

# The Diet Factor in Pediatric and Adolescent Migraine

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Diet can play an important role in the precipitation of headaches in children and adolescents with migraine. The diet factor in pediatric migraine is frequently neglected in favor of preventive drug therapy. The list of foods, beverages, and additives that trigger migraine includes cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer. Underage drinking is a significant potential cause of recurrent headache in today's adolescent patients. Tyramine, phenylethylamine, histamine, nitrites, and sulfites are involved in the mechanism of food intolerance headache. Immunoglobulin E-mediated food allergy is an infrequent cause. Dietary triggers affect phases of the migraine process by influencing release of serotonin and norepinephrine, causing vasoconstriction or vasodilatation, or by direct stimulation of trigeminal ganglia, brainstem, and cortical neuronal pathways. Treatment begins with a headache and diet diary and the selective avoidance of foods presumed to trigger attacks. A universal migraine diet with simultaneous elimination of all potential food triggers is generally not advised in practice. A well-balanced diet is encouraged, with avoidance of fasting or skipped meals. Long-term prophylactic drug therapy is appropriate only after exclusion of headache-precipitating trigger factors, including dietary factors. © 2003 by Elsevier Science Inc. All rights reserved.

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## Introduction

Migraine headaches are severe and incapacitating, necessitating interruption of daily activities and absence from school. The migraine attack is frequently associated with nausea and vomiting, symptoms that prevent the administration of oral analgesics, complicate the maintenance of fluid and electrolyte balance, and hinder recovery. Treatment of acute migraine with drugs is often unsatisfactory, and long-term medications for the prophylaxis of migraine can be counterproductive and associated with potential toxicity. The documentation and avoidance of factors that act as migraine triggers in predisposed patients could provide a more effective approach to the management of migraine.

Unfortunately, the determination of dietary items that provoke headaches in an individual patient can be time consuming and susceptible to bias. The spontaneous remission common in migraine patients is an additional complicating variable. It is not surprising that attention to diet as a possible factor in the cause of migraine headaches is frequently neglected in favor of treatment with various drugs. This review is intended to provide a better understanding of the potential role of diet in the cause of migraine, and to emphasize the importance of excluding dietary and other migraine triggers before initiating long-term drug therapy.

## Prevalence of Migraine in Children

The prevalence of migraine in children has increased in the last 20 to 30 years [1]. In a 1962 Danish study [2], 1.4% of children had developed migraine by 7 years of age, and 5.3% by 15 years of age. In a 1994 study of school children in Aberdeen, Scotland [3] the prevalence of migraine was 11%, more than twice that reported in earlier pediatric studies. In Finland the prevalence of

migraine in 7-year-old children had increased from 1.9% in 1974 to 5.7% in 1992, the greatest increases occurring among children exposed to social instability and stress [4]. This threefold increase in prevalence of migraine in children is compared with the increase from 25% to 40% evident in adults in the United States [5]. The cause of the increase in migraine prevalence is not known, although environmental factors, including dietary changes (e.g., increased coffee ingestion, aspartame in diet drinks, and under-age alcohol consumption), are plausible explanations worthy of further study and inclusion in diagnostic evaluations.

### Pathophysiology of Migraine and Migraine Triggers

The pathophysiology of migraine headaches and the mechanism of migraine triggers have been reviewed by a number of authorities [6-8]. An understanding of the aura and headache components of migraine provides a basis for the potential mechanisms of action of dietary triggers. The primary event is neuronal, with depolarization of cortical neurons and sensitization of trigeminal nerve ganglia. A secondary phase of vasoconstriction, vasodilatation, and sterile vascular inflammation is mediated by chemical neurotransmitters, especially serotonin receptors. The close anatomic relation between the trigeminal innervation of cerebral vessels, dura, and scalp explains the forehead location of referred migraine pain. In support of the cortical migraine mechanism, electroencephalograms in 100 pediatric patients revealed epileptiform discharges in 18% [9].

Dietary migraine triggers may influence the pathophysiology of migraine at one or more phases of the migraine attack. They could affect the cerebral cortex, trigeminal nerve, brainstem trigeminal nuclei, thalamus, and brainstem or limbic pathways. The potential mechanisms of action and chemical mediators of these triggers include release of norepinephrine mediated by tyramine and phenylethylamine, release of nitric oxide by nitrates and nitrites, and effects on histamine and glutamate receptors by histamine and MSG. The chemical trigger may stimulate neuroreceptors, cause release of neurotransmitters, or have a direct effect on neurons within the trigeminovascular migraine pathways.

### Migraine Triggers

In addition to certain foods and beverages, factors known to precipitate headaches in migraineurs include stress, fatigue, exercise, sleep deprivation, bright lights, head trauma, infection, menstruation, and contraceptives. Children, like adults, often associate headache with stress [7], with adolescents, especially females, being particularly susceptible [10]. Stress and other triggers can be closely linked to migraine attacks in susceptible patients and anxiety will influence the severity and threshold to the occurrence and frequency of headaches.

**Table 1. Dietary items and chemical migraine triggers**

Offending Food Item	Chemical Trigger
Cheese	Tyramine
Chocolate	Phenylethylamine, theobromine
Citrus fruits	Phenolic amines, octopamine
Hot dogs, ham, cured meats	Nitrites, nitric oxide
Dairy products, yogurt	Allergenic proteins (casein etc.)*
Fatty and fried foods	Linoleic and oleic fatty acids
Asian, frozen, snack foods	Monosodium glutamate
Coffee, tea, cola	Caffeine, caffeine withdrawal
Food dyes, additives	Tartrazine, sulfites
Artificial sweetener	Aspartame
Wine, beer	Histamine, tyramine, sulfites
Fasting	Stress hormone release, hypoglycemia

\* Ice cream headache is probably a cold-induced vasoconstrictor reflex response.

### Dietary Migraine Triggers and Mechanisms

Evaluation of the role of diet in migraine is complex, because multiple triggers and variables may modify the threshold to pain in an individual [11]. In patient-based studies that include children and adults, the percentage of migraine patients reporting a particular food or drink as a precipitant varies from 7% to as high as 44% [5,12]. In two clinic-based studies the self-reported prevalence of food triggers was 18% and 30% [13,14]. In one clinic the prevalence of diet-related migraine varied with race; migraine prevalence was higher in white patients (61%) than in black patients (35%), and minority children were less likely to report food as a trigger [10].

A wide variety of foods and beverages have been implicated as migraine precipitants, the most common being chocolate, cheese, citrus fruit, and alcoholic drinks [15]. Among 500 food-sensitive migraineurs who received a newsletter and questionnaire, 75% implicated chocolate as a precipitant, 48% cheese, 30% citrus fruit, and 25% alcoholic drinks. In children, cheese, chocolate, and citrus fruit were the principal dietary triggers [16]. A highly significant correlation between responses was observed in at least one study, the same patients reacting to all foods or to none.

Table 1 shows a list of potential food items that have been reported to trigger migraine headaches and the chemical constituent thought to be specifically involved in the mechanism of the attack.

### Tyramine-Triggered Migraine

Tyramine, a biogenic amine, is found in aged cheese and various other foods and beverages, including wine, beer, broad beans, and sauerkraut [17]. Normally, tyramine ingested in the diet is metabolized by monoamine oxidase in the gut and liver and conjugated by enzymes, so that it fails to enter the systemic circulation. Patients with dietary migraine have a presumed deficiency in monoamine oxidase and conjugating enzymes, permitting tyra-

mine to be absorbed from the gut into the circulation. A vasoconstrictor effect may result, primarily by release of norepinephrine from sympathetic nerve endings [18].

The association of tyramine-containing foods and migraine was first reported in patients being treated with monoamine oxidase inhibitors for depression. Headaches developed after cheese consumption [15]. The high tyramine content of the cheese together with the inhibition of monoamine oxidase enzymes may lead to an abnormal concentration of tyramine in the circulation. Hypertensive crisis during monoamine oxidase inhibitor treatment can occur after eating cheese [19], another reason for an acute migraine.

Hanington [20] was the first to demonstrate the relation of tyramine to migraine in controlled studies. Tyramine capsules (125 mg) induced headache in 80% of dietary migraineurs, whereas placebo was followed by headache in only 8%. A recent review [8] of the tyramine trigger factor in migraine cites six controlled studies with positive results, mainly by Hanington et al. and three negative studies [21,22]. The evidence favors an association between high levels of tyramine and the precipitation of acute migraine headache. In tyramine-sensitive patients a trial of a low-tyramine diet might provide an effective method of prophylactic management in pediatric migraine.

### **Chocolate-Induced Migraine**

The ingredients in chocolate implicated in the mechanism of dietary-triggered migraine include phenylethylamine, theobromine, caffeine, and catechin. Phenylethylamine is a biogenic amine metabolized by monoamine oxidase enzymes, theobromine and caffeine are methylxanthines, and catechin a phenolic compound. These chemicals may initiate a headache by alteration of cerebral blood flow and release of norepinephrine from sympathetic nerve cells [8].

In a double-blind controlled study at a migraine clinic, adult migraineurs who believed that chocolate provoked their headaches were challenged with either chocolate (40 gm bar) or a closely matched placebo. Chocolate ingestion was followed by a typical migraine headache in 5 of 12 patients, whereas 0 of 8 patients receiving placebo responded with headache ( $P = 0.05$ ). The median time interval to onset of symptoms was 22 hours (range = 3.5-27 hours) [23].

A study in children that demonstrated a positive association between chocolate and migraine used an elimination "oligoantigenic" diet followed by the reintroduction of one or more food items. Of 99 patients treated, 82 responded to the diet, and 30% had headaches provoked when challenged with chocolate [24,25]. In negative contrast, two controlled trials have failed to confirm chocolate as a migraine trigger [26,27]. The variation in prevalence of responders suggests that a subgroup of migraine patients may be sensitive to chocolate.

### **Caffeine and Caffeine-Withdrawal Headaches**

Caffeine consumed regularly in large amounts and the abrupt withdrawal of caffeine may lead to headaches and the exacerbation of migraine. Headaches begin within 24-48 hours after discontinuing caffeine ingestion and last for 1-6 days [28]. Caffeine contained in commonly consumed stimulant drinks varies from a high of 150 mg in a 5-ounce cup of coffee to approximately 35 mg in a 12-ounce can of cola. Mountain Dew has a higher caffeine content than colas, estimated at approximately 50 mg, and similar to that contained in a cup of tea [29].

Children, especially adolescents, drink large volumes of caffeine-containing carbonated drinks daily, and adolescent girls frequently use diet colas as substitutes for food, being unaware of the risk of caffeine dependency [30]. Headaches usually occur with caffeine withdrawal. Cerebral vasoconstriction during caffeine intake is followed by a rebound vasodilatation and increased arterial blood flow when caffeine is discontinued [31]. Children who regularly consume 200 mg of caffeine daily or more are at risk of withdrawal headaches, especially migraine sufferers. Analgesics, such as Anacin or Excedrin, containing approximately 30-50 mg of caffeine, are taken to control the pain, and lead to caffeine addiction. Hospitalization is sometimes necessary to manage serious caffeine dependency. Aspartame is a further risk factor for headache after consumption of diet sodas.

### **Aspartame-Triggered Migraine**

Despite the U.S. Food and Drug Administration [32] and the Centers for Disease Control and Prevention [33] decision to clear aspartame for general consumption, excepting phenylketonuric children, many scientists have expressed caution concerning its use by patients with migraine, epilepsy, and neuropsychiatric problems. In recent years, several studies have demonstrated that headaches may be exacerbated in patients suffering from migraine. In three double-blind, placebo-controlled studies involving more than 200 adult migraineurs, headaches were significantly more frequent during aspartame consumption over a 14-24 day treatment period [34-37]. In a study that failed to confirm an aspartame-migraine association, the exposure was only 1 day [38].

The evidence is overwhelmingly in favor of aspartame as a significant trigger of headaches in migraineurs, especially when the exposure is prolonged. The effect of aspartame in pediatric migraine needs to be confirmed by controlled studies, although patients and parents should be cautioned regarding the potential adverse effect of this ubiquitous sugar substitute.

### **Nitrites and "Hot-Dog Headache"**

Nitrites, a chemical migraine trigger, are formed from nitrates in the saliva and intestine, accounting for 75% of

the daily intake. Cured meats contain estimates of 3.5-20% of the daily nitrite intake, and 2% comes from vegetables. Most disorders associated with the consumption of nitrates result from the conversion of nitrates to nitrites [29]. The headache associated with nitrite consumption has been termed *hot-dog headache*.

Henderson and Raskin [39] reported an adult who had complained of headaches within 30 minutes after ingesting frankfurters, bacon, salami, or ham. In a blinded controlled challenge with nitrite solution or sodium bicarbonate (placebo), headaches developed after 8 of 13 nitrite doses compared with none of the placebo. This is the only confirmed report of nitrites in food and headache, although numerous instances are recorded of headache after nitrovasodilators, such as nitroglycerine [8,40]. The release of nitric oxide is postulated as the mechanism of the nitrite-induced headache, acting on the vascular endothelium to produce vasodilatation [8]. The prevalence of nitrite-induced "hot-dog headache" is uncertain.

### **Monosodium Glutamate and MSG Symptom Complex**

Monosodium glutamate is added to many foods, particularly Asian dishes, as a flavor enhancer. It is found in frozen foods, canned soups, salad dressings, processed meats, sauces, and snack foods. Manufacturers are required to list MSG when added to food in its free form, although they are not required to list it in its hydrolyzed protein form, which contains 5-20% MSG.

The term *Chinese restaurant syndrome* was coined after a report by Kwok [41], which associated Chinese food with headache and a group of symptoms, including flushing, paresthesias, sweating, palpitations, and facial swelling. MSG is a potent vasoconstrictor, and a vascular basis for the symptoms appears most likely [42]. When the symptoms were later attributed to MSG, the name was changed to *MSG symptom complex*. Symptoms generally appear within 15-60 minutes after ingesting relatively large amounts of MSG on an empty stomach. In a double-blind placebo-controlled randomized study of patients with prior reaction to MSG, 2.5- and 5-gm MSG doses induced headache and other symptoms more frequently than placebo, and doses of 1.25 gm were without effect [43]. When administered in food and to patients with no history of MSG intolerance, MSG failed to induce headaches [44]. It is estimated that the MSG symptom complex occurs in only 1.8% of the patients [45] after ingestion of relatively large amounts of MSG, and usually after ingestion of an Asian, not exclusively Chinese, meal. The term *MSG symptom complex* is more appropriate than *Chinese restaurant syndrome*.

### **Alcoholic Beverages as Migraine Triggers**

Wine and especially red wine has been implicated as a potential migraine trigger in adults. Alcoholic beverages

may seem an unlikely cause of headaches in children, but a recent report entitled "Teen Tippers" found children 12-17 years of age accounted for 25% of alcohol consumed in the United States, and this includes wine in addition to beer and liquor. From ninth grade up, one in five children is abusing alcohol, and females are involved almost as frequently as males [46]. Although the government disputes the 25% figure, finding that 11% is a closer estimate of total alcohol consumption by adolescents, the report emphasizes the need to address this epidemic of underage drinking and binge drinking.

Ingested in large quantities, alcohol will lead to a hangover headache, but wine even in moderate amounts can trigger a migraine headache in susceptible patients. Tyramine, histamine, phenolic flavonoids, and sulfites are generally invoked in the headache mechanism. Red wine has larger levels of histamine and phenolic flavonoids than white wine. These chemicals induce headache by various mechanisms: tyramine by the release of norepinephrine, histamine by releasing nitric oxide from the vascular endothelium, and flavonoids by releasing serotonin from platelets [47]. In children and adolescents presenting with recurrent headaches, alcohol may be added to the list of potential causes.

### **Fatty Foods and Migraine**

Fatty acids, primarily linoleic and oleic acids, may be involved in the mechanism of migraine headaches. During a migraine attack, a significant rise in the blood levels of free fatty acids and blood lipids occurs simultaneously with platelet aggregability, decrease of serotonin, and heightened prostaglandin levels. Free fatty acids may cause the release of serotonin from platelets, with variable effects on cerebral blood vessels, especially vasodilatation. A decrease in dietary fat to a maximum of 20 gm/day is associated with a significant decrease in headache frequency, intensity, and duration [48].

### **"Ice Cream" Headache**

Migraineurs may complain of headache while eating ice cream or other frozen foods. The pain is usually located over the forehead or behind the eyes. The application of a cold stimulus to the mouth or throat may cause a reflex constriction of blood vessels around the head, resulting in the initiation of a headache in susceptible individuals. In one study, 93% of migraine patients reported ice cream headaches compared with 31% of nonmigraine control subjects [49]. In contrast, after palatal application or a swallow of ice cream, only 17% of migraine patients compared with 46% of control volunteers developed headache. In this study the pattern of the headache induced by ice cream was similar in the two groups, although ice cream headache was less common in migraine patients than in control subjects [50]. Ice cream headache is not specific for migraine sufferers.

**Table 2. Dietary migraine triggers and relatively safe alternatives for food-sensitive migraineurs**

Foods to Limit or Avoid	Safe Alternative Foods
Dairy: aged or processed cheese, whole milk, ice cream	American or cottage cheese, low-fat milk
Bread: sourdough, wheat cereal	Rice cereal, potato, pasta
Meats: canned or processed meats, hot dogs, salami, fried foods	Lamb, chicken, some fish
Vegetables: broad beans, limas, tomatoes, peas, olives, extracts	Broccoli, cabbage, cauliflower
Soups: canned soup, soup with MSG	Homemade cream soup, broths
Fruit: citrus, figs, raspberries	Bananas, apples
Desserts: chocolate, licorice	Sherbet, cake, cookies, gelatin
Snacks: TV dinners, pizza, peanuts, peanut butter, soya sauce, chips	Hard candy, jelly, jam, honey
Beverages: red wine, beer, sulfites, aspartame, excess caffeine	Some juices, decaffeinated cola, decaffeinated coffee, sugar

### Food Allergy and Migraine

The term *food allergy* is sometimes used loosely and collectively to describe a group of clinical syndromes with diverse causes related to food intolerance. Food sensitivity is more correctly representative of the broad range of individualistic reactions to food. Pure food allergy is restricted to one category of food sensitivity that is IgE-mediated, as with cow's milk, eggs, peanuts, or wheat. Nonimmunologic food sensitivities are called *food idiosyncrasies* or *food intolerances*, as for example the headaches associated with chemicals in chocolate, dyes, and sulfites [51,52].

The subject of food sensitivity is controversial. It generates much public interest but an equal amount of medical skepticism, as evidenced by the number of scientific publications with titles such as "Food Allergy: Fact or Fiction" [53], and "Food Sensitivity or Self-Deception" [54]. Psychologic bias is demonstrated by studies in which double-blind testing confirms a headache response in only four of 23 patients who considered themselves allergic to foods [55]. Skin tests for food allergy are often unreliable, and elimination diets designed to avoid the offending allergen are troublesome and tedious. Dietary migraine is likely mediated by a variety of mechanisms, including direct chemical effects, and only rarely immunologically mediated [7,29,51]. Table 2 shows dietary migraine trigger foods and beverages to be avoided and relatively safe alternatives for food-sensitive migraineurs.

### Elimination Diets in Migraine Treatment

In one large-scale double-blind trial of an elimination diet involving 88 patients treated with an oligoantigenic diet, a diet that eliminates all but a few sensitizing food antigens, 93% with severe frequent migraine responded and were free of headaches [24,25]. The diet consisted of

lamb or chicken, rice or potato, banana or apple, Brassica, water, and vitamin supplements.

Of the 82 patients who improved on the diet, all but eight patients relapsed on the reintroduction of one or more foods. A remarkable fondness for migraine-provoking foods was a common finding, some patients craving them and eating them in large amounts. Cow's milk and cheese caused headaches in most of the patients in the study, but none of the patients complained of headaches after substituting goat's milk cheese.

Notwithstanding the impressive response demonstrated in this double-blind investigation, in practice the relationship between food allergy or intolerance and migraine is difficult to prove, because the elimination diet is too demanding and skin tests and antibody titers demonstrate inconsistent results. The concept remains controversial, and many neurologists and allergists are skeptical of the use of restrictive diets in treatment.

Before considering the elimination of certain foods, specific headache triggers should first be identified by carefully completed headache diaries. The use of a universal migraine diet with simultaneous elimination of all known dietary triggers is not generally recommended for safety and nutritional reasons. A well-balanced diet is important, and skipping of meals or fasting should be avoided.

### Fasting and Hypoglycemia as Migraine Triggers

Headache is often associated with a missed meal, a finding reported in 20-25% of children evaluated for headache by computerized behavioral assessment [56]. In patient-based and subspecialty clinic-based studies, fasting is reported to precipitate headaches in 56% and 45% of migraineurs, respectively [8,57]. Headaches after fasting are more common in individuals with a history of chronic migraine than those without. The headache usually occurs

approximately 16 hours into the fast, but occasionally it may be delayed until the first meal is taken.

Theoretic mechanisms proposed for fasting-induced headaches include altered levels of serotonin and norepinephrine, release of stress hormones, hypoglycemia, or withdrawal of caffeine beverages [8]. The role of hypoglycemia is questioned because migraine attacks are rarely associated with insulin-induced hypoglycemia in diabetics [58].

## Conclusions

A diet factor and possible migraine triggers should be investigated in the management of children with recurrent headaches. Parents and patients should be urged to maintain a careful diary of headaches and eating habits, so that a possible association between diet and migraine may be excluded. The prevention of debilitating headaches by attention to precipitating factors may be preferable to long-term prophylactic drug treatment with attending adverse reactions.

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### Web Update: Human Developmental Anatomy Center

The Human Developmental Anatomy Center (HDAC; <http://www.natmedmuse.afip.org/collections/hdac/index.htm>), part of the Research Collections division of the National Museum of Health & Medicine, acquires and maintains collections pertaining to general developmental anatomy and neuroanatomy. HDAC maintains and archives the largest collection of human and comparative developmental material in the United States. A noteworthy example is the Arey-Dapena Pediatric Pathology Collection. This collection contains over 7000 lantern slides of pathologies, including over 1300 brain-related images. Both gross and histological material are represented. A database of 2000 of the "best" cases is available at the Center, searchable by organ type or pathology.