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MIGRAINE (R COWAN, SECTION EDITOR)

Dietary Considerations in Migraine Management: Does a Consistent Diet Improve Migraine?

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Abstract The clinical expression of migraine is significantly impacted by dietary and gastrointestinal issues. This includes gut dysfunction during and between attacks, food triggers, increase in migraine with obesity, comorbid GI and systemic inflammation influenced by diet, and specific food allergies such as dairy and gluten. Practitioners often encourage migraineurs to seek consistency in their lifestyle behaviors, and environmental exposures, as a way of avoiding sudden changes that may precipitate attacks. However, rigorous evidence linking consistency of diet with improvement in migraine is very limited and is, at best, indirect, being based mainly on the consistency of avoiding suspected food triggers. A review of current data surrounding the issue of dietary consistency is presented from the perspective of migraine as an illness (vulnerable state), as a disease (symptom expression traits), and with a view toward the role of local and systemic inflammation in its genesis. Firm recommendations await further investigation.

Keywords Migraine · Diet · Inflammation · Lifestyle · Orexin · Inflammatory Bowel Disease · Obesity · Triggers · Umami

This article is part of the Topical Collection on *Migraine*

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Introduction

One lovely evening, there was a modest soiree with friends. All were enjoying a fantastic meal starting with an iceberg wedge smothered in a walnut vinaigrette, and a side of bacon wrapped lobster bites. After a crisp beer rinses these flavors from the discerning palates, the main course of aged beef tips with a side of grilled tomatoes covered in toasted parmesan cheese is rinsed down with a glass of beautiful rich merlot. A dessert of creamy vanilla bean ice cream, sits in a nest of fried banana slices, all smothered in a sauce of dark chocolate, completing the evening's epicurean delight. What happens within the next hour is enough to negate the pleasure of the meal that was just experienced. A migraine headache, requiring medication and bed rest, ensues. The friends understand and are left in the restaurant, as the migranous mind becomes focused on only the comfort of a dark cool room.

Growing interest in the factors influencing the burden of disease in migraine has included increasing attention on the importance of diet and body habitus. Original suggestions that higher body mass index (BMI) as a predictor of migraine chronification [1] have been replicated [2–9] and additional evidence from biomarker studies confirm the presence of abnormal inflammatory states in patients with concurrent bowel disorders [10] . Basic research studies, including animal models, have linked diet to inflammation and have suggested that this connection has relevance to human migraine [11]. An extremely detailed study of obesity and migraine currently underway hopes to show unequivocally that interventions

aimed at weight loss can lessen the burden on migraine in those most affected [12•]. For these reasons, we propose to answer a central question: *Why do care-givers and patients believe that a consistent diet improves migraine?*; and the corollary: *Is there evidence that once you have eliminated foods that trigger migraine, or that stimulate an immune reaction leading to migraine, creating a consistent diet, that it also improves migraine*?

Sensory Disorders

Sensory disorders including migraine have been studied as conditions affecting large segments of the population. In one study it was calculated that migraine has a lifetime incidence of nearly 45 % in American females [13]. Together with other non-lethal disorders such as fibromyalgia (FM), irritable bowel syndrome (IBS), temporal mandibular disorder (TMD), and pelvic and joint pain syndromes, these sensory illnesses take up a large portion of health care resources. Whether they are linked to each other by pathogenesis, genetics, or environmental factors remains a challenge to determine.

Whereas most of these painful syndromes are relatively continuous disorders with fluctuations, migraine is unique in that it most often presents symptomatically as an episodic disorder similar to epilepsy. Thus, there is a view that the attacks of migraine are both triggered and triggerable. The more recent attention to the chronic form of migraine suggests that it is a progressive and transformable disorder with the end result being nearly continuous headache. In this context, changes in migraine, especially improvement, needs strict definitions. Does improvement in migraine mean lower attack frequency and attacks with less impact, or is it the lessening of the total burden of disease including inter-ictal distress [14]? Do factors that compel progression necessarily affect all individuals in a similar way?

Sensory Sensitivity in Migraine

Increased sensitivity of the nervous system to sensory stimuli is the hallmark of migraine. Failure of attenuation to repetitive stimulation defines the irritability of the cerebral cortex and central connections [15–17]. Rapid variations in lighting, loud noises, certain smells, emotional turbulence, stress and its let down, disturbed sleep patterns, weather fronts, motion sickness, and menstrual events provoke and maintain migraine. Achieving consistency of sensory input and physiologic status is viewed as a way of reducing the migraine load. This can be defined as a derivative of headache frequency, intensity, duration, and other symptoms, including use of medications. Many therapeutic lifestyle suggestions are based on these observations and associated beliefs. Examples of such advice include: recommendations for stabilizing estrogen levels for those with menstrual migraine [18], C-PAP use to optimize sleep [19], biofeedback training of autonomic and somatic responses and psychological counseling [20], regular exercise and wake-sleep habits [21], and even headache diary maintenance [22] to enhance awareness of events that bring on headache.

In the list of preferred preventive strategies for migraine, we often advise patients to avoid erratic dietary habits and promote dietary consistency which includes the patterned avoidance of known migraine-triggering foods. Questions that arise from this dietary advice include: 1) what is the evidence that a consistent diet improves migraine; 2) is a consistent diet a "good diet"; with highest nutritional value and avoidance of "toxins", e.g. trans fats; and/or 3) is simply eating regular meals at usual times enough?

We have chosen to frame the questions using the following schema: that the relationship between diet and migraine is a function of changes in: 1) illness, 2) disease, and 3) inflammation. By *illness* we mean living with a state of the brain which makes an individual susceptible to migraine, whether in terms of attacks or overall burden, e.g. a disorder of daily life. By *disease* we mean changes in brain, i.e. states, with susceptibility that is intimately linked to including specific components of certain foods, e.g. glutamate, polyunsaturated fatty acids, caffeine, alcohol, which are presumed to provoke attacks or propel progression with or without other illnesses or diseases associated with migraine. By *inflammation* we mean the response in neural tissues, implicated in migraine, to substances or states which food and diet may influence.

Illness Model

Migraine is a disorder of the brain and the gut. In the young, vomiting and abdominal pain ARE migraine [23]. This persists into adulthood where anorexia replaces vomiting as the main GI accompaniment, though vomiting persists in 30 – 70 % [24–26]. Research has confirmed gastric stasis and gastroparesis [27], and central nervous system centers for motility and satiety are cited as both generators and effectors during migraine attacks [28, 29•, 30–32].

At the extremes of BMI, migraine worsens. Dietary restriction has been a cornerstone of care. Elimination of food items or even groups has often been tried as a way of reducing migraine attacks and migraine burden [33•, 34]. Using this strategy to identify triggers in individuals, many types of diets have been tried with variable results suggesting that finding a subtle "food allergy" has been and remains a key to many plans of care [35–38]. This, though, has been frustrated by the inconsistent occurrence of migraine when the "allergen" has been found, including even chocolate [39–41]. In its most extreme form of dietary restriction, e.g. fasting, migraine has been consistently

triggered [42, 43]. Yet, In terms of an illness model, is it the pattern of "use" (degree of regularity), or the object of "use" (specific foods), that conditions the individual's susceptibility?

Migraine Triggers

Most of the published literature on this subject studies specific food triggers as opposed to eating patterns [33•]. Amongst all triggers, food is second only to stress as the most cited cause for headache [44•, 45]. The usual lists of triggers include processed, fermented, pickled, or marinated foods. Monosodium glutamate, in pure or included form, is always cited. Histamine, especially in sea foods, is another, as are baked goods, meats, dairy products, and tyramine-containing foods such as red wine, aged cheese, smoked fish, figs, beans, citrus fruits, avocados, bananas, and onions. Caffeine and alcohol join processed meat products containing nitrates, such as hot dogs, bacon, salami, as major triggers. Foods containing omega-6 fatty acids may have a net pro-inflammatory effect on body chemistry and most contemporary western diets are poorly balanced by anti-inflammatory omega-3 fatty acid consumption [46, 47, 48•]. Removing identifiable triggers AND balancing dietary components are the basis of the historical use of elimination and replacement diets. More recent advances in food science have identified a fifth taste: umami, meaning "delicious." It has been found to enhance the enjoyment of food while having the identified agonist glutamate, a well established excitatory and pro-inflammatory compound. Foods high in umami are sometimes considered common migraine triggers (see Table 1).

This model, where the chemicals making up food are treated as potential "toxins", is based upon an assumption that the constituent chemicals in foods act as mediators of migraine. This may take the form of direct action at receptors, such as histamine or glutamate, causing acute attacks. This would follow the ideas put forward in the 1950s, requiring that a neurotransmitter fulfill specific criteria especially "when applied exogenously (as a drug) in reasonable concentrations, it mimics exactly the action of the endogenously released transmitter" [49]. Other longer-term modifiers of brain chemistry might include foods high in phytoestrogens or tryptophan.

Considering this aspect of diet, consistency becomes a behavioral set where self-teaching by trial and error or guidelines (which do not exist), may lead to reduction in migraine frequency. The implications of this also include a mindfulness towards food that can focus on "goodness" of fit, or of anxiety about ingredients. In this vein, one study suggests that regular water intake, without reference to ingestion of solid foods, is associated with improvement in migraine [50].

Table 1 Foods Containing Umami and Monosodium Glutamate (MSG)

	Umami	MSG
Kombu	*	
Seaweed	*	
Dried bonito flakes	*	
Dried sardines	*	
Mackerel	*	
Tuna	*	
Oysters	*	
Shellfish	*	
Cod	*	
Prawns	*	
Squid	*	
Smoked fish	*	
Walnuts	*	
Baked foods		*
Beer		*
Red wine		*
Aged cheese		*
Breast milk	*	*through mother
Tomatoes	*	
Shitake mushrooms	*	
Truffles	*	
Soy beans and soy products	*	*
Potatoes	*	
Sweet potatoes	*	
Chinese cabbage	*	
Carrots	*	
Beans		*processed and canned
Figs	*	
Citrus fruits	*	
Avocados	*	
Bananas	*	
Onions	*	
Pickled foods		*
Marinated foods		*
Beef	*	
Pork	*	
Chicken	*	
Hot dogs	*	*
Salami	*	*
Pepperoni	*	*
Other processed meats	*	*
Bacon	*	*

Diet and Patterns

Virtually all of the migraine subtypes have dietary issues that may impact chronic patterns of eating independent of nutrient content. How these shifts in eating patterns affect migraine characteristics, or underlying migraine vulnerability, is not known. Examples include the shifts in eating that accompany the changing phases of the menstrual cycle. A reduction in appetite near the beginning of the menses may lead to irregular

timing of food intake and associated headache [51–53]. Also, eating patterns can change significantly with the development of comorbid depression in the setting of high frequency episodic headache, perhaps facilitating the development of chronic migraine [54]. Dietary changes often occur with use of preventive medications for migraine, especially noted with use of topirimate (nausea, anorexia, weight loss), valproic acid (gastritis, weight gain), and the tricyclics (stimulated appetite, weight gain) [55–57]. There are no studies linking benefits of topirimate or valproate, for example, to their anorexigenic or gastritic side effects. The use of tricyclics is associated with clinical improvement in migraine while stimulating appetite. How those benefits are linked to changes in appetite is also unstudied. Examination of these medication-related side effects, favorable or not, to underlying illness vulnerability may be a productive line of future research.

Lastly, there is the issue of the act of eating and the events surrounding it. Is it better or worse to miss breakfast, lunch or supper, and what is meant be having a meal vs. snacking as it relates to headache illness? What about fast food? Could it be that irregularly taken meals, excessive snacking, and poorly matched intake with nutrient needs impacts negatively on migraine vulnerability? Consideration might be given to the quality of the dining experience in all its aspects. Eating-related stress vs. pleasure and satisfaction might be usefully examined prospectively. Additional areas of inquiry could include food acquisition, preparation, the eating environment, pace of consumption, socializing during meals and the clean-up. The most recently proposed study [12•] will address satisfaction associated with behavioral dietary change.

The Illness Model lends itself to examination of the impact of food, food culture, and diet on the biopsychosocial well being of an individual with migraine. Opposing this, there is known impact of concurrent diseases on the experience of migraine. Type II diabetes has been found to have a protective effect in older migraineurs and the opposite effect in younger individuals with migraine [58]. Obesity leads to more headaches and elaborate efforts to define common factors have stimulated thinking about mechanisms of vulnerability including, most prominently, inflammation (see below). Gastrointestinal disorders such as Crohn's disease, ulcerative colitis, and celiac disease have a higher than normal prevalence of migraine, suggesting a shared vulnerability [59].

Disease Model

Diseases are defined by clearly identifiable clinical characteristics (phenotypic characteristics) or the availability of reliable biomarkers. Migraine phenotypes are classified using the ICHD. While no reliable biomarkers currently exist for migraine, its comorbidity with diseases having identifiable biological tests, such as depression, may provide an opportunity to discover similar markers for migraine. Presuming a disease, therefore, requires identifying reproducible events and their chemical or neural changes which inevitably lead to migraine attacks. This is different from presumptions about disease expression. One such question would be: are there subsets of migraineurs who have lower thresholds to nutrient deficiencies? The original enthusiasm about magnesium is a recent and disappointing example [60–64]. Another might ask, do these repeated exposures to food and inflammation, or the sum of them, determine chronic migraine, even if genetic predisposition (trait) is not present?

Inflammatory and Irritable Bowel Diseases

Inflammatory bowel disease, especially Crohn's disease, is comorbid with migraine [10]. Our finding of a smaller association of migraine with ulcerative colitis is of interest since the former is an upper intestinal disorder whose epidemiology may seem similar to migraine, e.g. female, young [59]. While immune complexes have been implicated in Crohn's disease, some have observed that the treatment of Crohn's disease with TNF-alpha antagonists reduces migraine burden. Though less well characterized from a biomarker point of view, irritable bowel syndrome (IBS) has recently been shown to share a common cause with migraine disease [65, 66]. Assuming that these disorders and their attendant biochemistry are responsible for migraine disease, eliminating substances which induce "flairs" should lessen disease expression or induction. In the past, empiric elimination diets with add-back food groups were used more extensively to identify food triggers specific for an individual.

In a more sophisticated approach, Aydinlar et al. [67•]. show that attacks of IBS are changed in a predictable way when food allergens are identified, removed, and then re-challenged. They tested 21 patients diagnosed according to the ICHD for migraine and Rome III for IBS. The authors tested subjects for biological variables including IgG antibody titers to 270 food allergens. During the diet phase of 6 weeks, patients were allocated to either an elimination or provocation diet and diaries of bowel and migraine symptoms were kept. They were then crossed over for an additional 6 weeks. The mean age of patients was 38 years and 85.7 % were female. None took IBS preventives and only four (19 %) were taking migraine preventives. IgG antibodies showed abnormally high titers to 23 allergens, most frequently seeds, nuts and grain with gluten. Salads showed the lowest titers and half the subjects or more had titers elevated to eggs, seafood and more to fruits and spices. After crossover, reversal of improvement or worsening occurred. Additional findings of improved well being, including happiness and reduction of fear of illness, were statistically significant during elimination. This study, though small, confirms the possible link between circulating antibodies, migraine burden, and better quality of life. The

authors propose that inflammation, including circulating cytokines and attack related activation of mast cells [68, 69], link migraine to food which induces IgG. Could this be true of those with bowel disorders or symptoms not meeting criteria based diagnosis of IBS? Does the pattern of antigen ingestion make a difference in terms of migraine burden? Do many migraineurs live on a spectrum of food based inflammation?

Inflammation

Migraine attacks are presumed to be the end result, in part, of inflammation at the level of trigeminovascular connections, resulting in abnormal transmission of pain signals [70]. Repeated attacks sensitize peripheral and central neurons and frequent headaches are a risk factor for chronicifcation. Long term changes in brain anatomy ensue [71].

Current research on inflammation supports a dietary model involving omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acid (PUFA) [46, 72]. There is limited information on the effects of reducing that ratio as a way of treating migraine by reducing inflammation associated with high n-6 consumption. Use of oral supplementation with n-3 PUFAs as a treatment intervention for migraine in adults showed no benefit [73]. That study looked only at clinical outcome measures and did not consider the impact of diet in calculating the relative amounts of the two PUFA classes consumed. No potential biomarkers were measured in the blood or other tissues. Another recent dietary study without oral supplements compared a low n-6 PUFA diet with a low n-6/high n-3 diet in adult subjects with chronic headache, primarily chronic migraine [74]. Those taking the low n-6/high n-3 diet, showed significant clinical improvement and biomarker shifts in the direction toward reduced inflammation [48•, 75]. Based upon these findings and other research, strong advocacy exists in some quarters for adopting an anti-inflammatory diet as a health promoting strategy [75]. Specific linkage with migraine prevention remains controversial in terms of dietary recommendations.

Headache and Obesity

Obesity is associated with a pro-inflammatory/pro-thrombotic metabolic state [76, 77, 78•, 79]. Many neurotransmitter and neuropeptide regulated systems, including those involved with serotonin, orexin, adiponectin, and leptin, are key to both feeding and migraine pathophysiology [77].

Orexin A and B are neuropeptides synthesized in neuronal cell bodies of the hypothalamus with broad projections to other CNS areas and to the GI tract. They are important in food intake, regulation of metabolism, arousal, and pain [77]. They participate in inflammation and have predominantly anti-nociceptive properties [78•]. They stimulate locomotor activity when food is restricted [79]. Reduction in orexin signaling may explain disrupted sleep/wake cycles, reduced appetite, and psychomotor retardation such as seen in depressed patients [80, 81]

Increased doses of exogenous orexin facilitate sleep in humans without changes in mood or the mind altering feelings of hypnotics [82]. Increased levels of orexin A in chronic migraine are thought to be due to compensatory responses to chronic head pain or hypothalamic responses to stress due to chronic pain [82].

The original question posed by the editors for this review was: "Why does a consistent diet improve migraine?" The literature was found to break out into two essential topics. The first and most obvious points to general health and wellness, concentrating on the importance of feeding behaviors driven by systems, such as the orexigenic, which determine hunger and satiety with the eventual morphologic outcome of body habitus. In this scenario, recurrent headaches would result in impaired hypothalamic function and reduced orexin secretion or activity. This would lead to poor pain modulation and weight gain secondary to reduced physical activity. As this progresses, more weight gain and increased inflammation provide a substrate for more frequent headache and chronicifcation of migraine. This cycle would then be negatively augmented by: 1) non-pain related weight gain (psychological response to chronic pain), 2) poor nutrition (low intake of omega-3 PUFAs), 3) depression (reduced physical inactivity), 4) medication side effects (weight gain with tricyclics), and 5) new triggering factors (late life allergies and sensitivities).

The consequences of obesity are well known, including cardiovascular and cerebrovascular catastrophes. The associations with obesity, on the other hand, appear to have wider ranging implications for the nervous system including psychological disorders, e.g. depression, and neurologic illnesses including migraine. Food groups which complicate the genetic dispositions to obesity, such as saturated fats, also influence migraine through the immune system and inflammation. The finding of reduction in migraine with diets tailored to reduce individual amplifiers of systemic IgG in patients with IBS, and the improvement with balanced, lower inflammatory fatty acid ratios, points toward a complicated system of basal metabolism and point-in-time consumption.

The cycle of inconsistent nutrition and poor control of migraine could then be ameliorated by close attention to: 1) obesity awareness, prevention, and treatment; 2) meal content optimizing nutrition, reducing pro-inflammatory PUFA consumption, and avoiding triggering nutrients;3) treatment of depression and anxiety); 4) guided analgesic, abortive and preventive medication use; 5) awareness of the multifaceted nature of migraine, its genetic basis, developmental aspects, impact of comorbidities, illness and disease distinctions, and the role of inflammation.

An upcoming study hopes to answer these questions. The investigators will enroll 140 subjects with BMI 25.0 – 49.9

who meet criteria for migraine to include chronic migraine. State-of-the-art smart-phone based diaries will be used throughout and controls will be closely monitored after a general education on migraine symptoms/triggers and treatment. The study interventions will include 4 months of group-based behavioral weight loss where they will be taught strategies to increase physical activity and consume fewer calories. The goals will be to compare those interventions with markers of inflammation and depression. Only through meticulous studies such as this [12•], will we ultimately know how to counsel and treat our patients.

These approaches, then, suggest a medical model of planned biometric and biochemical evaluations leading to planned diet and exercise, etc. Determining the content of meals and the setting in which they are eaten would certainly establish "consistency" with an end result of lesser burden of disease in patients with migraine.

The second topic, that being reduction in migraine burden via "consistent" attention to triggers, defines the difference between diet, as discussed above, and food. Data linking reduction of attack frequency to reduction in chronicifcation is just being published. Yet, this important area addresses the question of how the rituals associated with food may also play a part in the individual experience of migraine. Timing of meals, as shown by missing meals or fasting, is obviously a potent trigger and one most recognized by patients. Regularity of meals may be of the same order, but the drive to link individual foods has different neuroanatomic and neurochemical systems, including brain and chemical systems. What about preparation, content and taste? Are these individual, and does the culture in which an individual eats impact on susceptibility to migraine attacks and progression? There is little, yet, in the literature which addresses this interesting topic. How cravings and "deliciousness" influence the outcomes in migraine has not been studied. These alternative drives to ingest substances that are known to trigger migraine oppose common sense. The presence of umami receptors on the tongue may confound the science of dietary consistency. Resolving the tension between these two opposing forces , of restraint and planning vs. enjoyment and abandon, e.g. self-inflicted ingestion of triggers, may offer the patient the choices and the clinician the tools to treat.

Discussion

In her original thought experiment, Elizabeth Loder posed the question: "What is the evolutionary advantage of migraine? [83]" She hypothesizes five evolutionary explanations for the persistence of migraine in human populations: 1) migraine as a defense mechanism, 2) migraine as a result of conflict with other organisms, 3) migraine as result of novel environmental factors, 4) migraine as a trade-off between genetic harms and benefits, and 5) migraine as a design constraint. She goes on to explain how the phenomenology of the migraine attack, including triggers, may contain behavioral elements which predispose the individual to making conscious and unconscious choices whose end result reduce the susceptibility to, or provocation of, migraine. At the simplest level, this tries to explain the sensory phobias and nausea, while at the most complex it proposes that the mismatch of original traits with current conditions leaves a large population of humans with few options but to suffer.

These same choices appear to be very contemporary. In a culture that opposes fine dining with fast food, food science with consumerism, and personal choices with societal good, the individual with migraine must make immediate, short, middle, and long term decisions about the fundaments of daily living. Consistency in daily living requires educated and, probably, scientifically driven patterns which many find difficult to establish and maintain. For those, dietary and food choice is that challenge where drives meet needs - and oppose each other.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Alan G. Finkel, Juanita A. Yerry PA-C, and Dr. J. Douglas Mann reported no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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