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High leptin levels are associated with migraine with aura

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ABSTRACT

Background Migraine is a prevalent disorder characterized by recurrent headache attacks preceded or accompanied by aura in a subgroup of patients. Migraine often occurs together with major depressive disorder (MDD). Alterations of adipokine levels have been reported both in migraine and MDD. In this cross-sectional study we aimed to assess the associations between serum leptin and adiponectin levels and migraine or migraine subtypes. Analyses were adjusted for a lifetime history of MDD in order to investigate the association between adipokines and migraine under consideration of depression status.

Methods We included 3,025 participants from the CoLaus/PsyCoLaus study. The impact of leptin and adiponectin levels on diagnosis of migraine was analyzed by binary regression analyses, adjusting for variables known to influence adipokine levels. Subgroup analyses were conducted based on the presence of aura.

Results Crude leptin levels were significantly higher in subjects with migraine than controls (Mann-Whitney $U = 515,102$, $p = 6E-07$). When performing adjusted analyses, leptin levels were found to be significantly higher in subjects with migraine (OR = 1.22, $p = 0.024$) and migraine with aura (OR = 1.34 $p = 0.004$).

Discussion High leptin levels might play a role in the pathogenesis of migraine and migraine with aura.

Key words: migraine, aura, leptin, adiponectin, major depressive disorder.

INTRODUCTION

Migraine is a disabling primary headache disorder of neurovascular origin that is three times more frequent in women (1), with a prevalence of 1 billion of people worldwide (2). Ranked as the third most prevalent disorder and seventh-highest specific cause of disability worldwide (2), migraine has a profound socio-economic and personal impact. Migraine without aura (MWOA) is the most common form of migraine and is characterized by the recurrence of unilateral, severe headache attacks lasting 4-72 hours with associated symptoms (3). In migraine with aura (MWA), migraine is preceded or accompanied by reversible focal neurological symptoms that last for less than 60 minutes (3). Recent findings suggest an association between migraine and obesity (4). This association could be mediated by adipokines, i.e. cytokines mainly secreted by adipose tissue, which participate in a number of processes that may play a role in migraine pathophysiology, such as inflammation and endothelial function (5). Among adipokines, the 16-kDa peptide hormone leptin leads to the reduction of food intake and increase of energy consumption through induction of anorexigenic factors. Importantly, leptin is able to act as a proinflammatory cytokine and modulate immune responses (6). Adiponectin is a 30-kDa protein involved in fatty acid oxidation and glucose synthesis (6, 7) and has been suggested to exert both pro- and antiinflammatory properties (6). While leptin levels are usually increased in obesity (8), adiponectin levels have been shown to be reduced (9). Studies that assessed the levels of these two adipokines in subjects with migraine have provided conflicting results (5, 10-17). One reason for the contradictory findings could be the heterogeneity of migraine. Indeed, the two subtypes MWOA and MWA could be differentially associated with adipokines. However, previous studies that assessed the association between adipokines and migraine have only partially taken into account these subtypes.

Major depressive disorder (MDD), which has been frequently shown to be associated with both migraine and obesity, could also play a role in the association between migraine and obesity. Indeed, migraine patients have a 2-4 fold higher risk for MDD (18, 19) and several reviews and meta-analyses found depression to be associated with obesity (20-22). MDD could either be a condition predisposing to both migraine and obesity or a mediator of the association between the two conditions; i.e. if obesity predisposes to MDD, which predisposes to migraine, or the converse.

In the present study we aimed to assess the associations between serum leptin and adiponectin levels and migraine or migraine subtypes. Analyses were adjusted for a lifetime history of MDD in order to investigate the association between adipokines and migraine under consideration of depression status.

METHODS

Subjects and cohort

The data of the present paper stem from CoLaus|PsyCoLaus (23, 24), a cohort study designed to study mental disorders and cardiovascular risk factors (CVRFs)/cardiovascular diseases (CVD) in the general population. A total of 6,733 individuals (CoLaus), aged between 35 and 75 years, were randomly selected between 2003 and 2006 from the residents of the city of Lausanne (Switzerland) according to the civil register. In addition to anthropometric measures, DNA, serum and plasma samples were collected for the study of genetic variants and biomarkers associated with CVRFs (23). Subsequently, 67% of the participants of CoLaus in the age range of 35 to 66 years (N=5,535) agreed to take part in the psychiatric evaluation (PsyCoLaus), which resulted in a sample of 3,719 individuals who underwent both the somatic/cardiovascular and psychiatric exams (24). Ninety-two percent of these individuals were Caucasians. The gender distribution of the PsyCoLaus sample (47% men) did not differ significantly from that of the general population in the same age range (24). Although the youngest 5-year band of the cohort was underrepresented and the oldest 5-year band overrepresented, participants of PsyCoLaus [mean age 50.9; standard deviation (SD) 8.8 years] and individuals who refused to participate revealed comparable scores on the General Health Questionnaire (GHQ-12) (25), French translation (26), a self-rating instrument completed at the somatic exam.

Of the initial 3,719 individuals, 656 were excluded because of missing adipokine levels, 30 because of missing migraine assessment, 6 because of missing lifetime MDD assessment, 1 because of missing blood glucose levels and 1 because of missing BMI, leaving a total of 3,025 subjects included in the present study. Excluded subjects were less frequently women (Chi-square = 24.8, < 0.001) and younger (Mann-Whitney U = 983,654, p = 0.012) than non-excluded ones.

The CoLaus and PsyCoLaus studies were approved by the Institutional Ethic's Committee of the University of Lausanne. Informed written consent was obtained from all participants.

Assessment of clinical and biological data

The lifetime prevalence of migraine was assessed according to the criteria of the International Classification of Headache Disorders (ICHD-II) (3), using the validated French version of the Diagnostic Interview for Headache Syndromes (DIHS). Prevalence of MDD was assessed using the validated French translation (27) of the Diagnostic Interview for Genetic Studies (DIGS) (28). The French translation of the DIGS revealed excellent inter-rater reliability in terms of kappa and Yule's Y coefficients for major mood and psychotic disorders, whereas the 6-week test-retest reliability was slightly lower (29). Interviews were conducted by trained psychologists or psychiatrists and reviewed by an experienced senior psychologist.

Body weight and height were assessed and a venous blood sample was obtained after an overnight fast (with a minimum fasting time equal to 8 hours). Samples were stored at -80°C and sent on dry ice to the laboratory. Total serum leptin levels were measured by Pathway Diagnostics (Los Angeles, CA) using enzyme linked immunosorbent assay (ELISA) [(American Laboratory Products Company, Windham, USA; maximum inter-assay coefficient of variability (CV) = 12.8%; maximum intra-assay CV = 5.8%)]. Total serum adiponectin levels were measured using ELISA (R&D Systems, Inc, Minneapolis, USA; maximum inter-assay CV = 8.3%, maximum intra-assay CV = 8.3%). Fasting plasma glucose levels were measured by the Centre Hospitalier Universitaire Vaudois (CHUV) laboratory using a glucose dehydrogenase assay (Roche Diagnostics, CH; maximum inter-assay CV = 2.1%; maximum intra-assay CV = 1.0%).

Statistical analysis

Normal distribution of continuous variables was assessed using Kolmogorov-Smirnov test. Differences in continuous or categorical variables between subjects with migraine and controls were assessed using Mann-Whitney or Pearson Chi-Square tests, respectively. Correlations between adipokine levels and continuous variables were analyzed using Spearman correlation. The association of adipokine levels and diagnosis of migraine was assessed using binary logistic regression analysis. Three models of increasing

complexity were constructed. In model 1 the association was adjusted for age and sex; model 2 included adjustments applied in model 1 and was additionally adjusted for body mass index (BMI). Model 3 was same as model 2 and also adjusted for fasting plasma glucose levels, lifetime MDD and regular intake of antidepressants. In all these models, the dependent variable was the presence of migraine. In subsequent analysis based on migraine subtypes, the dependent variable was the presence of MWA or the presence of MWOA.

In order to assess if sex or a lifetime history of MDD exerted an impact on the association between adipokine levels and migraine, models were first tested for potential interactions between adipokine levels, sex and lifetime diagnosis of MDD with respect to migraine and migraine subtypes. Specifically, the following interactions terms were included in the model: “sex x leptin levels”, “sex x adiponectin levels”, “MDD x leptin levels” and “MDD x adiponectin levels”. In the final model interaction terms that did not reach the level of statistical significance were removed.

A p-value < 0.05 was considered significant. Statistical analyses were performed using SPSS v. 21 (IBM, Armonk, NY, USA).

RESULTS

Demographic and clinical characteristics of the sample

Demographic and clinical characteristics of the sample are shown in Table 1. Within the sample of 3,025 participants 472 subjects (15.6%) met the lifetime diagnostic criteria for migraine. Among them 35% fulfilled also the criteria for MWA. All subjects except one had a diagnosis of episodic migraine according to ICHD-II criteria. Subjects with migraine were more likely to be younger and female, to have a lower BMI and lower fasting glucose levels, but higher leptin levels than controls (Table 1). Furthermore, individuals with migraine displayed more frequently a lifetime history of MDD and reported more frequently a regular intake of antidepressants.

Adipokine levels and the prevalence of migraine and MWA

Leptin levels were higher in women (mean = 16.2 ng/mL, SD = 11.4) than men (mean = 8.2 ng/mL, SD = 7.2, $p < 0.001$), and were positively correlated with age ($\rho = 0.14$), and BMI ($\rho = 0.38$, $p < 0.001$ for both variables). Similarly, adiponectin levels were higher in women (mean = 12.3 $\mu\text{g/mL}$, SD = 9.4) than men (mean = 7.2 $\mu\text{g/mL}$, SD = 5.7, $p < 0.001$), correlated positively with age ($\rho = 0.13$) and inversely with BMI ($\rho = -0.29$, $p < 0.001$ for both variables). Before adjustments leptin levels were significantly higher in subjects with migraine than controls regardless of the migraine subtype (Table 1). In contrast there was no association between adiponectin levels and migraine or its subtypes.

In order to test the impact of sex or comorbidity with MDD on the association between adipokine levels and migraine, a binary logistic regression model with interaction terms for sex and lifetime history of MDD was applied in a first step. We found no significant interactions between sex or lifetime MDD and adipokine levels regarding the risk for migraine, MWA or MWOA (Supplementary Table 1). Therefore, all interaction terms were removed from the model.

Table 2 provides the results of the binary logistic regression analyses adjusting for sex and age (Model 1), Model 1 + BMI (Model 2) and Model 2 + fasting plasma glucose levels, lifetime MDD and regular intake of antidepressants (Model 3). In model 2 and model 3 higher leptin levels were still significantly

associated with an elevated lifetime prevalence of migraine and the MWA subtype but not with the MWOA subtype. The associations with leptin significantly differed between the two migraine subtypes evidenced by the established odds ratios for each subtype which lay beyond the 95% confidence interval of the other subtype. These models also revealed the absence of significant associations between adiponectin and migraine or migraine subtypes.

Among the covariates included in the models female sex was associated with migraine and the MWOA subtype. Moreover, increasing age was associated with a reduced prevalence of migraine and the MWOA subtype and increasing BMI with a reduced prevalence of the MWA subtype. Finally, the lifetime history of MDD and migraine and its subtypes were strongly associated.

DISCUSSION

In the current study we evaluated the association between adipokine levels and diagnosis of migraine in a large population sample including 3,025 participants from the CoLaus (23) and PsyCoLaus (24) studies. The major finding was the strong association between high leptin levels and migraine after adjustment for a comprehensive series of variables known to influence leptin levels, including demographic characteristics, BMI, and fasting glucose levels. Although a lifetime history of MDD was strongly associated with migraine and its two subtypes, the association between migraine and leptin levels was not explained by depression status.

Previous studies that explored the relationship between leptin levels and migraine yielded inconsistent results. Given our evidence of differential associations between leptin levels and migraine subtypes the conflicting results of previous research could be due to variance of subtypes across studies. One study found lower leptin levels in 61 patients with episodic migraine compared with 64 healthy subjects before adjusting for fat mass (11), whereas another study documented higher crude but not adjusted leptin levels in 44 non-obese female migraine patients (13 of them with symptoms of aura) compared with 40 female controls (12). Another study assessing migraine subtypes reported negative results in a sample of 72 patients with migraine, 59 with the diagnosis of probable migraine and 850 controls (14). However, only 23 patients with migraine and 12 with probable migraine had a history of aura, which consisted in having experienced a visual aura in the past, rather than having met the MWA criteria according to ICHD-II.

Interestingly, an association between leptin levels and migraine was in our study specifically seen for subjects with MWA. This finding is well in line with preclinical study results showing that hyperleptinemia has the potential to increase cortex susceptibility to cortical spreading depression (CSD), a mechanism that is suggested to induce auras during migraine attacks. CSD is characterized by a slowly propagating neuronal and glia depolarization wave followed by hyperpolarization (30). Chronic hyperleptinemia has been recently found to increase CSD in a rat model after intraperitoneal leptin administration (31) and Zucker fatty (ZF) rats (a model for obesity with intrinsic hyperleptinemia) display a significant higher frequency of KCl induced CSDs than Zucker lean (ZL) rats (31).

Mechanistically, it cannot be excluded that higher levels of leptin in patients with MWA may also be a feedback response to prolonged stress and hypothalamic–pituitary–adrenal (HPA) axis activation. Interestingly, in food deprived mice, leptin administration was shown to prevent the induction of corticotropin-releasing hormone (CRH) production in the paraventricular nucleus and to lower corticosterone levels (32). Moreover, *in vivo* photostimulation of orexin neurons in the lateral hypothalamic area was shown to induce a stress response through regulation of CRH secretion. Leptin administration inhibited orexin neuron activation through leptin receptor b-expressing inhibitory neurons, in this way suppressing the HPA axis (33).

Our finding of a lack of association between migraine and adiponectin levels is in line with results of a meta-analysis (13) and one recent study (16) and contrasts with one study which revealed higher adiponectin levels in 68 migraine patients than 65 controls, independently of psychiatric comorbidities, migraine impact and allodynia (15). Another study documented an association only in men older than 50 years but not in women with migraine (14).

Our results need to be interpreted in the light of several limitations. First, participation rate was relatively low, which was probably due to the comprehensive physical and psychiatric assessments. 2) The cross-sectional nature of the data reported herein did not allow us to determine the temporal sequence between adipokine level increases and the onset of migraine. 3) Total adiponectin but not high and low molecular weight oligomers were measured and assessed for association with migraine. These oligomers could be differentially associated with migraine (10). 4) All subjects except one had a diagnosis of episodic migraine. Therefore, we were not able to specifically evaluate if chronic migraine was associated with higher adiponectin levels as suggested by a previous study (10). In conclusion, the present study suggests that high leptin levels are associated with the risk of migraine and MWA. Prospective studies which can provide clues to the temporal sequence between leptin levels increase and the onset of migraine are needed to confirm our findings and to further elucidate the role of leptin in migraine pathogenesis. Future studies should also subtype into high and low molecular weight oligomers in order to unravel potential differential effects of these specific oligomers on the risk of migraine.

CONTRIBUTORS

CP: Study design, statistical analysis, interpretation of data, manuscript writing

MP: Data recruitment, interpretation of data, manuscript writing

EC: Data recruitment, manuscript writing

JG: Data recruitment, manuscript writing

JLC: Manuscript writing

MDZ: Manuscript writing

KRM: Data recruitment, manuscript writing

HBS: Interpretation of data, manuscript writing

JM: Study design, interpretation of data, manuscript writing

Conflict of Interest Statement:

The authors have nothing to declare

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Article Highlights

- Subjects with migraine showed higher leptin levels than controls
- Higher leptin levels were specifically associated with migraine with aura
- The association between leptin levels and migraine was observed independently from major depressive disorder

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Table 1. Demographic and clinical characteristics of the sample (n = 3,025)

	Controls	Migraine	Migraine vs. controls	MWA	MWA vs. controls	MWOA	MWOA vs. controls
N	2,553	472	-	165	-	307	-
Age (years)	50.4 (± 8.9)	48.8 (± 8.5)	< 0.001	49.4 (± 8.8)	0.10	48.4 (± 8.3)	< 0.001
Gender female, n (%)	1,326 (52%)	335 (71%)	< 0.001	99 (60%)	0.044	236 (76.9%)	< 0.001
BMI (Kg/m ²)	25.6 (± 4.3)	25.1 (± 4.3)	0.01	25.2 (± 4.2)	0.20	25.1 (± 4.3)	0.018
Glucose (mmol/L)	5.5 (± 1.1)	5.4 (± 0.8)	0.001	5.4 (± 0.8)	0.42	5.3 (± 0.7)	< 0.001
Lifetime MDD, n (%)	1,027 (40%)	274 (58%)	< 0.001	101 (61.2%)	< 0.001	173 (56.4%)	< 0.001
Regular intake of antidepressants, n (%)	191 (7%)	68 (14%)	< 0.001	23 (13.9%)	0.003	45 (14.7%)	< 0.001
Leptin (ng/mL)	12.2 (± 10.4)	14.6 (± 11)	< 0.001	14.2 (± 10.8)	0.013	14.8 (± 11.2)	< 0.001
Adiponectin (µg/mL)	10.0 (± 8.4)	10.1 (± 7.9)	0.15	9.3 (± 5.2)	0.83	10.5 (± 9.0)	0.09

BMI, body mass index; MDD, major depressive disorder; MWA, migraine with aura; MWOA, migraine without aura

Continuous variables are expressed as mean ± standard deviation; p-values are calculated using Mann-Whitney test or Pearson chi square test, comparing subjects with migraine or migraine subtypes vs. controls. Significant differences are indicated in bold.

Table 2. Association between adipokine levels and diagnosis of migraine and migraine subtypes according to logistic regression models

	Migraine (N = 472)		MWA (n = 165)		MWOA (N = 307)	
	Vs. controls (N = 2,553)					
	Adj OR (95% CI)	P-value	Adj OR (95% CI)	P-value	Adj OR (95% CI)	P-value
Model 1						
Leptin	1.11 (1.01-1.23)	0.041	1.15 (0.99-1.34)	0.078	1.08 (0.96-1.22)	0.195
Adiponectin	0.92 (0.82-1.03)	0.166	0.94 (0.70-1.10)	0.192	0.94 (0.83-1.08)	0.398
Sex female	2.22 (1.75-2.83)	< 0.001	1.36 (0.94-1.96)	0.106	3.05 (2.25-4.14)	< 0.001
Age	0.98 (0.97-0.99)	< 0.001	0.99 (0.97-1.00)	0.130	0.97 (0.96-0.99)	< 0.001
Model 2						
Leptin	1.18 (1.04-1.35)	0.011	1.34 (1.10-1.63)	0.004	1.10 (0.94-1.28)	0.270
Adiponectin	0.91 (0.81-1.03)	0.121	0.84 (0.67-1.05)	0.118	0.94 (0.83-1.08)	0.388
Sex female	2.02 (1.55-2.65)	< 0.001	1.08 (0.72-1.63)	0.701	3.00 (2.13-4.21)	< 0.001
Age	0.98 (0.97-0.99)	< 0.001	0.99 (0.97-1.01)	0.237	0.97 (0.96-0.99)	< 0.001
BMI	0.98 (0.95-1.01)	0.133	0.94 (0.90-0.99)	0.022	1.00 (0.96-1.03)	0.831
Model 3						
Leptin	1.17 (1.03-1.34)	0.018	1.34 (1.10-1.63)	0.004	1.09 (0.92-1.02)	0.328
Adiponectin	0.91 (0.81-1.03)	0.106	0.83 (0.66-1.03)	0.098	0.94 (0.83-1.08)	0.371
Sex female	1.77 (1.35-2.33)	< 0.001	0.89 (0.58-1.36)	0.593	2.70 (1.91-3.81)	< 0.001
Age	0.98 (0.97-0.99)	0.001	0.99 (0.97-1.01)	0.375	0.97 (0.96-0.99)	< 0.001
BMI	0.98 (0.94-1.01)	0.126	0.94 (0.89-0.99)	0.018	0.99 (0.96-1.03)	0.795
Glucose	0.98 (0.88-1.10)	0.780	0.99 (0.83-1.18)	0.896	0.98 (0.85-1.13)	0.779
Lifetime MDD	1.63 (1.32-2.01)	< 0.001	2.13 (1.52-2.99)	< 0.001	1.40 (1.09-1.8)	0.009
Regular intake of antidepressants	1.69 (1.24-2.30)	0.001	1.62 (1.00-2.61)	0.050	1.77 (1.22-2.55)	0.002

Adj, adjusted; BMI, body mass index; CI, confidence interval; MDD, major depressive disorder; MWA, migraine with aura; MWOA, migraine without aura; OR, odds ratio. In Model 1 adipokine levels are adjusted for age and sex; in model 2 adipokine levels are adjusted for variables included in Model 1 + BMI; in Model 3 adipokine levels are adjusted for variables included in Model 2 + fasting glucose levels, lifetime history of MDD and regular intake of antidepressants. Significant results are reported in bold.

OR with 95% CI are calculated in relationship to the increase of 1 unit of standard deviation in leptin or adiponectin levels