

Chocolate and migraine: the history of an ambiguous association

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Summary. Migraine is a highly prevalent condition and an important cause of disability. Although the pathogenesis of this condition is complex and multifaceted, several environmental factors have been associated with development and aggravation of headache attacks. Among the various foods that have been implicated in migraine, chocolate has been regarded as detrimental on the basis of old and mostly anecdotal evidence. Therefore, this article is aimed to provide an overview on the current scientific evidence about the relationship between chocolate and migraine. Taken together, the information gathered from epidemiological and provocative studies attests that the potential causal association between chocolate and migraine remains largely enigmatic. The analysis of epidemiological surveys reveals a highly heterogeneous picture, with frequency of migraine episodes attributable to chocolate ranging from 0 to 22.5%. Even in those studies reporting a more convincing association, the risk of migraine after chocolate ingestion was found to be 2- to 3-fold lower than that reported for exposure to other conventional triggers such as stress, fasting, lack of sleep and alcohol beverages. The results of the double-blind studies are instead unequivocal, and clearly demonstrate that the risk of developing a headache attack after ingestion of chocolate is as likely as administering placebo in patients with migraine. It can hence be concluded that the widespread belief that chocolate and cocoa-containing foods should be absolutely avoided by migraine patients lacks of a reliable scientific basis.

Key words: Migraine; Headache; Chocolate; Cocoa.

Introduction

Migraine is conventionally defined as a head pain localized in the supraorbital region, and can be classified into migraine without aura (i.e., clinical syndrome characterised by headache with specific features and associated symptoms) and migraine with aura (i.e., clinical syndrome characterised by focal neurological symptoms that usually precede and less frequently accompany a headache) (1). Recent statistics attests that migraine is a highly prevalent condition, ranked third among the most frequent diseases worldwide, and is also the leading cause of disability among neurological disorders (2). Due to the high prevalence, coupled with the remarkable clinical and economical consequences

attributable to headache disability, migraine should hence be considered a public healthcare problem.

Although the pathogenesis of migraine is complex and multifaceted, an initial decreased of cerebral blood flow has now been recognized as the leading trigger mechanism, which is then followed by reactive cerebral hyperaemia, plasma protein extravasation, sterile neurogenic inflammation and increased sensitization of pain pathways (3). It is noteworthy, however, that the biological abnormalities supporting both cerebral blood flow changes and central neuronal hypersensitivity that are typically observed in patients with migraine remain mostly enigmatic. The effect of a variety of environmental factors on promotion or aggravation of migraine attacks has been the matter

of inconclusive debates for long. Migraine patients frequently describe that certain foods, alcohol, meteorological or atmospheric variations, along with light exposure may promote or even amplify the severity of a headache attack (4). This evidence has paved the way to a large number of studies aimed to identify causal relationships between such stimuli and migraine.

Among the various foods that have been epidemiologically implicated in triggering migraine attacks, chocolate occupies a prominent position. Chocolate is a processed food originating from the pod or caboss-ide of cacao plants, which mostly grows in the tropical belt. Its origin can be traced back to the Maya, who probably were the first population to actively cultivate the cacao plant (5). The composition of marketed chocolate varies widely, with protein content ranging from 3.2 to 7.5 g per 100 g, lipids content from 33 to 37 g per 100 g, carbohydrate content from 52 to 60 g per 100 g. The commercial chocolate also contains a variety of beneficial substances such as the natural antioxidant flavonoids and several vitamins (especially Vitamin C, D and E) (5), which support the inverse association observed between daily chocolate ingestion and prevalence of cardiovascular disease (6).

Chocolate consumption across all ages and in both genders has now become commonplace, worldwide. As such, the aim of this narrative review is to provide an overview on the current scientific evidence about the potential relationship existing between chocolate and migraine.

The origin of the chocolate-migraine association

The evidence that a remarkable proportion of migraine sufferers usually attribute their headache attacks to consumption of certain types of food, especially cheese, citrus fruits, alcohol and chocolate, has been known for decades, and has also been emphasized in a historical editorial published in the *British Medical Journal*, nearly 50 years ago (7), in which phenylethylamine and tyramine were identified as the putative trigger compounds of pain attacks.

The potential association between tyramine-containing foods and migraine was first postulated in 1967 (8). Hannington performed a double-blind study

on 12 migrainous patients with dietary history of migraine ($n=4$), possible dietary history of migraine ($n=4$) and non-dietary history of migraine ($n=4$). All patients were administered with capsules containing either 100 mg of tyramine or 100 mg of lactose. A total number of 6 headache attacks were recorded, all following ingestion of tyramine and none after administration of placebo. It is also noteworthy that all four patients with dietary history of migraine developed a headache attack after ingestion of tyramine (8). However, these results were contradicted by a following investigation by Moffett et al (9), who conducted a double-blind study in 25 migrainous patients. Overall, 12 headache attacks occurred after ingestion of capsules containing either 125 mg tyramine or 125 mg lactose in 50 patient sessions, but the frequency was equally distributed between tyramine and placebo (6 versus 6 attacks; $p=1.00$).

As regards phenylethylamine, the first association between this substance and migraine was published by Sandler et al in the journal *Nature*, in 1974 (10). In a double-blind study, 46 patients who claimed that migraine was precipitated by chocolate were administered with either lactose or 3 mg phenylethylamine (i.e., the approximate content of a small bar of chocolate). In those subjects who completed the trial, a remarkable increased incidence of headache was recorded after phenylethylamine administration as compared to placebo.

On the basis that chocolate contains tyramine in the range between 0.1 and 2.8 $\mu\text{g/g}$ (11) and phenylethylamine in the range between 3.6 and 8.3 $\mu\text{g/g}$ (12), combined with the anecdotal evidence of an association between chocolate consumption and migraine, a wide series of studies have been performed to explore the existence of a real biological basis underlining this relationship.

Chocolate and migraine

Although the original evidence of an association between migraine attacks and allergy to chocolate was originally published by Blamoutier in 1966 (13), the results of the following epidemiological studies were rather controversial.

Peatfield et al interviewed 490 patients with classical or common migraine, with the aim of identifying potential triggers of headache attacks (14), and reported that migraine could be potentially attributed to chocolate in 19% of them, a percentage that was higher than citrus fruit (11%; $p < 0.001$), similar to that of cheese (18%; $p = 0.74$), but significantly lower than that of alcohol (29%; $p < 0.001$) and oral contraceptives in females (31%; $p < 0.001$).

Van den Bergh et al recruited 217 migraineurs using a newspaper and women's magazine (15), to identify potential triggers of headache attacks by means of open questions. Among the various foods potentially associated with onset of migraine, alcoholic beverages were ranked first (51.6%), followed by chocolate (22.5%), cheese and dairy products (18.5%).

Peatfield also questioned 577 consecutive patients with migrainous headaches about dietary precipitants of their headaches (16), and found that 16.5% of them reported that headache attacks could be precipitated by cheese or chocolate, a percentage that was much lower than that of beer (28.0%; $p < 0.001$) and similar to that of other alcoholic drinks (18.4%; $p = 0.44$).

Ulrich et al conducted a personal interview of 293 migraine subjects by means of a semistructured survey containing questions about dietary as well as other potential triggers (17), and reported that the headache was attributable to chocolate in only 1.7% of cases.

Bánk and Márton used a self-administered headache questionnaire to 62 migraine patients to assess potential correlates of migraine headache (18), and found that chocolate was a rather modest precipitating factor (i.e., 1.4% of cases) compared to stress (90% of cases), sleep deprivation (58% of cases) and alcohol (30% of cases).

Takeshima et al administered a structured questionnaire specific to headache to 234 migraine patients with the aim of surveying food preferences and possible association with headache attacks (19). Interestingly, none of the patients reported chocolate consumption as a potential trigger of migraine.

Wöber et al performed a cross-sectional study for examining potential trigger factors of headache attacks in 66 patients with migraine (20). Interestingly, a marked discrepancy was found by comparing personal experience and theoretical knowledge about the trig-

gering effect of chocolate, wherein 80% of patients reported to be aware of this potential association but less than 20% of them effectively experienced headache attacks after chocolate ingestion ($p < 0.001$).

In a following study, Fukui et al interviewed 200 consecutive migraine patients about possible trigger factors for migraine attacks (21), and reported that only 41 of them (i.e., 20.5%) described chocolate consumption as a potential dietary trigger. This percentage was much lower than that of other potential migraine triggers such as stress (70.0%; $p < 0.001$), fasting (63.5%; $p < 0.001$), lack of sleep (61.5%; $p < 0.001$) and alcohol (34.0%; $p = 0.003$).

Chakravarty et al retrospectively and prospectively studied headache diaries of 200 migraine children aged 7 to 15 years to identify the incidence of various triggers (22). The frequency of chocolate as a trigger was found to be 1.5% in retrospective analysis and 0.13% in the prospective assessment, respectively.

Finally, Yadav et al recorded all episodes of headache attack in 182 patients with migraine over a period of 6 to 260 months (23), and reported that none of these could be likely attributable to chocolate.

As regards provocative trials, the first double-blind study which explored the effect of chocolate in migraine patients was performed by Moffett et al, in 1974 (24). In a first double-blind placebo investigation, 25 subjects with classical migraine were administered with samples consisting of either 44 g chocolate or its matching placebo. The frequency of headache attacks following ingestion of chocolate did not differ between chocolate trigger (9/25) and placebo (6/25; $p = 0.54$). In a second investigation, 15 subjects who had participated to the former study were administered with two additional samples of chocolate varying in weight from 44 to 62 g or placebo. Also in such case the frequency of headache attacks following ingestion of chocolate did not significantly differ between chocolate trigger (6/15) and placebo (4/15; $p = 0.70$).

In a subsequent investigation, Gibb et al performed a double-blind parallel group study in 20 migraineurs patients who were challenged with chocolate or placebo (25), and reported that although the frequency of headache attacks was higher after chocolate ingestion (5/12 compared to 0/8 in placebo), this difference did not reach statistical significance ($p = 0.051$).

Marcus et al also performed a provocative double-blind study on 63 women with chronic headache (50% migraine, 37.5% tension-type, 12.5% combined migraine and tension-type) (26). The subjects initially followed a diet with restriction of vasoactive amine-rich foods, which was then followed by double-blinded provocative trials entailing two samples of 60 g chocolate and two of carob, in random order. Interestingly, chocolate was found to be as likely as carob in triggering headache in any group (17 versus 41%; $p=0.68$ for trend), regardless of personal beliefs about the role of chocolate in provoking headache (18 versus 36%; $p=0.39$).

Conclusions

Myths and legends have been highly pervasive throughout the history of medical science, and modern medicine maintains some notable examples (27). There is widespread perception, especially among migraineurs, that headache attacks may be precipitated by a variety of lifestyle habits and environmental factors, including the ingestion of certain foods and bev-

erages (20). Among these, alcohol and chocolate have been portrayed as detrimental for decades by migraine patients, on the basis of old and mostly anecdotal evidence.

Taken together, the evidence gathered from the epidemiological and provocative studies reviewed in this article attests that the potential causal association between chocolate and migraine remains enigmatic. The analysis of epidemiological surveys aimed at identifying potential triggers of headache attacks reveals a highly heterogeneous picture, with frequency of migraine episodes attributable to chocolate ranging from 0 to 22.5%, at best (Table 1). Even in those studies reporting a more convincing association, the risk of migraine after chocolate ingestion was 2- to 3-fold lower than that reported for exposure to other conventional triggers such as stress, fasting, lack of sleep and alcohol beverages. If any causal relationship does hence exist between migraine attacks and chocolate, this should be regarded as secondary compared to other and more pervasive triggering factors. The results of the three double-blind studies are instead unequivocal, and clearly demonstrate that the risk of developing a headache attack after ingestion of chocolate is as likely

Table 1. Synthesis of epidemiological studies exploring the association between chocolate and migraine.

Author	Study design	Study population	Outcome
Peatfield et al, 1984	Epidemiologic survey	490 patients with migraine	Chocolate trigger identified by 19% of subjects
Van den Bergh et al, 1987	Epidemiologic survey	217 patients with migraine	Chocolate trigger identified by 22.5% of subjects
Peatfield et al, 1995	Epidemiologic survey	577 patients with migraine	Chocolate trigger identified by 16.5% of subjects
Ulrich et al, 1996	Epidemiologic survey	293 patients with migraine	Chocolate trigger identified by 1.7% of subjects
Bánk and Márton, 2000	Epidemiologic survey	62 patients with migraine	Chocolate trigger identified by 1.4% of subjects
Takeshima et al, 2004	Epidemiologic survey	234 patients with migraine	Chocolate trigger identified by none of the subjects
Wöber et al, 2006	Epidemiologic survey	66 patients with migraine	Chocolate trigger identified by <20% of subjects
Fukui et al, 2008	Epidemiologic survey	200 patients with migraine	Chocolate trigger identified by <20.5% of subjects
Chakravarty et al, 2009	Epidemiologic survey	200 children with migraine	Chocolate trigger identified by 0.1-1.5% of subjects
Yadav et al, 2010	Epidemiologic survey	182 patients with migraine	Chocolate trigger identified by none of the subjects
Moffett et al, 1974	Double-blind study	25 patients with migraine	No significant difference of migraine attacks between chocolate and placebo
Gibb et al, 1991	Double-blind parallel study	20 patients with migraine	No significant difference of migraine attacks between chocolate and placebo
Marcus et al, 1997	Double-blind study	63 patients with headache (50% with migraine)	No significant difference of migraine attacks between chocolate and placebo

as administering placebo in patients with migraine (Table 1).

It is also noteworthy that some recent studies have convincingly shown that chocolate may even exert beneficial effects on migraine. Abbey et al showed that a methanol extract of cacao beans was effective to repress the expression of calcitonin gene-related peptide (CGRP) from trigeminal nerves, thus inhibiting inflammation in peripheral tissues and nociception, two leading mechanisms in the pathogenesis of this condition (28). In another study, Cady et al showed that cocoa was effective to inhibit the expression of proinflammatory mediators in spinal trigeminal nucleus, thus preventing sterile inflammation and central pain hypersensitization (29).

From the analysis of the current scientific literature it can hence be concluded that the widespread belief that chocolate and cocoa-containing foods should be absolutely avoided by migraine patients lacks of a reliable scientific basis. Further randomized studies, involving larger populations of migraine patients, are probably necessary to definitely establish whether the popular belief that chocolate ingestion is an important trigger of headache attacks in migraine patients can be definitely negated.

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