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# Low-lipid diet reduces frequency and severity of acute migraine attacks

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**KEYWORDS**
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**Abstract** *Background and aim:* There is uncertainty regarding the prevention of migraine crises by changing the lifestyle of patients. The aim of this randomized, crossover intervention trial was to evaluate the effects of a low lipid intake on the incidence and severity of migraine crises, in comparison to a diet with moderate lipid intake.
*Methods and results:* After a 2-month run-in when patients received preventive medication but were left on their habitual diet, a low-lipid or a normal-lipid diet was randomly prescribed for 3 months and thereafter diets were crossed over for the following 3 months. Headache was diagnosed based on the International Classification of Headache Disorders (IHCD) III criteria. The number and severity of attacks were assessed using a self-reported calendar. Adherence to the diet was assessed by a food frequency questionnaire. An analysis was performed on the 83 episodic or chronic migraineurs (63 female and 20 male), in the age range of 18–57 years, who completed both intervention periods. Obese subjects had a significantly higher number of attacks than those overweight or with normal body weight (24.7 ± 8, 16.3 ± 12, and 15.6 ± 11, respectively, $p < 0.03$) with a significant relationship between the body mass index (BMI) and the number of monthly attacks ($r = 0.238$, $p < 0.03$). The number (2.9 ± 3.7 vs. 6.8 ± 7.5, $p < 0.001$) and severity (1.2 + 0.9 vs. 1.7 ± 0.9, $p < 0.01$) of attacks significantly decreased during both intervention periods, with a significant difference in favour of the low-lipid diet.
*Conclusions:* In this group of patients, the low-lipid diet significantly affected the number and severity of migraine attacks in comparison to a normal-lipid diet.
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## Introduction

Headache is a common disease in the general population that affects adult women more frequently than men [1]. Among different factors that might be involved in the pathophysiology of the disease, eating particular foods such as aged cheese or drinking red wine may trigger acute migraine attacks [2,3].

Moreover, a close relationship has been detected between overweight/obesity and migraine severity [4–7] although other authors have shown that obesity at baseline does not seem to be related to follow-up refractoriness to preventive treatment [8–10].

For this reason, some studies have been designed in order to investigate the effects of dietary intervention on the number and severity of headache attacks. First, in a small trial including only seven patients with no control

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group, a carbohydrate-rich diet, low in protein-tryptophan, was shown to favourably affect headache, and the efficacy of the dietary intervention was related to a reduced intake of migraine-precipitating foods with a concomitant increase in the brain serotonin levels [11]. Thereafter, the lipid components of the diet were investigated: it has been suggested that a lipid-rich diet might be responsible for headache because the plasma serotonin levels are reduced in relation to the increased platelet aggregation [12], whilst a very low-lipid diet (about 20 g daily) might help in preventing headache [13]. More recently, the use of a ketogenic diet has been proven to reduce the frequency of migraine attacks [14,15].

The aim of the present study was to investigate the possibility of affecting the frequency and severity of headache attacks by reducing only moderately the intake of lipids to amounts usually prescribed in a low-lipid diet in the Mediterranean area (never reducing total fat <45 g daily with a marked prevalence of the monounsaturated olive oil), without inducing a drastic reduction in the energy intake coming from carbohydrates.

## Patients and methods

Over a period of 1 year, 128 patients consecutively presenting to the Headache Outpatient clinic of the Department of Clinical Medicine were invited to enter the study group.

The inclusion criteria were as follows:

- Age range of 18–60 years
- One or more monthly attacks of episodic or chronic migraine without aura
- Arterial blood pressure <180/110 mmHg
- No renal, hepatic or inflammatory chronic bowel diseases
- No use of nitrates or dihydropyridines
- No neurological disease

Before participating in the study, the protocol was fully explained to the patients and their informed consent was obtained.

At the first visit, the patients underwent a complete clinical examination including measurement of body weight (BW), height (Ht), blood pressure (systolic blood pressure (SBP)/diastolic blood pressure (DBP)), and heart rate (HR). The body mass index (BMI) was calculated as $BW/Ht^2$ and expressed in kilogram per square metre. Headache was classified in the Headache Outpatient Clinic according to the III beta International Headache Classification criteria (IHCD [16]).

Obesity was defined as BMI ≥30, whilst patients were classified as overweight if their BMI was ≥25 and <30 [17].

After the baseline visit, patients who accepted to enter the study were prescribed the calcium entry blocker *flunarizine* 5 mg daily as preventive medication of headache, and they were left on their habitual diet for a run-in period of 2 months.

At the end of this run-in period, all patients were randomly attributed to one of the following two dietary regimens: a low-lipid diet with a lipid content <20% of the total daily energy intake and a normal-lipid diet with a lipid intake between 25% and 30% of the total daily energy intake. The diets were similar in terms of total energy (1977 vs. 2048 in the low- and normal-lipid diets, respectively), proteins (77 vs. 75 g) and fibres (32 g for both). Carbohydrates were slightly higher in the low-lipid diet (330 g, 63% of the total energy vs. 307 g, 56%). In both diets, the lipid intake was mostly represented by monounsaturated fatty acids (14% in the low-lipid diet and 19% in the normal-lipid diet) with a low intake of saturated fats (<8% of the total calories, which is the percentage usually recommended in our diets). Patients were followed up for 3 months at the end of which they were switched to the alternative dietary regimen.

After baseline control, the patients were followed up at the Headache Outpatient Clinic of our department at 1-month intervals during the observation period. At each visit, they were given a form to be filled in at home, summarizing the number of monthly headache attacks, the severity of each one graded from mild to severe pain (1 indicated mild, 2 moderate and 3 very severe headache) and which drug and how many times they had assumed for the therapy of the attacks during the last month. Headache attacks with severe pain were considered those receiving the score of ≥2.5. Moreover, at each visit, patients filled in a food questionnaire, validated in comparison to the 7-day food record [18], with the help of a well-trained dietician. The data were expressed as daily percentage caloric intake from each macronutrient and as the weekly number of a medium-sized serving. Finally, they were invited to fill in a questionnaire regarding physical activity both at work and during leisure time: according to the response, patients were classified as sedentary, moderately active and active [19].

In addition to the medication for headache prevention, patients could use drugs of their choice for pain relief (the selective serotonin receptor agonists triptans, which are abortive migraine medications, or non-steroidal anti-inflammatory agents).

### *Statistical analysis*

Results were analyzed using the SPSS Statistical Package. Data are expressed as mean ± standard deviation. The differences between means were analyzed by paired and unpaired *t*-tests and one-way analysis of variance. Non-parametric variables were analyzed using the $\chi^2$ test. The strength of correlation between variables was evaluated by the Pearson correlation analysis. The differences were considered significant when $p < 0.05$. The sample size was determined in order to detect a difference of four headache attacks monthly between the two dietary periods, with a first-type error ($\alpha$) of 0.05 and a second-type error ($\beta$) of 0.1. The allocation sequence was generated by one of the authors (LAF), who also assigned participants to the groups. Patients were enrolled by doctors of the

Outpatient Clinic (VDF, BFR, VC, FG and FF), who also assessed the outcomes of the study and were unaware of the dietary treatment. The diets were administered by the dieticians (DP and ES).

## Results

Of the 128 patients participating in the study, 66 were of normal weight and 62 were overweight or obese, according to the criteria defined in the methods. As the first diet, 73 of these patients were randomly attributed to the normal-lipid diet and 55 to the low-lipid diet. Forty-five patients, despite showing a marked reduction of the number and severity of crises at the end of the first intervention period, spontaneously left the Outpatient Clinic and were considered dropouts. Eighty-three patients (63 female and 20 male, age range of 18–57 years) completed both dietary phases, and therefore they were included in the present analysis.

The headaches were diagnosed as infrequent episodic migraine in 3 cases, frequent episodic migraine in 36 cases and chronic migraine in 44 cases. Normal-weight subjects suffered more frequently from episodic than chronic migraine (23 vs. 18 cases); overweight subjects showed a similar prevalence (15 vs. 15 cases), whilst obese subjects mostly suffered from chronic migraine (10 vs. one case).

At baseline, the number (16.4 ± 11.1) and severity (2.7 ± 0.6) of monthly attacks were rather high as well as the number of severe pain attacks (10.9 ± 10.9). We found that obese subjects had a significantly higher number of headache attacks than those with normal BW or overweight (24.7 ± 8, 15.6 ± 10 and 16.3 ± 12 in the obese, normal-weight and overweight group, respectively, $p < 0.03$ for obese vs. both normal-weight and overweight migraineurs). A significant relationship between BMI and the number of monthly headache attacks was observed ($r = 0.292$, $p = 0.03$). The severity of pain was, on the other hand, inversely related to age ($r = -0.235$, $p = 0.03$).

With respect to physical activity, most of the patients ($n = 54$, 65%) were sedentary at baseline and remained in the same position throughout both intervention periods; of the remaining patients, 13 (16%) were moderately active and 16 (19%) were classified as active.

The nutritional intake of these patients, evaluated according to the frequency food questionnaire, during the free diet (run-in) and both intervention periods is shown in Table 1.

During the run-in, when preventive therapy was prescribed to almost 80% of patients, the number of monthly attacks dramatically reduced to 7.4 ± 7.1 as well as their severity (1.7 ± 0.5). The effects of the two diets are shown in Table 2. No significant changes in BW and blood pressure were detected in comparison to the values collected at the end of the run-in. A further decrease in the number of attacks was, on the other hand, observed during the two intervention periods with a significant difference in favour of the low-lipid diet. In fact, the number of attacks fell to 6.8 ± 7.5 during the normal-lipid diet and to 2.9 ± 3.7 during the low-lipid regimen ($p < 0.001$ for both vs. baseline and $p < 0.05$ between the normal- and low-lipid periods). Furthermore, the severity of attacks (1.7 ± 0.9 vs. 1.2 ± 0.9, $p = 0.001$) and the number of severe pain attacks (1.8 ± 1.6 vs. 0.4 ± 1.3, $p = 0.01$) were lower during the low-lipid dietary regimen (Table 2).

The beneficial effect of the low-lipid diet was independent of drugs as the number of patients taking medications for the headache attack and the mean number of pills during each attack were almost similar during the two intervention periods (Table 2, on the bottom). Moreover, during the normal-lipid diet, two patients did not need medication, whilst the number of patients not requiring drugs increased to six during the low-lipid diet.

We also evaluated the sequence effect of the dietary periods: the characteristics of the two groups at entry are described in Table 3. They were similar with respect to age, sex, education, marital status, prevalence of obesity, number of monthly migraine attacks and prevalence of episodic or chronic migraineurs. Only BMI was significantly lower in the group of patients starting with the low-lipid diet. With regard to the response to the treatment, patients who started with the normal-lipid diet showed a marked reduction in the number and severity of attacks with the first diet and a significantly more marked reduction with the second diet. In the other group,

**Table 1** Daily diet composition of 83 patients with headache at baseline and in the two intervention periods, derived from the food frequency questionnaires.

| Daily diet composition | Habitual diet $n = 83$ | Normal-lipid diet $n = 83$ | Low-lipid diet $n = 83$ |
|---|---|---|---|
| Energy intake (kcal/day) | 2531 ± 885 | 2090 ± 660** | 1951 ± 438** |
| Proteins daily g (% of energy intake) | 90 ± 29 (15) | 83 ± 22 (16) | 80 ± 18 (17)* |
| Lipids | 99 ± 32 (35) | 64 ± 19 (27)** | 51 ± 14 (23) **,° |
| Saturated | 37 ± 15 (13) | 17 ± 7 (7)** | 13 ± 4 (6)**,° |
| Monounsaturated | 46 ± 13 (16) | 38 ± 3 (16)** | 29 ± 7 (13)**,°° |
| Polyunsaturated | 16 ± 6 (6) | 9 ± 3 (4)** | 9 ± 2 (4)** |
| Carbohydrates | 332 ± 141 (50) | 311 ± 112 (57)* | 309 ± 89 (60)** |
| Cholesterol (mg) | 259 ± 112 | 178 ± 85** | 152 ± 82** |
| Fibres (g) | 27 ± 10 | 28 ± 10 | 29 ± 8 |

Significances versus baseline: *$p < 0.01$; **$p < 0.001$.
Significances versus normal-lipid diet: °$p < 0.05$; °°$p < 0.001$.

**Table 2** Number and intensity of monthly headache attacks, number of patients using medications and mean consumption of pills for each attack before diet and during the two dietary regimens (normal-vs. low-lipid diet) in 83 patients who completed the crossover study.

| | Run-in | Normal-lipid diet | Low-lipid diet |
|---|---|---|---|
| Body weight (kg) | 68.5 ± 12.7 | 67.4 ± 11.7 | 67.3 ± 11.0 |
| Body mass index ($kg/m^2$) | 25.7 ± 4.4 | 24.8 ± 3.7 | 24.8 ± 3.7 |
| Systolic blood pressure (mmHg) | 121.3 ± 16.6 | 120.8 ± 11.0 | 121.6 ± 12.0 |
| Diastolic blood pressure (mmHg) | 74.7 ± 9.6 | 74.3 ± 8.9 | 76.7 ± 7.6 |
| Heart rate (beats/min) | 72.8 ± 10.1 | 72.0 ± 10.8 | 69.5 ± 7.6 |
| Headache attacks (*n*) | 7.4 ± 7.1 | 6.8 ± 7.5 | 2.9 ± 3.7** |
| Severity | 1.7 ± 0.5 | 1.7 ± 0.9 | 1.2 ± 0.9** |
| Severe pain attacks (*n*) | 2.0 ± 3.4 | 1.8 ± 1.6 | 0.4 ± 1.3* |
| Drugs used | | | |
| Triptans | | | |
| Patients (*n*) | 17 | 27 | 29 |
| Pills (*n*) | 1.4 | 1.4 | 1.3 |
| FANS | | | |
| Patients (*n*) | 56 | 35 | 31 |
| Pills (*n*) | 1.2 | 1.1 | 1.0 |
| Flunarizine | | | |
| Patients (*n*) | 5 | 60 | 48 |

Significances (normal-vs. low-lipid diet): $^*p < 0.01$; $^{**}p < 0.001$.

patients demonstrated a dramatic reduction in the number of crises with the low-lipid diet and a subsequent slight increase with the alternative diet; a reduction in the severity of attacks and in the number of severe pain attacks was observed with both diets being more marked during the low-lipid period. In this subgroup, however, the differences between diets did not reach statistical significance (Table 4).

**Table 3** Baseline characteristics of patients divided into two groups according to the sequence of the diets.

| | Normal lipid before ($n = 47$) | Low lipid before ($n = 36$) |
|---|---|---|
| Age (years) | 37.1 ± 11 | 32.7 ± 12 |
| Sex | | |
| F (*n*, %) | 37 (79) | 26 (72) |
| M (*n*, %) | 10 (21) | 10 (28) |
| Caucasians (*n*, %) | 47 (100) | 36 (100) |
| Marital status | | |
| Not married (*n*, %) | 16 (34) | 15 (42) |
| Married (*n*, %) | 31 (66) | 21 (58) |
| Education level | | |
| Higher education (*n*, %) | 9 (19) | 3 (8) |
| High school diploma (*n*, %) | 31 (66) | 28 (78) |
| Junior high school graduation (*n*, %) | 7 (15) | 5 (14) |
| BMI ($kg/m^2$) | 26.5 ± 4.6 | 24.5 ± 3.9* |
| Lean (*n*, %) | 20 (43) | 22 (61) |
| Overweight (*n*, %) | 19 (40) | 11 (30) |
| Obese (*n*, %) | 8 (17) | 3 (9) |
| Monthly mean headache attacks (*n*) | 17.7 ± 11 | 16.1 ± 11 |
| Episodic migraineurs (*n*, %) | 22 (47) | 18 (50) |
| Chronic migraineurs (*n*, %) | 25 (53) | 18 (50) |

Statistical differences between groups.
$p < 0.05$.

## Discussion

This intervention trial, focused on the relationship between food intake and migraine, suggests that dietary habits strongly affect the frequency and severity of the attacks as an almost 50% reduction in total daily lipid intake (particularly saturated fats) combined with a 20% decrease in food energy intake significantly reduces the frequency and severity of migraine attacks even in comparison to a normal-fat diet with similar energy intake.

The study offers several points to the discussion.

First of all, the daily energy intake of patients with headache calculated according to their food reports was very high for the standard of our population. The Italian National Institute for Food and Nutrition Research reported an energy intake of about 2000 kcal for women and of about 2500 kcal for men [20]. In the Neapolitan area, the suggested intake is even less (about 1500 and 2000 kcal for women and men, respectively). An intake of 2500 kcal/day, therefore, is to be considered definitely high for this geographical area, particularly if we consider that >65% of the patients were female. According to recent investigations, we observed a significant correlation between BMI and the number of attacks in the female gender. During the dietary intervention, patients lost about 1.2 kg and the reduction of BW might have helped, at least in part, in the reduction of the frequency of headache attacks. Some hypotheses were suggested for the association of migraine and obesity: adipocytes, particularly those in the visceral adipose tissue, secrete inflammatory-related proteins, which might be implicated in the pathophysiology of migraine. This disease, on the other hand, might predispose to obesity either through pathophysiologic changes that happen in patients with migraine, as the reduction in serotonin levels found between crises which is responsible for the reduction of satiety and the consequent increase in the intake of high-

**Table 4** Number and intensity of headache attacks, and number of severe pain attacks during the two dietary regimens (normal-vs. low-lipid diet) in 83 patients who completed the crossover study, according to the sequence of the diets.

| | Normal lipid before ($n = 47$) | | Low lipid before ($n = 36$) | |
|---|---|---|---|---|
| | Normal lipid | Low lipid | Low lipid | Normal lipid |
| Headache attacks (*n*) | 7.4 ± 7.1 | 2.8 ± 2.4** | 3.0 ± 5.0 | 5.9 ± 8.0 |
| Severity | 1.8 ± 0.9 | 1.2 ± 0.8** | 1.2 ± 0.9 | 1.6 ± 1.0 |
| Severe pain attacks (*n*) | 1.6 ± 3.4 | 0.3 ± 0.7* | 0.5 ± 1.8 | 2.1 ± 5.6 |

Significances versus the alternative diet, according to the sequence: $^*p < 0.01$; $^{**}p < 0.001$.

energy food, or because migraineurs prefer a sedentary lifestyle for fear of a headache attack. Responses to the questionnaire on physical activity suggesting a very high prevalence of sedentary lifestyle strongly support this hypothesis and are in agreement with previous observations [21].

Second, the dietary composition of our patients at baseline is worth emphasizing: the total lipid intake was >100 g daily representing about 35% of the energy intake, and saturated fats accounted for about 12% of the daily energy, 50% more than the suggested amount. In both diets under investigation, the lipid intake was significantly lower, averaging 65 g in the normal-lipid diet and 50 g in the low-lipid diet, with saturated fats representing no more than 6% of the total daily energy intake. In view of the observation that a reduced lipid amount might help in reducing headache attacks, it is not surprising that both dietary interventions were able to effectively contribute to headache prevention. An alternative hypothesis that can be suggested is that weight loss might be responsible by itself for the reduction in migraine attacks [22]; however, this does not seem the case as patients in this study only lost about 1 kg of BW. Furthermore, the hypothesis that ketogenesis, with its implications on cortical excitability [23], inflammation [24] and reduction of oxidative stress [25], plays a role in the reduction of migraine attacks does not apply to the present findings as the two diets were not low in carbohydrates or in total daily energy intake.

Third, we would like to stress on the moderate restriction in lipid intake in the present study. A previous trial investigating the effects of lipid restriction on the frequency and severity of headache attacks was performed prescribing no more than 20 g of lipids daily for an 8-week intervention period without any control with an alternative diet [13]. This study showed that low lipid intake was associated with a significant reduction in the frequency, intensity and duration of headache attacks as well as in medication intake. Compliance with this type of diet for a long period of time is especially difficult as the amount of lipids is very low; in addition, as shown in another observation not involving patients with headache, it is associated not only with healthy effects such as weight loss in the 5–10% range and reduction of body fat but also with unwanted effects such as decreased vitamin E and $n$−3 fatty acid intake [26]. This effect implies a subsequent need to encourage these patients to consume food particularly rich in these nutrients. Nevertheless, it is desirable to encourage a reduction of the daily lipid intake as, in the group able to complete both dietary periods, we observed a significantly more marked reduction in the number and intensity of the attacks as well as in the number of severe pain attacks during the low-lipid intervention period, despite the suggested diets being similar and the differences in fat intake being even less marked than those suggested with the diets, on the basis of the self-reported food questionnaire of the patients.

A fourth point to be discussed is linked to the sequence of the treatments. The design was prepared in order to avoid any interference of the sequence of the diets on the results of the study, and the randomization of patients was considerably effective as the groups were comparable for all parameters except BMI, which was higher in the group starting with the normal-lipid diet despite the prevalence of obese and overweight patients being similar in the two groups. However, when patients received the normal-lipid diet as the first diet, they experienced a reduction in the number of crises of headache and got further significant benefits in terms of reduction in the number and intensity of attacks during the following alternative diet. On the other hand, when they started with the low-lipid diet, the number and intensity of attacks markedly decreased with a moderate increase in the following period on the normal-fat diet, but the difference did not reach statistical significance. It is conceivable to suppose that patients starting with the low-lipid diet were less prone to accept changing a diet that had already contributed to a sizeable clinical success. This might be the reason why differences in the lipid amount of the two diets were less marked in the self-reported questionnaire than in the prescribed diets.

In conclusion, the results of the present clinical trial indicate that patients with headache frequently follow an unhealthy nutritional approach, particularly rich in the total energy and fat intake, particularly saturated fats. Conversely, the reduction in total energy and saturated fat intake helps in control of the attacks. This observation might expand to the prevention of headache the use of low-saturated-fat diets, as already shown in the prevention and treatment of hypertension [27–29], by using either low-fat dairy products or monounsaturated olive oil as the prevalent, if not the sole, source of fat in the diet.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2014.12.006.

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