



## Research article

## Evaluation of body composition in patients with migraine on prophylactic treatment with topiramate

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## ABSTRACT

Migraine is a primary headache with high prevalence in the general population but is considered a disabling medical condition. It is suggested that obesity is a risk factor for chronic migraine. Thus treatment with drugs, such as topiramate, which reduces pain and weight, is ideal for obese patients with migraine. The aim of this study was to evaluate the effects of topiramate on body composition in patients with chronic migraine and to verify whether these effects could be related to nutritional status. We studied 26 female patients with age ranging from 18 to 45 years with prophylactic treatment with topiramate (50 mg/day) for three months. Body composition indexes (body mass index, BMI; body fat, BF; fat-free mass, FFM) were obtained through anthropometric assessment. After treatment, topiramate reduced BMI (0,82 kg/m<sup>2</sup>) and in BF (3.3 %), but increased FFM (1.1 kg). When considering nutritional status, FFM was increased only in obese patients. In conclusion, our main finding is that besides the reduction in BMI and BF, topiramate led to an increase in FFM in overweight and obese patients. Our results open new perspectives for future studies on the relationship between body composition and migraine, indicating that more studies on this body compartment are needed, especially in patients with chronic migraine.

## 1. Introduction

Migraine is a type of headache that is very common in the general population but can be disabling when not adequately treated. It is defined by episodic attacks of moderate to severe and unilateral pulsatile headache associated with other symptoms such as photophobia, phonophobia, nausea, and vomiting [1]. Migraine is classified as with or without aura, which is characterized by symptoms that precede headache attacks. The following symptoms are examples of auras: visual, sensory, motor, brainstem, retinal, or changes in speech or language. Quality of life is worse when the frequency of headache exceeds 15 days per month in a period of more than three months, a condition called chronic migraine. Some studies suggest that obesity may be a risk factor for chronic migraine in adults, so patients with obesity and migraine require additional care [2, 3, 4]. Patients with increased body fat and high body mass index (BMI) were related to more frequent, more intense and

disabling migraine attacks [3,4]. This association could be due to a possible influence of body inflammation, migraine progression, or a higher prevalence of the disease in obese individuals [5].

Treatment of migraine in overweight or obese patients is complicated because medications used to prevent headache attacks can lead to weight gain [2,6]. Thus, the indication of drugs for migraine treatment, which could induce weight loss, would increase patient adherence to prophylactic treatment [2]. Topiramate is the only approved drug for prophylactic treatment of migraine, that resulted in a reduction in weight, which made it the ideal drug for patients with migraine and obesity [7, 8, 9]. However, only a few studies focused on body composition changes in migraine patients treated with topiramate and showed a reduction in body fat (BF) [10,11].

The aim of this study was to evaluate the effects of topiramate on body composition in patients with chronic migraine and to verify whether these effects could be related to nutritional status. Our results

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showed that besides a reduction in body fat (BF), topiramate also led to an increase in fat-free mass (FFM) in obese patients, suggesting that other body compartments can be affected by the drug.

## 2. Patients and study design

This study was carried out at the Headache Research and Treatment Division at Escola Paulista de Medicina, Universidade Federal de São Paulo. Female patients aged between 18 and 45 years and who met the diagnostic criteria for chronic migraine were included. The detailed inclusion and exclusion criteria are shown in Table 1.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics and Research Committee of Escola Paulista de Medicina (registration number 67425517.8.0000.5505). All subjects signed a written informed consent form for inclusion before they participate in the study.

Patients participating in the study underwent an initial evaluation (visit 1) with a neurologist, when the clinical diagnosis of migraine was established, together with the prescription and delivery of prophylactic medication, topiramate 50mg/day (25mg BID), and delivery of the headache diary to control the frequency of crises. The patients were recommended to maintain food intake routine. Then, the patients underwent an evaluation with the nutritionist (visit 1), when an anthropometric evaluation was performed to define body composition at the beginning of the study. Follow-up was carried out every 30 days with three more visits (visits 2, 3, and 4). On visit 4, after 90 days, the patients again visited the nutritionist for a new anthropometric assessment to define the final body composition.

### 2.1. Anthropometric assessment

The measures taken in this study were: weight, height and skin folds (right biceps, right triceps, right subscapularis, right middle axillary, right supra iliac, right abdominal, right thigh and right calf). Based on these measures, we calculated the following indexes: BMI, percentage of body fat (% BF) and fat-free mass (FFM; weight subtracted from BF).

Weight and height were measured on a mechanical scale and stadiometer. Skin folds were measured with an adipometer, as follows: always measured on the right hemibody, with the equipment in a comfortable position and with relaxed muscles. Measurements were taken three times at each anatomical point, separating the subcutaneous body fat. We used the measurements mean for the analysis.

The following formula was used to calculate BMI:

$$\text{BMI} = \text{weight} / (\text{height})^2$$

To calculate the % BF, we used the formula of Pollock et al. (1980) with measurement of 7 skinfolds (subscapular, middle axillary, triceps, thigh; supra iliac; abdomen and chest) for women aged 18–65 years [12]. Then body density (BD) was calculated:

$$\text{BD for women} = 1.0970 - [0.00046971 (\text{sum of 7 folds}) + 0.00000056 (\text{sum of 7 folds})^2] - [0.00012828 (\text{age})]$$

BD was applied to the Siri Formula (1961) to calculate the % BF:

$$\% \text{ BF} = [(4.95 / \text{BD}) - 4.50] \times 100$$

Considering the initial BMI, nutritional status was classified as eutrophic (BMI of 18.50–24.99 kg/m<sup>2</sup>), overweight (BMI of 25–29.99 kg/m<sup>2</sup>) and obesity (BMI above 30kg/m<sup>2</sup>).

### 2.2. Statistical analysis

Results were expressed as means and standard deviation. Statistical analysis and graphing were performed with Prism version 6.00 for MacOS X (GraphPad Software Inc.). Comparisons were made using the t-

test for paired samples. Statistical significance was established for values of  $P < 0.05$ .

Statistical significance was indicated with the symbol \* in the graphs and according to the criteria below: \* $P \leq 0.05$ /\*\* $P \leq 0.01$ /\*\*P  $\leq 0.001$ /\*\*\*\* $P \leq 0.0001$ .

## 3. Results

Thirty nine patients were included, but 13 had dropped out after the first consultation. The reasons for the dropping out were: family decision (N = 1), moved to another city (N = 1), started investigation of a breast nodule (N = 1) and side effects (N = 10). The reported side effects were: decreased appetite/nausea (N = 4), somnolence (N = 2), slowed thinking/memory problems (N = 5), tingling (N = 6), depression/anxiety (N = 1). Twenty six patients concluded the study and reported no side effects or decreased appetite. The group had a mean age of  $31 \pm 7$  years, 88.5 % of patients had migraine with aura and 11.5% had migraine without aura (Table 2). According to initial BMI, 46,2% of patients were classified as eutrophic, 30.8 % as overweight, and 23 % as obese (Table 2).

After three months of treatment, topiramate led to a significant reduction in the frequency of headache attacks ( $26 \pm 6.0$  vs.  $9 \pm 8.5$ ; Figure 1), demonstrating that the treatment was effective for the control of headache. Thus, we evaluated the evolution of the indicators obtained through anthropometric measurements (BMI, BF, and FFM) at the end of 3 months of treatment. We observed that topiramate modified the three indicators, with a reduction of  $0.82 \text{ kg/m}^2$  ( $P = 0.0008$ ) in BMI, a reduction of 3.3% ( $P < 0.0001$ ) in BF and an increase of 1.1 kg ( $P = 0.0173$ ) in FFM (Figure 2).

We also discriminated the patients according the nutritional status at the beginning of the study. BMI decreased in eutrophic (final-initial difference =  $-0.6 \pm 0.9 \text{ kg/m}^2$ ;  $P = 0.0235$ ) and obese (final-initial difference =  $-1.6 \pm 1.3 \text{ kg/m}^2$ ;  $P = 0.029$ ) patients (Figure 3a, b, c). BF also decreased but in all three groups: eutrophic (final-initial difference =  $-2.0 \pm 1.6\%$ ,  $P = 0.001$ ), overweight (final-initial difference =  $-2.2 \pm 1.4\%$ ,  $P = 0.0031$ ) and obese (final-initial difference =  $-7.2 \pm 3.7\%$ ,  $P = 0.005$ ; Figure 3d, e, f). On the other hand, there was an increase in FFM in obese patients ( $4.0 \pm 2.4 \text{ kg}$ ;  $P = 0.010$ ; Figure 3i), but no change in the group with eutrophy (difference =  $-0.11 \pm 1.2 \text{ kg}$ ; Figure 3g), or overweight (difference =  $0.79 \pm 1.2 \text{ kg}$ ; Figure 3h).

## 4. Discussion

Obesity is considered a global public health problem and a chronic, multifactorial disease characterized by excess body fat. The association of migraine with obesity makes the treatment of headaches more difficult,

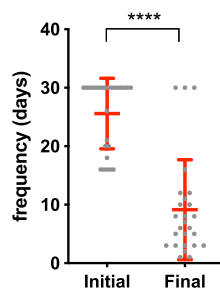
**Table 1.** Inclusion and exclusion criteria.

Inclusion criteria
Age 18 to 45 years
Women
Diagnosis of chronic migraine according to the criteria of The International Classification of Headache Disorders (ICHD-3 edition: beta)
Without previous prophylactic treatment in the last six months
Non-physical exercise practitioners
Exclusion criteria
BMI over 35.00kg/m <sup>2</sup> (obesity grade II)
Use of prophylactic medications for migraine
Presence of other types of primary headache
Presence of other neurological and/or systemic diseases
Use of continuous medications for neurological and/or systemic diseases
Pregnant women, in climacteric period or post menopause
Individuals using alcohol and/or recreational drugs
Diagnosis of headache from excessive use of painkillers

**Table 2.** Main features of patients with chronic migraine.

Features	Total	Without aura	With aura
N	26	3	23
Age (years)	31 ± 7 (18–44)	26.7 ± 2.9 (22–31)	31.5 ± 7 (18–44)
Nutritional status			
Eutrophic (N)	12	2	10
Overweight (N)	8	0	8
Obese (N)	6	1	5
Frequency (days/month)	26 ± 6 (16–30)	20.7 ± 8.1 (16–30)	26.2 ± 5.6 (16–30)
Body composition			
BMI (kg/m <sup>2</sup> )	26.6 ± 4.3 (20.6–37.2)	27.5 ± 6.7 (22.8–35.2)	26.5 ± 4.1 (20.6–37.2)
BF (%)	37.3 ± 11.3 (21.0–62.5)	36.7 ± 18.7 (24.3–58.2)	37.4 ± 10.9 (21.0–62.5)
FFM (kg)	43.2 ± 5.9 (31.7–56.7)	43.5 ± 3.8 (40.0–47.6)	43.2 ± 6.3 (31.7–56.7)
Weight (kg)	71 ± 14.4 (51.8–99)	72.8 ± 20.3 (56.9–95.7)	70.7 ± 14.0 (51.8–99)

Age, frequency and body composition are expressed as mean ± standard deviation and range is between parentheses; N: number of patients.



**Figure 1.** Frequency of migraine attacks after treatment with topiramate. The graph shows a statistically significant reduction in the number of days in pain after three months of treatment. Individual values (gray dots), mean, and standard deviation (red lines) are shown. Two-tailed Student's t-test with paired samples. \*\*\*\* $P < 0.0001$ .

as the chance of chronicity is much greater in these patients [3,4]. Thus, the use of a medication with a beneficial effect in both conditions is ideal.

Similar to previous studies, our results demonstrated that topiramate reduced BMI and BF in patients with migraine with only three months of treatment [11,13]. Adelman et al. showed that the weight loss was related to topiramate dose, with a reduction of 2.3 kg (50 mg/day), 3.2 kg (100mg/day), and 3.8 kg (200 mg/day) [13]. Yaman et al. studied 40 patients with migraine treated with 100 mg/day of topiramate for three months [11] and found a 1.6% reduction in BF, which is similar to the 2.8% reduction shown in our study. These results could be explained by decreased appetite, which was reported as a topiramate side effect [6]. Our patients did not complain of reducing appetite, however food intake data were not collected.

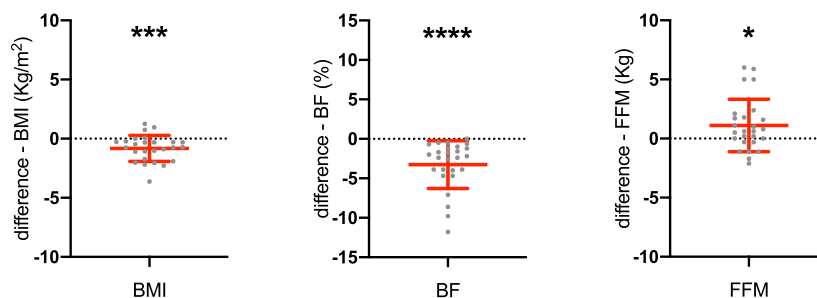
Only a few studies reported results on FFM after topiramate treatment in patients with migraine. Yaman et al. found no change in FFM after

three months of treatment. However, there are differences between this study and ours. Yaman et al. used a higher dose, included men and women, with a broader age range (from 18 and 72 years), and they did not discriminate among the types of migraine [11]. In another study, Di Sabato et al. also found no change in FFM after 3 and 6 months of treatment in a group of 30 patients with migraine without aura [10]. In this study, topiramate's dosage gradually increased from 25 mg/day to 100mg in 4 weeks. In our study, we had a very small number of patients with migraine without aura, which did not allow any conclusion about this group. However, it is still unknown whether migraine with and without aura are different entities [14].

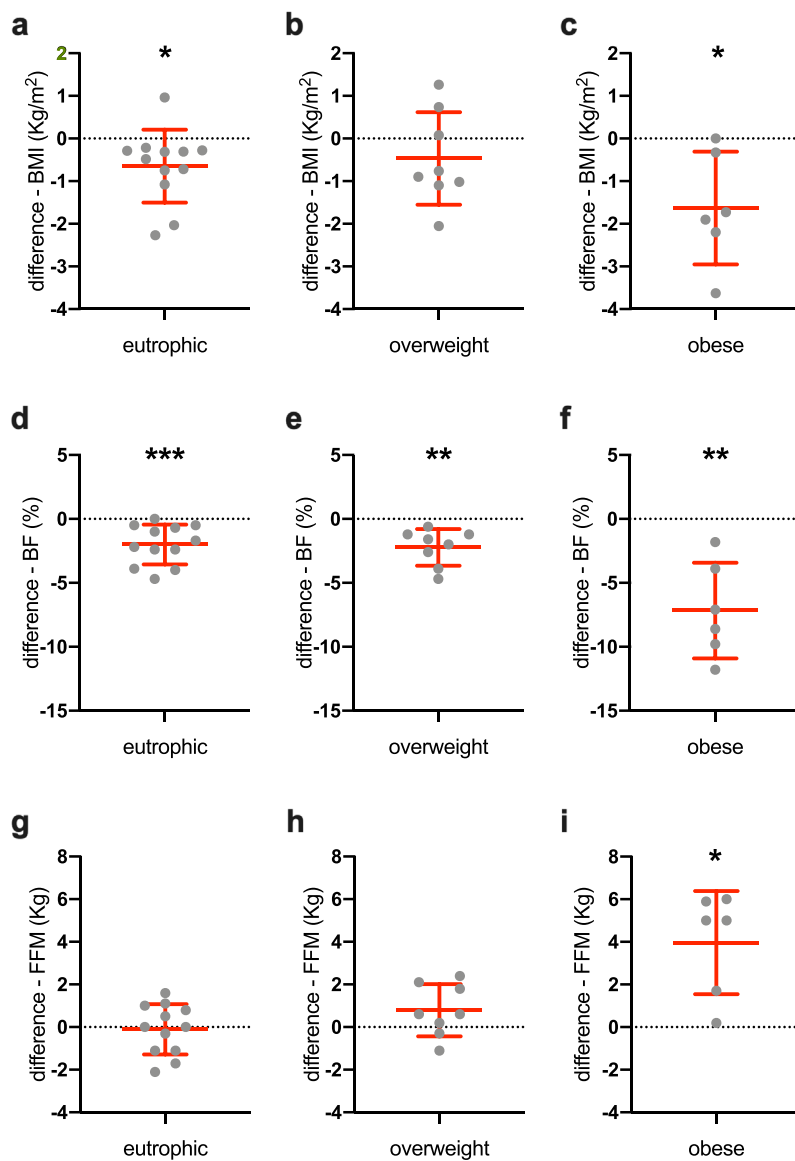
Comparing our results with other studies is quite challenging due to differences, as pointed above, but especially regarding the method in assessing FFM. Yaman et al. assessed FFM by bioelectric bioimpedance, and Di Sabato et al. used absorptiometry. We used skinfold measurements to determine BF and then estimate FFM. This method is simple, easy, quick, and highly informative [15]. But all methods have limitations and inaccuracies [15].

The mechanisms involved in FFM increase remain unexplained. We could think of two possibilities: an increase in body water or an increase in muscle mass. Experimental studies with rats showed that besides reducing BF [16], topiramate increased the percentage of water and protein, which is compatible with our results. Yaman et al. showed an increase in body water content after three months with topiramate treatment [11].

Regarding a possible increase in muscle mass, our patients did not practice regular physical activity, so this change may be related to the obesity pathophysiological process since only obese patients had increased FFM. In obesity, there is chronic low-grade systemic inflammation, which also affects the skeletal muscle [17]. It was proposed that several factors contribute to the decline in muscle mass and function in obesity and aged individuals [17]. Excessive fatty acids accumulate in



**Figure 2.** Evolution of body composition after treatment with topiramate. We demonstrate the differences (final-initial values) of the following indicators: BMI (left), BF (middle) and FFM (right). The analysis showed a significant reduction in BMI and BF, but with an increase in FFM. Individual values (gray dots), mean, and standard deviation (red lines) are shown. Two-tailed Student's t-test with paired samples. \*\*\*\* $P < 0.0001$ ; \*\*\* $P \leq 0.001$ ; \* $P \leq 0.05$ .



**Figure 3.** Evolution of body composition considering nutritional status. Evolution of body composition was evaluated considering the initial classification of nutritional status (eutrophic, N = 12; overweight, N = 8; obese, N = 6). We demonstrate the differences in the final-initial values of the following indicators: BMI (a, b, c), BF (d, e, f), and FFM (g, h, i). The analysis with all patients showed a significant reduction in BMI in eutrophic (a) and obese (c) patients. BF was reduced in all three nutritional groups (d, e, f) while FFM was increased only in obese patients (i). Individual values (gray dots), mean, and standard deviation (red lines) are shown. Two-tailed Student's t-test with paired samples. \*\*\* $P \leq 0.001$ ; \*\* $P \leq 0.01$ ; \* $P \leq 0.05$ .

muscle fibers, leading to impaired muscle mitochondria and further enhanced reactive oxygen species production (oxidative stress). Lipotoxic effects on the insulin signaling pathway result in an insulin resistance state. In an obese state, adipose tissue produces proinflammatory cytokines, exacerbating the decline in skeletal muscle mass and function. Additionally, the proinflammatory state reduces adiponectin, one of the factors involved in maintaining skeletal muscle status. Interestingly, a process of neuroinflammation may also be associated with migraine chronification [18] and patients with migraine treated with topiramate had increased adiponectin concentrations and reduced inflammatory cytokines, such as  $\text{TNF-}\alpha$ , IL-1, IL-6, and  $\text{IFN-}\gamma$  [19]. Thus, we hypothesize that the increased FFM observed in our study may be due to a reduction in the inflammatory process affecting the skeletal muscle that had already been affected by the adipose tissue inflammation. However, we must emphasize that this is a theoretical hypothesis.

Further studies are still necessary to investigate FFM changes in topiramate treatment in patients with migraine, especially considering the different types of migraine and muscle mass. It is unknown whether

increased FFM is a response to pathophysiological changes in obesity only or with migraine.

Our results open new perspectives for future studies on the relationship between body composition and migraine. Our results suggest that topiramate can also affect FFM indicating that more studies on this body compartment are needed, especially in patients with chronic migraine. More sensible and precise methods to determine how topiramate affects muscle mass and body water may reveal other beneficial effects for overweight or obese patients with migraine.

## Declarations

### Author contribution statement

Camila Naegeli Caverni: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Thais Rodrigues Villa: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Aline Turbino da Costa, Caio Grava Simioni and Rosemeire Rocha Fukue: Performed the experiments.

Celia Harumi Tengan: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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#### *Data availability statement*

Data will be made available on request.

#### *Declaration of interests statement*

The authors declare no conflict of interest.

#### *Additional information*

No additional information is available for this paper.

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