine, which is a precursor of norepinephrine.[45] Therefore, ingestion of these foods might increase serum norepinephrine levels and subsequently trigger attacks of headache.

Caffeine is a competitive antagonist of adenosine A_1 and A_{2A} receptors. The mechanism through which caffeine withdrawal produces headache may be vascular, as abstinence from caffeine produces increased cerebral blood flow velocities.[46,47] Caffeine effects on the central nervous system include increased sleep latency, shortened sleep time, and reduced cerebral blood flow.[47,48] Caffeine inhibits the action of excitatory amino acid transporter type 3 (EAAT3) leading to an elevation of glutamate levels.[49] EAAT3 has been found in the trigeminal ganglion, and increased interstitial levels of glutamate have been found to increase mechanical sensitization of nociceptors in the temporalis muscle.[50]

Nitrites produce vasodilation through the formation of nitric oxide (NO) while histamine causes it through other mechanisms as a nitric oxide inhibitor did not prevent dilation of the middle cerebral artery after administration of intravenous histamine.[51] Both produce both a mild headache 0–2 hours within 2 hours after their administration as well as a late headache resembling migraine 5–6 hours later.[52] Since NO has a short half-life and can only diffuse 150–160 microns, it is very unlikely that NO derived from dietary sources could ever reach the central nervous system (CNS). Thus it is likely that these chemicals produce headache through a direct vascular effect.

Celiac disease may produce a vasculitis of the CNS that can produce ataxia, peripheral neuropathy, and migraine-like headaches.[53,54] In addition, white matter lesions have been reported in these patients.[55] There have been case series demonstrating that the migraine may improve and the white matter lesions may not progress with institution of a gluten free diet.[55]

Low folate diets might elevate homocysteine levels and provoke headaches in persons with certain genotypes of the MTHFR gene. Elevated homocysteine levels within the central nervous system might activate N-methyl-D-aspartate receptors and promote spreading cortical depression.[56] Homocysteine is an antagonist to gamma-amino-butyric acid-A (GABA-A) receptors, which are important inhibitory receptors within the CNS.[57] Homocysteine may also increase oxidative stress with the CNS that could provoke headache.[58]

High or low sodium diets could alter neurotransmission through their effects on sodium channels within the CNS.[59] Concentrations of sodium within the CSF are elevated in migraineurs compared to controls.[60] In addition, CSF sodium levels increase during a migraine attack as compared to interictal time periods. Extracellular concentrations of sodium have been shown to influence firing rates of hippocampal pyramidal neurons.[61] Concentrations of sodium increase in brain, intracranial CSF, and vitreous humor after administration of nitroglycerin in rats.[62] Therefore, sodium homeostasis may be important in the pathophysiology of migraine.

Ketones as produced with the KD may have a direct inhibitory effect on the cortex. Migraineurs placed on a KD reverse a habituation deficit noted on visual and somatosensory evoked potentials.[63] Normalization of habituation may occur as a result of decreased cortical excitability from the ketones. Ketones increase ATP-sensitive potassium channel activity, enhance tonus of inhibitory GABAergic neurons, and decrease release of glutamate, which is an excitatory neurotransmitter.[64–66]

A poorly studied area is the alteration of cerebral glucose metabolism and/or energy metabolism by foods and/or ingredients within foods. Caffeine inhibits glucose transport through competitive binding at the glucose-1 transporter (GLUT-1) nucleotide binding site.[67] GLUT-1 is an important protein responsible for glucose transport in the CNS. Caffeine enhances symptoms of hypoglycemia even with serum levels of glucose that are not typically associated with hypoglycemia.[68] Since ingestion of a high carbohydrate meal can cause blood sugars in the low normal range, it is possible that hypoglycemic symptoms including headache might be induced after large meals in moderate caffeine users.

It may not be the diet itself, but the weight loss induced by the diet that is preventive for headache, as obesity is associated with both episodic and chronic migraine, particularly in younger persons aged 20–55 years of age.[69–71] Bariatric surgery and weight loss programs reduce the frequency of headache in obese headache patients.[72,73] Obesity may increase the frequency of migraine through an increase in adipocytokines or secondary to associated headache disorders that are produced by obesity (eg, obstructive sleep apnea or idiopathic intracranial hypertension).[74–76] An animal study also found enhanced dural release of calcitonin gene-related peptide (CGRP) in basal and provoked conditions in obese as compared to control rats.[77,78]
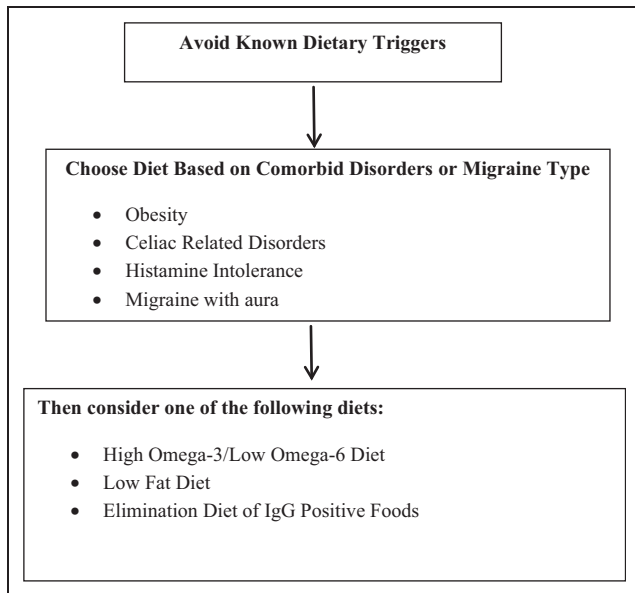
RATIONAL APPROACH TO DIET

It is not reasonable for persons with headache to avoid all know dietary triggers, as individuals may only be susceptible to a small number of foods or beverages. The authors recommend that if a food, beverage, or ingredient is identified as a trigger, it should be avoided to reduce the frequency of headache. The triggers could be identified by simple observation if the association is strong or through the use of a food diary if it is less obvious. The ideal would be to use a food diary as part of an app that would then determine statistically if a given food or beverage was associated with headache.

There are a number of diets that could be employed for persons with headache. The choice of a specific diet may in part depend on comorbid medical conditions as well as the type of migraine encountered by the patient. One may wish to place obese patients with headache on a diet that will reduce their weight, such as low fat or low carbohydrate diets.

A 2015 meta-analysis showed that low carbohydrate diets (<120 mg carbohydrates per day) were more effective for weight loss than low fat diets (<30% of their energy from fat).[79] Persons with diarrhea, ataxia, autoimmune disorders, or peripheral neuropathy should be checked for celiac sprue or nonceliac gluten sensitivity with IgG and IgA antibodies against transglutaminase and gliadin. If positive for one or more of these antibodies, they might be consider following a gluten free diet.

Those with symptoms of histamine intolerance (eg, flushing, diarrhea, wheezing, urticaria, or rhinitis) on ingestion of

Avoid Known Dietary Triggers

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Choose Diet Based on Comorbid Disorders or Migraine Type

- Obesity
- Celiac Related Disorders
- Histamine Intolerance
- Migraine with aura

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Then consider one of the following diets:

- High Omega-3/Low Omega-6 Diet
- Low Fat Diet
- Elimination Diet of IgG Positive Foods

Fig. 2.—Rational approach to diet in the headache patient.

foods might be considered for a low histamine diet and anti-histamine medications. Patients with migraine with aura that have a C allele of the MTHFR gene mutation might be placed on a high folate diet or a supplement that contains folate (2 mg), vitamin B6 and vitamin B12.

The question remains as to whether a single diet could be used to prevent headaches regardless of underlying medical disorders or type of migraine. The authors think that the three diets with the most promise include the high omega-3/low omega-6 and low fat diets as well as the elimination diet of IgG positive foods. Each of the three diets has randomized controlled trials supporting their efficacy. However, there are significant limitations to these studies, including small sample sizes and lack of blinding of diets.

Ketogenic diets might also be considered in some patients. However, there are only noncontrolled trials of these diets in the prevention of migraine, and their long term safety is unknown. Past studies raised concerns regarding hypercholesterolemia, impaired renal function, and osteoporosis with long term KDs.[28] Given the lack of medical evidence and their potential for harm, we cannot recommend these diets at this time.

We propose a rational approach to diet in the headache patient. First, persons with headache should avoid all recognized food triggers. Second, consider a specific diet based on underlying comorbid medical disorders or type of migraine (eg, aura). Third, if there are no specific comorbid medical disorders to guide choice of a diet, then consider a diet that has some proven efficacy (eg, high omega-6/low omega-3 diet,

low fat diet or elimination diet of IgG positive foods). Use of one dietary intervention does not preclude use of another. It may be necessary to employ two or more dietary interventions in patients to see an optimal response (Fig. 2).

CONCLUSIONS

Foods and ingredients within foods and beverages precipitate headache through a variety of mechanisms including their effects on neuropeptides, ion channels, receptors, inflammation, sympathetic nervous system, vasodilation, release of nitric oxide, and alterations in cerebral glucose metabolism. Specific elimination and comprehensive diets show promise as preventive therapies for patients with migraine and other headache disorders. However, the results of the above studies need to be replicated in future large scale RCTs before widespread use of these diets can be recommended in clinical practice.

Statement of Authorship
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References
1. Samaan Z, Gaysina D, Cohen-Woods S, et al. Methylenetetrahydrofolate reductase gene variant (MTHFR C677T) and migraine: A case control study and meta-analysis. *BMC Neurol.* 2011;11:66.
2. Isobe C, Terayama Y. A remarkable increase in total homocysteine concentrations in the CSF of migraine patients with aura. *Headache.* 2010;50:1561-1569.
3. Sadeghi O, Maghsoudi Z, Khorvash F, Ghiasvand R, Askari G. Assessment of pyridoxine and folate intake in migraine patients. *Adv Biomed Res.* 2016;5:47.
4. Menon S, Lea RA, Ingle S, et al. Effects of dietary folate intake on migraine disability and frequency. *Headache.* 2015;55:301-309.

5. Lippi G, Mattiuzzi C, Meschi T, Cervellin G, Borghi L. Homocysteine and migraine. A narrative review. *Clin Chim Acta.* 2014; 433:5-11.

6. Menon S, Lea RA, Roy B, et al. Genotypes of the MTHFR C677T and MTRR A66G genes act independently to reduce migraine disability in response to vitamin supplementation. *Pharmacogenet Genomics.* 2012;22:741-749.

7. Lea R, Colson N, Quinlan S, Macmillan J, Griffiths L. The effects of vitamin supplementation and MTHFR (C677T) genotype on homocysteine-lowering and migraine disability. *Pharmacogenet Genomics.* 2009;19:422-428.

8. Menon S, Nasir B, Avgan N, et al. The effect of 1 mg folic acid supplementation on clinical outcomes in female migraine with aura patients. *J Headache Pain.* 2016;17:60.

9. Motaghi M, Haghjooy Javanmard S, Haghdoost F, et al. Relationship between vitamin D receptor gene polymorphisms and migraine without aura in an Iranian population. *Biomed Res Int.* 2013;2013:351942.

10. Kjaergaard M, Eggen AE, Mathiesen EB, Jorde R. Association between headache and serum 25-hydroxyvitamin D: The Tromso study: Tromso 6. *Headache.* 2012;52:1499-1505.

11. Zandifar A, Masjedi SS, Banihashemi M, et al. Vitamin D status in migraine patients: A case-control study. *Biomed Res Int.* 2014; 2014:514782.

12. Lippi G, Cervellin G, Mattiuzzi C. No evidence for an association of vitamin D deficiency and migraine: A systematic review of the literature. *Biomed Res Int.* 2014;2014:827635.

13. Knutsen KV, Brekke M, Gjelstad S, Lagerlov P. Vitamin D status in patients with musculoskeletal pain, fatigue and headache: A cross-sectional descriptive study in a multi-ethnic general practice in Norway. *Scand J Prim Health Care.* 2010;28:166-171.

14. Prakash S, Makwana P, Rathore C. Vitamin D deficiency mimicking chronic tension-type headache in children. *BMJ Case Rep.* 2016;2016.

15. Prakash S, Kumar M, Belani P, Susvirkar A, Ahuja S. Interrelationships between chronic tension-type headache, musculoskeletal pain, and vitamin D deficiency: Is osteomalacia responsible for both headache and musculoskeletal pain? *Ann Indian Acad Neurol.* 2013;16:650-658.

16. Knutsen KV, Madar AA, Brekke M, et al. Effect of vitamin D on musculoskeletal pain and headache: A randomized, double-blind, placebo-controlled trial among adult ethnic minorities in Norway. *Pain.* 2014;155:2591-2598.

17. Mottaghi T, Askari G, Khorvash F, Maracy MR. Effect of Vitamin D supplementation on symptoms and C-reactive protein in migraine patients. *J Res Med Sci.* 2015;20:477-482.

18. Buettner C, Nir RR, Bertisch SM, et al. Simvastatin and vitamin D for migraine prevention: A randomized, controlled trial. *Ann Neurol.* 2015;78:970-981.

19. Ferrara LA, Pacioni D, Di Fronzo V, et al. Low-lipid diet reduces frequency and severity of acute migraine attacks. *Nutr Metab Cardiovasc Dis.* 2015;25:370-375.

20. Bic Z, Blix GG, Hopp HP, Leslie FM, Schell MJ. The influence of a low-fat diet on incidence and severity of migraine headaches. *J Womens Health Gend Based Med.* 1999;8:623-630.

21. Sadeghi O, Maghsoudi Z, Khorvash F, Ghiasvand R, Askari G. The relationship between different fatty acids intake and frequency of migraine attacks. *Iran J Nurs Midwifery Res.* 2015;20: 334-339.

22. Pradalier A, Bakouche P, Baudesson G, et al. Failure of omega-3 polyunsaturated fatty acids in prevention of migraine: A double-blind study versus placebo. *Cephalalgia.* 2001;21:818-822.

23. Tajmirriahi M, Sohelipour M, Basiri K, Shaygannejad V, Ghorbani A, Saadatnia M. The effects of sodium valproate with fish oil supplementation or alone in migraine prevention: A randomized single-blind clinical trial. *Iran J Neurol.* 2012;11:21-24.

24. Harel Z, Gascon G, Riggs S, Vaz R, Brown W, Exil G. Supplementation with omega-3 polyunsaturated fatty acids in the management of recurrent migraines in adolescents. *J Adolesc Health.* 2002;31:154-161.

25. Wagner K, Vito S, Inceoglu B, Hammock BD. The role of long chain fatty acids and their epoxide metabolites in nociceptive signaling. *Prostaglandins Other Lipid Mediat.* 2014;113-115:2-12.

26. Ramsden CE, Faurot KR, Zamora D, et al. Targeted alteration of dietary n-3 and n-6 fatty acids for the treatment of chronic headaches: A randomized trial. *Pain.* 2013;154:2441-2451.

27. Ramsden CE, Zamora D, Makriyannis A, et al. Diet-induced changes in n-3- and n-6-derived endocannabinoids and reductions in headache pain and psychological distress. *J Pain.* 2015; 16:707-716.

28. Paoli A. Ketogenic diet for obesity: Friend or foe?. *Int J Environ Res Public Health.* 2014;11:2092-2107.

29. Schoeler NE, Cross JH. Ketogenic dietary therapies in adults with epilepsy: A practical guide. *Pract Neurol.* 2016;16:208-214.

30. Keene DL. A systematic review of the use of the ketogenic diet in childhood epilepsy. *Pediatr Neurol.* 2006;35:1-5.

31. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: A meta-analysis of randomised controlled trials. *Br J Nutr.* 2013;110:1178-1187.

32. Di Lorenzo C, Coppola G, Sirianni G, et al. Migraine improvement during short lasting ketogenesis: A proof-of-concept study. *Eur J Neurol.* 2015;22:170-177.

33. Kossoff EH, Huffman J, Turner Z, Gladstein J. Use of the modified Atkins diet for adolescents with chronic daily headache. *Cephalalgia.* 2010;30:1014-1016.

34. Amer M, Woodward M, Appel LJ. Effects of dietary sodium and the DASH diet on the occurrence of headaches: Results from randomised multicentre DASH-Sodium clinical trial. *BMJ Open.* 2014;4:e006671.

35. Haghdoost F. Is there an inverse relationship between migraine and dietary sodium intake? *Headache.* 2016;56:1212-1213.

36. Nomura DK, Morrison BE, Blankman JL, et al. Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. *Science.* 2011;334:809-813.

37. Martin YB, Avendano C. Effects of removal of dietary polyunsaturated fatty acids on plasma extravasation and mechanical allodynia in a trigeminal neuropathic pain model. *Mol Pain.* 2009;5:8.

38. Yehuda S, Carasso RL. Modulation of learning, pain thresholds, and thermoregulation in the rat by preparations of free purified alpha-

linolenic and linoleic acids: Determination of the optimal omega 3-to-omega 6 ratio. *Proc Natl Acad Sci U S A.* 1993;90:10345-10349.

39. Hong MP, Kim HI, Shin YK, Lee CS, Park M, Song JH. Effects of free fatty acids on sodium currents in rat dorsal root ganglion neurons. *Brain Res.* 2004;1008:81-91.

40. Baad-Hansen L, Cairns B, Ernberg M, Svensson P. Effect of systemic monosodium glutamate (MSG) on headache and pericranial muscle sensitivity. *Cephalalgia.* 2010;30:68-76.

41. Shimada A, Cairns BE, Vad N, et al. Headache and mechanical sensitization of human pericranial muscles after repeated intake of monosodium glutamate (MSG). *J Headache Pain.* 2013;14:2.

42. Kuwahara K, Okita Y, Kouda K, Nakamura H. Effects of modern eating patterns on the cardiac autonomic nervous system in young Japanese males. *J Physiol Anthropol.* 2011;30:223-231.

43. Corti R, Binggeli C, Sudano I, et al. Coffee acutely increases sympathetic nerve activity and blood pressure independently of caffeine content: Role of habitual versus nonhabitual drinking. *Circulation.* 2002;106:2935-2940.

44. Ghose K, Coppen A, Carrol D. Intravenous tyramine response in migraine before and during treatment with indoramin. *Br Med J.* 1977;1:1191-1193.

45. Eagle K. Toxicological effects of red wine, orange juice, and other dietary SULT1A inhibitors via excess catecholamines. *Food Chem Toxicol.* 2012;50:2243-2249.

46. Mathew RJ, Wilson WH. Caffeine consumption, withdrawal and cerebral blood flow. *Headache.* 1985;25:305-309.

47. Couturier EG, Laman DM, van Duijn MA, van Duijn H. Influence of caffeine and caffeine withdrawal on headache and cerebral blood flow velocities. *Cephalalgia.* 1997;17:188-190.

48. Nehlig A. Effects of coffee/caffeine on brain health and disease: What should I tell my patients? *Pract Neurol.* 2016;16:89-95.

49. Shin HJ, Ryu JH, Kim ST, Zuo Z, Do SH. Caffeine-induced inhibition of the activity of glutamate transporter type 3 expressed in Xenopus oocytes. *Toxicol Lett.* 2013;217:143-148.

50. Laursen JC, Cairns BE, Dong XD, et al. Glutamate dysregulation in the trigeminal ganglion: A novel mechanism for peripheral sensitization of the craniofacial region. *Neuroscience.* 2014;256:23-35.

51. Schmetterer L, Wolzt M, Graselli U, et al. Nitric oxide synthase inhibition in the histamine headache model. *Cephalalgia.* 1997;17:175-182.

52. Lassen LH, Thomsen LL, Olesen J. Histamine induces migraine via the H1-receptor. Support for the NO hypothesis of migraine. *Neuroreport.* 1995;6:1475-1479.

53. Rush PJ, Inman R, Bernstein M, Carlen P, Resch L. Isolated vasculitis of the central nervous system in a patient with celiac disease. *Am J Med.* 1986;81:1092-1094.

54. Mumford CJ, Fletcher NA, Ironside JW, Warlow CP. Progressive ataxia, focal seizures, and malabsorption syndrome in a 41 year old woman. *J Neurol Neurosurg Psychiatry.* 1996;60:225-230.

55. Hadjivassiliou M, Grunewald RA, Lawden M, Davies-Jones GA, Powell T, Smith CM. Headache and CNS white matter abnormalities associated with gluten sensitivity. *Neurology.* 2001;56:385-388.

56. McCully KS. Chemical pathology of homocysteine. IV. Excitotoxicity, oxidative stress, endothelial dysfunction, and inflammation. *Ann Clin Lab Sci.* 2009;39:219-232.

57. Lominadze D, Tyagi N, Sen U, Ovechkin A, Tyagi SC. Homocysteine alters cerebral microvascular integrity and causes remodeling by antagonizing GABA-A receptor. *Mol Cell Biochem.* 2012;371:89-96.

58. Borkum JM. Migraine triggers and oxidative stress: A narrative review and synthesis. *Headache.* 2016;56:12-35.

59. Harrington MG, Fonteh AN, Arakaki X, et al. Capillary endothelial Na(+), K(+), ATPase transporter homeostasis and a new theory for migraine pathophysiology. *Headache.* 2010;50:459-478.

60. Harrington MG, Fonteh AN, Cowan RP, et al. Cerebrospinal fluid sodium increases in migraine. *Headache.* 2006;46:1128-1135.

61. Arakaki X, Foster H, Su L, et al. Extracellular sodium modulates the excitability of cultured hippocampal pyramidal cells. *Brain Res.* 2011;1401:85-94.

62. Harrington MG, Chekmenev EY, Schepkin V, Fonteh AN, Arakaki X. Sodium MRI in a rat migraine model and a NEURON simulation study support a role for sodium in migraine. *Cephalalgia.* 2011;31:1254-1265.

63. Di Lorenzo C, Coppola G, Bracaglia M, et al. Cortical functional correlates of responsiveness to short-lasting preventive intervention with ketogenic diet in migraine: A multimodal evoked potentials study. *J Headache Pain.* 2016;17:58.

64. Sato K, Kashiwaya Y, Keon CA, et al. Insulin, ketone bodies, and mitochondrial energy transduction. *FASEB J.* 1995;9:651-658.

65. Kawamura M Jr, Ruskin DN, Geiger JD, Boison D, Masino SA. Ketogenic diet sensitizes glucose control of hippocampal excitability. *J Lipid Res.* 2014;55:2254-2260.

66. Stafstrom CE, Wang C, Jensen FE. Electrophysiological observations in hippocampal slices from rats treated with the ketogenic diet. *Dev Neurosci.* 1999;21:393-399.

67. Sage JM, Cura AJ, Lloyd KP, Carruthers A. Caffeine inhibits glucose transport by binding at the GLUT1 nucleotide-binding site. *Am J Physiol Cell Physiol.* 2015;308:C827-C834.

68. Kerr D, Sherwin RS, Pavalkis F, et al. Effect of caffeine on the recognition of and responses to hypoglycemia in humans. *Ann Intern Med.* 1993;119:799-804.

69. Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic tension-type headache. *Neurology.* 2006;67:252-257.

70. Ford ES, Li C, Pearson WS, Zhao G, Strine TW, Mokdad AH. Body mass index and headaches: Findings from a national sample of US adults. *Cephalalgia.* 2008;28:1270-1276.

71. Peterlin BL, Rosso AL, Williams MA, et al. Episodic migraine and obesity and the influence of age, race, and sex. *Neurology.* 2013;81:1314-1321.

72. Bond DS, Vithiananthan S, Nash JM, Thomas JG, Wing RR. Improvement of migraine headaches in severely obese patients after bariatric surgery. *Neurology.* 2011;76:1135-1138.

73. Novack V, Fuchs L, Lantsberg L, et al. Changes in headache frequency in premenopausal obese women with migraine after bariatric surgery: A case series. *Cephalalgia.* 2011;31:1336-1342.

74. Chai NC, Bond DS, Moghekar A, Scher AI, Peterlin BL. Obesity and headache: Part II–potential mechanism and treatment considerations. *Headache.* 2014;54:459-471.

75. Tilg H, Moschen AR. Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol.* 2006;6:772-783.

76. Peterlin BL, Sacco S, Bernecker C, Scher AI. Adipokines and migraine: A systematic review. *Headache.* 2016;56:622-644.

77. Marics B, Peitl B, Varga A, et al. Diet-induced obesity alters dural CGRP release and potentiates TRPA1-mediated trigeminovascular responses. *Cephalalgia.* 2016.

78. Veggiotti P, Teutonico F, Alfei E, et al. Glucose transporter type 1 deficiency: Ketogenic diet in three patients with atypical phenotype. *Brain Dev.* 2010;32:404-408.

79. Sackner-Bernstein J, Kanter D, Kaul S. Dietary intervention for overweight and obese adults: Comparison of low-carbohydrate and low-fat diets. A meta-analysis. *PLoS One.* 2015;10: e0139817.