▪ Headache Medicine 2023, 14(4):214-220 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2023.38

Original

Association of altered serum vitamin D, glucose and lipid profiles with headaches in young women: clinical, cross-sectional study

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Edited by:
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Abstract

Introduction
Headaches, including migraines and tension headaches, affect millions of people globally. Migraines are the most common neurological disorder, with around 14.4% of the world's population affected. It is suggested that dysregulation of biochemical markers and individual metabolic differences may contribute to headaches.

Objective
We evaluated the frequency of headaches or migraines with changes in lipid, glucose and vitamin D serum levels in young women.

Methods
Clinical, cross-sectional study with 139 young women, aged at least 18 years, based on the third edition of the International Classification of Headache Disorders (ICHD-3). The individuals were divided into two groups: one without headache and another with headache. Anthropometric analyzes (BMI, WC, BP and DBP) and blood samples were collected for analysis of vitamin D, glycemia and lipid profile.

Results
Mean age was 22 (±4.6) years. We observed associations between headache and the following factors: high glucose levels (97 mg/dL, p=0.028), total cholesterol (180.4 mg/dL, p=0.002), HDL (44.2 mg/dL, p=0.017), and LDL (121.6 mg/dL, p=0.005). Longer duration of headache attacks was associated with increased levels of glucose (97.9 mg/dL, p=0.028), total cholesterol (186.8 mg/dL, p=0.05), diastolic blood pressure (74 mmHg, p=0.038), and BMI (24.6 kg/m2, p=0.024). High glucose levels were found to be directly related to the presence of migraine, particularly those with aura (105 mg/dL, p=0.034). However, there was no significant difference in vitamin D levels (p=0.640).

Conclusion
Elevated levels of blood glucose and total plasma cholesterol and its fractions seems to be associated can increase with bouts of headache attacks, especially migraine, prolonging the duration of pain.

Keywords:
Headache
Migraine
Blood Glucose
Cholesterol
Vitamin D

Submitted: November 23, 2023
Accepted: December 22, 2023
Published online: December 21, 2023

Introduction

Headaches, especially migraines or tension headaches, are a common health problem that affects millions of individuals worldwide. According to the Migraine Research Foundation, approximately 12% of the global population suffers from migraines, with over 90% of these individuals experiencing reduced productivity in their daily lives.[1] Among the different types of headaches, migraine is the most prevalent neurological disorder, affecting approximately 14.4% of the global population.[2–4] In recent years, studies have suggested a possible association between the incidence of headaches and vitamin D levels, blood glucose, total cholesterol, and anthropometric measurements, especially in adult women[5–8], due to hormonal fluctuations.[9–11] The pathophysiology of migraines is complex and includes various factors such as genetics, environmental triggers, and lifestyle factors.[12–14]

Vitamin D is essential for maintaining bone health[15], regulating the immune system[7], and maintaining a healthy.[16] Low levels of vitamin D have been shown to increase the risk of various health conditions, including metabolic disorders, autoimmune diseases, and cardiovascular diseases[17,18]. Research has suggested a possible association between migraine and low levels of vitamin D[19], hypercholesterolemia, high blood glucose[5], hypertension[20], insulin resistance, diabetes[21], anthropometric measurements, including body mass index (BMI) and waist circumference.[22,23] However, the association between migraines is not well established, and further research is required to determine the exact mechanism underlying this relationship.

Individual differences in the metabolic profile may modulate the severity and development of headache.[24] However, published studies on the influence of vitamin D, blood glucose, cholesterol levels on headache have been inconsistent. In a large French prospective population-based study in women with associated migraine and type 2 diabetes, observed a lower risk of developing type 2 diabetes for women with active migraine suggest a potential role of hyperglycemia[24]. Recent research suggested that dysregulation of biochemical markers may predispose an individual to headaches[25,26]. Low levels of HDL cholesterol, were associated with a higher prevalence of migraines among young adults.[27] The increased total body obesity and abdominal obesity was associated with a higher prevalence of migraines in adults (women and men) limited to individuals <50 years of age 25. Nonetheless, a study indicated that insulin resistance and metabolic syndrome were not associated with migraine in women and was an inverse relationship between central obesity and migraine.[21]

Most studies involving the migraine have been performed in predominantly populations if aged mean of 40-60 years. Little is known about the involving young women, especially Brazilian young women. We hypothesized that young women with low levels of vitamin D, dysregulation of the biochemical profile (such as high blood glucose and cholesterol levels) and anthropometric measurements indicative of obesity or central obesity have a higher frequency of headache or migraine compared to those with adequate levels of vitamin D and healthy metabolic profile. This association is not yet well established and therefore further research is needed to understand the exact mechanism underlying this relationship, especially in young Brazilian women. Based on the above-described findings, we evaluated to assess the frequency of headache or migraine and its association with vitamin D levels, biochemical profile, and anthropometry in young women.

Methods

Study Design

This is the primary analysis of these clinical, cross-sectional study that evaluated the frequency of headaches or migraines and its association with vitamin D, glucose, cholesterol total, HDL, LDL and triglycerides serum levels in young women Brazilian. Across clinic-based sample, the population group consisted of young women Brazilian seen at the biochemistry laboratory of the Faculty of Medicine of Oeste Paulista University – UNOESTE from March 2021 to May 2022 from city in the interior of São Paulo-Brazil, located in the central region of the state of São Paulo, at latitude 22°17'44" south and longitude 48°33'28" west, at an altitude of 541 meters.

A priori sample calculation was performed before the study using G*Power software (version 3.1.9.2) to determine the required sample size, based on evidence of the effect of vitamin D on headache disorders.25 The probability of type I error (α) was 5% and the power ($1-\beta$) was 80%. A minimum of 100 participants were required for statistical significance. Young women aged at least 18 and less than 40 years and who agreed to participate in the initial interview were included. The non-inclusion criteria were women who reported secondary headaches, (MRI showing structural brain damage), history of metabolic disease that affects vitamin D status, such as infectious disorders, liver or kidney disease, gastrointestinal disease, cancer, sarcoidosis, or tuberculosis, consumption of vitamin D supplements in the previous 3 months (any dose) and pregnant women.

The flow chart shows the recruitment of participants (Figure 1).

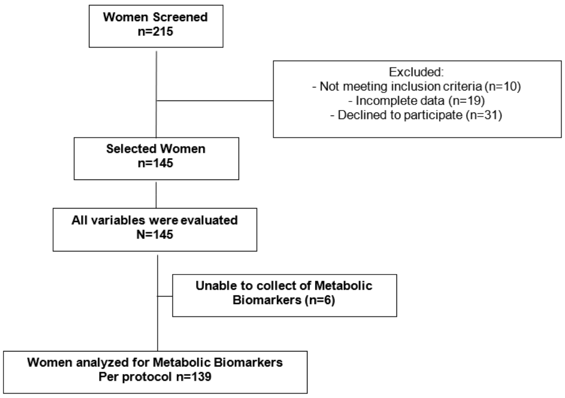

Figure 1. Flow diagram.

Participants in the study were informed of the research purposes, procedures, and data confidentiality, with no harm in coming to them. The participants signed an Informed Consent Form under the requirement of resolution number 466/2012 of the National Health Council. The study was approved by the Research Ethics Committee – CEP in February 2021, from the Oeste Paulista University – UNOESTE (Nº: 4511769) and was conducted under the Declaration of Helsinki and Principles of Good Clinical Practice.

Sample selection

The following data were collected during the interview: age, smoking status, contraceptive use, headaches, migraine, and aura status. The participants' migraine and aura status were diagnosed by neurologists (JBLF and VCRP) based on the third edition of the International Classification of Headache Disorders (ICHD-3).[28] The international physical activity questionnaire - IPAQ, short version, was also applied to verify physical fitness (supplement). The individuals were divided into two groups: one without headache and another with headache.

Following the initial interview eligible volunteers were submitted to anthropometric assessment: weight, height, body mass index (BMI= weight/height^2) and waist circumference. Weight measurement was performed using a microdigital electronic anthropometric platform-type scale (Filizola®, Brazil), with a capacity of 150 kg, with precision of 0.1 kg and 0.5 cm (weight and height), in which the individual was barefoot and wearing minimum clothing. Blood pressure was measured with the patient in the sitting position and the forearm in rest at the level of the precordium, the palm of the hand facing upwards, and a standard aneroid sphygmomanometer was used. For height measurement, the volunteer held her arms along her body in the upright position and keeping her eyes fixed on a horizontal plane parallel to the floor, measured by a vertical 0.5-cm grading ruler which was coupled to the scale. The 2002 World Health Organization criteria were used to classify individuals, according to the BMI: less than 18.5 kg/m^2 as low weight, from 18.5 to 24.9 kg/m^2 normal, from 25 to 29.9 kg/m^2 overweight, from 30 to 34.9 kg/m^2 grade-I obesity, from 35 to 39.9 kg/m^2 grade-II obesity and greater than or equal to 40 kg/m^2 grade-III obesity. For waist measurement, the smallest circumference between the last rib and the antero-superior iliac crest was considered, and reading was performed during of exhalation. Waist measurement over 88 cm was considered increased.[29]

Biochemical evaluations

Blood (20 ml) was directly collected into a dry tube with a serum separator gel after 12 hours of fasting, which were centrifuged for 15 min (3,000 rpm). The serum obtained was separated into 500 μL aliquots and frozen at -20°C.

Lipid and glucose profiles were evaluated by measuring the total cholesterol (TC), HDL, LDL, triglycerides (TG), fasting glucose, in addition to vitamin D. All biochemical evaluations were performed by the Biochemistry Laboratory at the Faculty of Medicine – UNOESTE. The measurements were performed by the colorimetric method, in triplicate samples of 100 μL, using the corresponding specific kits (Labtest, Brazil). LDL was obtained by subtracting the TC value from the sum of HDL and TG divided by five. When TG values exceed 400mg/dL LDL was calculated using a formula that has limited use. Optimal/normal values were TC <200 mg/dL, HDL >40mg/dL, LDL <100 mg/dL, TG <150 mg/dL and blood glucose >100mg/dL[29]. Serologic 25-hydroxyvitamin D [25(OH)D] was considered the most reliable indicator for assessing vitamin D status, therefore it was measured using a chemiluminescence assay as described by the manufacturer.[30] Serum vitamin D levels were classified as sufficient (≥30 ng/mL), insufficient (20–29 ng/mL), or deficient (<20 ng/mL).

Statistics

Frequency counts, mean, standard deviation and percentages for each variable were calculated. Comparisons made between women with migraine and controls were performed in RxC tables and in ANOVA tables. Comparisons were performed using the chi-square test, for qualitative variables, and by Student's t test or Kruskal Wallis test to compare continuous variables. The degree of statistical significance adopted in the analysis was 5%. Analyzes were performed using the IBM SPSS Statistics program, version 9.2.

Results

Mean age of the 139 women was 22 (±4.6) years. 81.3% reported having headaches, the most frequent type of pain was throbbing/pulsating (65.6%), while 34.4% reported other types of pain. Regarding pain intensity, 45.3% reported mild headaches, 46.1% moderate headaches and 8.6% intense headaches. Monthly migraine attack was described to be present among 65.6% of participants and 34.4% had migraine attack more than once a month. During migraine crises, photophobia (45.2%), vomiting (13.4%) and nausea (32.8%) were reported. From 37.7% of women who had migraines, these being, 14.6% had aura. 24.5% of the women had family history of headaches and 20.9% performed physical activities regularly (Table 1).

Table 1 - General characteristics of young women with or without headache

Variables	Occurrence	Percentage (%)
Headaches (y/n)	113	81.3
Pain character (throbbing) (y/n)	91	65.6
Intensity		
Mild (y/n)	58	45.3
Moderate (y/n)	59	46.1
Intense (y/n)	12	8.6
Duration (4 to 72 hours)	81	64.8
Frequency of crises (more than once a month) (y/n)	82	65.1
Photophobia (y/n)	61	45.2
Nausea (y/n)	45	32.8
Vomiting (y/n)	18	13.4
Family history of headaches (y/n)	34	24.5
Migranes	49	37.7
With aura	19	14.6
Without aura	30	23.1
Regular physical activity (y/n)	29	20.9

y/n: yes/no

We observed association between the presence of headache and glucose profiles: 97±24.5 mg/dL (p=0.028), total cholesterol in serum: 180.4±104.9mg/dL (p=0.002), HDL: 44.2±17.6 mg/dL (p=0.017) and LDL: 121.6±98.9 mg/dL (p=0.005). No significant association was found between vitamin D levels (p>0.640) and headache, as described in Table 2.

Table 2 –Laboratory characteristics in young women with or without headache

Variable	Mean (SD)	p-value
Glucose (mg/dL)		0.028
Without headache	86.6 (20.6)	
With headache	97 (24.5)	
Total Cholesterol (mg/dL)		0.002
Without headache	129.5 (54.4)	
With headache	180.4 (104.9)	
HDL (mg/dL)		0.017
Without headache	34.7 (14.3)	
With headache	44.2 (17.6)	
LDL (mg/dL)		0.005
Without headache	81.6 (47.3)	
With headache	121.6 (98.9)	
Vitamin D (ng/mL)		0.640
Without headache	24.3 (9.4)	
With headache	23.2 (8.2)	

SD: standard deviation; HDL: high density lipoproteins LDL: low density lipoprotein

Table 3 reveals a positive relationship between a prolonged duration of headache attacks and high levels of serum glucose: 97.9±22.9 mg/dL (p=0.028), total cholesterol: 186.8±114.7 mg/dL (p=0.05), DBP (diastolic blood pressure): 74±7.7 mmHg (p=0.038), and BMI (body mass index): 24.6±4.3 kg/m² (p=0.024). It is important to note that the data analysis was conducted exclusively on patients who reported Duration (4 to 72 hours). Additionally, the results suggest that elevated glucose levels are also directly associated with the presence of migraine, especially with aura: 105±24.6 mg/dL (p=0.034), as observed in Table 3.

Table 3 – Associations between Health Metrics, Headache Duration, and Migraine Presence.

Variables	Mean (SD) Without headache	Mean (SD) Without headache	p-*value*
Glucose (mg/dL)	88.7 (26.3)	97.9 (22.9)	0.028
Cholesterol total (mg/dL)	152.1 (72.2)	186.8 (114.7)	0.050
DBP (mmHg)	71 (7.6)	74 (7.7)	0.038
BMI (kg/m2)	22.9 (3.3)	24.6 (4.3)	0.024
	Migraine without aura	**Migraine with aura**	
Glucose (mg/dL)	99 (27)	105 (24.6)	0.034

SD: standard deviation; DBP: diastolic blood pressure; BMI: body mass index.

Discussion

The identification of individuals who are more predisposed to develop chronic disease is crucial for the early initiation of effective preventive strategies[31] The main finding of the present study was the association between the presence of headache, duration and pain intensity with plasma glucose levels, total cholesterol, and fractions. Vitamin D was not associated with the presence or potentiation of the headache.

Headaches are a common complaint, affecting up to 90% of the population at some point in their live.[1] The association between headaches and various biochemical markers has been studied extensively, and recent research has suggested that there may be a significant association between the presence of headache and glucose profiles, total cholesterol in serum, HDL, and LDL.[12] This observation was supported by a study conducted by Rist et al.[32], found a strong association between increasing of total cholesterol and migraine, with odds ratio (95% confidence interval) was 4.67 (0.99-21.97). The authors also found strong associations between triglycerides and migraine (odds ratio 4.42 (1.32-14.77).[32]

A study hypothesized that alteration in glucose homeostasis could generate a chronic brain energy deficit promoting migraine chronification. Nonetheless, insulin resistance may link migraine with its comorbidities, such as obesity, metabolic syndrome and cerebrovascular diseases.[33] Was demonstrated higher plasma glucose values during spontaneous migraine attacks (interictal phase: 88.63 ± 11.70 mg/dL, ictal mean: 98.83 ± 13.16 mg/dL, SD mg/dL, difference 10.20 mg/dL, 95% CI = [4.30; 16.10]), P = 0.0014), independent of the presence of aura symptoms and not related to pain intensity, peaking in the early phase of attacks.[5]

However, the relationship between vitamin D levels and headache remains unclear. A recent study by Nowaczewska et al. summarized studies (observational, cross-sectional, case-control, and clinical trials) and Identified 18 studies showed some link between serum vitamin D levels and headaches, but inaccurate. The authors concluded that there is not enough evidence to recommend vitamin D supplementation to all headache patients, however, may be beneficial in some patients suffering headaches. The authors suggest that larger cohort studies are needed to draw a more definitive conclusion on this topic[19]. This study strengthens our findings, we were not able to found no significant association between vitamin D levels and headache (p>0.05), as shown in Table 2, our study is limited by a small sample, thus suggesting also that new studies with a larger population will bring more information.

Table 3 reveals significant associations between the duration of headache attacks and various metabolic parameters. A longer duration of headache attacks is positively correlated with elevated levels of serum glucose (p=0.028), total cholesterol (p=0.05), diastolic blood pressure (p=0.038), and body mass index (p=0.024). These findings align with an observational study that focused on total body obesity and abdominal obesity, indicating an increased risk of migraine in both obese men and women compared to those with normal weight, particularly among individuals under 50 years of age.[34] Despite decades of evidence supporting the independent and additive value of waist circumference in predicting morbidity and mortality, this measurement is not routinely collected in clinical practice. Merely relying on BMI alone is insufficient for accurately assessing or managing cardiometabolic risk associated with increased adiposity in adults. Recognizing knowledge gaps, including refining waist circumference threshold values for specific BMI categories, is crucial for optimizing dyslipidemic risk stratification across age, sex, and ethnicity.[35]

These observations emphasize the importance of incorporating anthropometric measures, such as waist circumference, in the assessment and management of conditions like migraines.[35] This approach provides valuable insights into the intricate relationships between metabolic factors and headache disorders. Moreover, the association between high glucose levels and migraines, particularly those with aura, suggests a potential link between glucose metabolism and the pathophysiology of migraines in young women. Fagherazzi et al.[24] study, which evaluated 74,247 women, proposed a potential role of both hyperglycemia and hyperinsulinism in migraine occurrence.

In a prospective epidemiological research study involving 10,000 individuals (46.6% males and 53.4% females) with episodic primary headaches and/or chronic primary headaches, 29% had episodic primary headaches, and 7.5% had chronic primary headaches. Hypertension was found in 24.27% of episodic primary headache cases and 31.98% of chronic primary headache cases.[20]

It's true that physical activity, management of obesity, a healthy diet, and a better lifestyle, such as adequate sleep and avoidance of drug abuse, significantly contribute to reducing the frequency and severity of attacks.[36] It is important to consider these factors in the overall management strategies for migraine sufferers.

In conclusion, our study suggest that high glucose levels, total cholesterol, and BMI are associated with the presence and duration of headaches, particularly migraines with aura.

Conflict Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions: CLO, NG, Study Design; JBLFilho, VCRP, KVZ, JKKVS, Data Collection; CLO, Statistical Analysis; CLO, BRAR, KVZ, JKKVS, Data Interpretation.

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