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## Investigating the role of adipokines in chronic migraine

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## Abstract

**Background and aims:** Adiponectin, leptin, and resistin are adipocyte-derived secretory factors involved in endothelial function, weight, inflammation, and insulin resistance. Recent studies suggested a role for adipokines in episodic migraine as mediators of inflammatory processes. The aim of this study was to investigate plasma concentrations of adiponectin, leptin, and resistin in patients with chronic migraine. **Materials and methods:** Twenty-seven chronic migraineurs (20 females, 7 males; mean age 49.0 9.0 yrs) and 37 healthy controls (23 females, 14 males; mean age 49.8 15.0 yrs) were selected for the study. Fasting plasmatic levels of total adiponectin, leptin, and resistin were measured using ELISA kits during a pain-free period. Fasting glucose, insulin, total and HDL-cholesterol, triglycerides, and ESR were also determined. **Results:** Serum levels of adiponectin and resistin were significantly increased in chronic migraineurs in comparison with controls ( $p \leq 0.001$  and  $p \leq 0.032$ , respectively). After correction for BMI, sex and age, leptin levels were significantly increased in chronic migraineurs ( $p \leq 0.007$ ). A positive correlation between leptin concentrations and both indices of insulin resistance and markers of inflammation was found. **Discussion:** Our data suggest that adiponectin and resistin are altered in non-obese chronic migraineurs. Further studies are needed to elucidate the neurobiological mechanisms underlying adipokine dysfunction in migraine.

## Keywords

Adiponectin, leptin, resistin, adipokines, migraine, chronic migraine

## Introduction

Migraine is a neurovascular disorder characterized by recurrent moderate to severe headache attacks associated with nausea, vomiting, phono- and photophobia, as well as other neurological symptoms. Migraine affects approximately 12% of the adult population in western countries, and imposes a great burden on the patient, the family and the society (1). The disease, according to the International Headache Society (IHS), may be classified into episodic migraine (EM), characterized by headache occurring on fewer than 15 days per month, and chronic migraine (CM), defined by attacks occurring more than 15 days per month for at least three months (2). Epidemiological data show that the prevalence of chronic migraine is about 2–3% of the general population (3). CM is associated with a substantially greater personal and societal burden, and frequent comorbidities (4,5).

The pathogenic mechanisms underlying both episodic and chronic migraine are still under investigation. Multiple processes are involved in the disease, including generalized neuronal hyperexcitability, cortical spreading depression, and activation of the trigeminovascular system with release of several pro-inflammatory mediators in the blood. In addition, recent studies have shown a complex association between migraine and the components of the metabolic syndrome, such as obesity, insulin resistance, inflammation, dyslipidemia and hypertension (5–9).

For a long time, adipose tissue was considered to be only a deposit of energy. Nowadays, it is well known that adipose tissue has a major endocrine function related to production and release of a variety of proinflammatory and anti-inflammatory factors, the so-called adipocytokines or adipokines (10). Adipokines include, at present, leptin, adiponectin, resistin, visfatin, vaspin, and chemerin (11). These peptides play an important role in several physiological functions, including the modulation of endothelial function, weight, immune response, inflammation, and insulin resistance (12). Recent studies suggested that some of these adipokines are involved in migraine and represent potential migraine biomarkers (13, 14). The first study investigating the association between adipokines and migraine found increased serum adiponectin levels in women with CM, or CM with medication overuse headache (15). Additional studies confirmed higher adiponectin concentrations both in episodic and chronic migraine in interictal periods (16,17). Interestingly, in episodic migraine, both adiponectin and resistin levels were shown to be significantly increased during migraine attack, along with pain severity, and decreased after successful treatment (18,19). On the contrary, studies evaluating interictal leptin concentrations in migraineurs have been inconclusive (13,17,20).

At present, few data regarding the involvement of adipokines in patients with chronic migraine are available. Therefore, the aims of this study were to investigate plasma concentrations of adiponectin, leptin, and resistin in patients with chronic migraine and to correlate the concentrations of these peptides with several metabolic parameters.

## Methods

### Subjects

Twenty-seven patients with chronic migraine (20 females, 7 males; mean age 49.0 ± 9.0 yrs; median age 49 yrs; age range 30–67 yrs), referring to the Headache Center of the Rita Levi Montalcini Department of Neuroscience, University of Torino, Italy, were selected for the study. Patients filled in a headache diary for at least 6 months before the enrollment. The following characteristics of headache were reported: frequency and duration of attacks, pain intensity and localization, aura, nausea, vomiting, photophobia, phonophobia, medication intake. All patients fulfilled the diagnosis of chronic migraine according to ICHD-III beta version criteria (2). No patients met the criteria for medication overuse headache. Exclusion criteria included

**Table 1.** Sociodemographic and clinical characteristics of patients with chronic migraine and controls.

	Chronic migraine	Controls	p value
Sex (F/M)	20/7	23/14	0.421
Age (yrs)	49.04 ± 8.99	49.81 ± 15.00	0.816
BMI	23.19 ± 3.15	22.73 ± 2.49	0.515
Education			0.444
8 yrs	28.6%	25.8%	–
13 yrs	42.9%	29.0%	–
>13 yrs	28.6%	45.2%	–
Marital status			0.565
Single	13.3%	24.0%	–
Married	80.0%	64.0%	–
Separated/divorced	6.7%	12.0%	–
Age at onset (yrs)	16.00 ± 3.41	–	–
Headache days per month	20.82 ± 3.66	–	–
Duration of chronification (yrs)	6.09 ± 3.02	–	–

other forms of headache, obesity, diabetes, hypertension, autoimmune and metabolic disorders. Thirty seven healthy subjects (23 females, 14 males; mean age 49.8 15.0 yrs; median age 51 yrs; age range 32–73 yrs), not affected by any form of primary headache, were used as controls. All subjects involved in the study were of Caucasian origin. The demographic and clinical characteristics are summarized in Table 1.

#### Assays

All blood specimens were drawn in a pain free period (at least 12 hours from the last migraine attack). Fasting plasmatic levels of total adiponectin, resistin, and leptin were measured using ELISA kits (Biovendor, Oxfordshire, UK). The kit used to measure the adiponectin concentration showed a limit of detection of 26 ng/ml, an interassay coefficient of variation (CV) of 6.7% and an intra-assay CV of 4.9%. The kit for leptin had a limit of detection of 0.2 ng/ml, an interassay CV of 5.6% and an intra-assay CV of 5.9%, while the kit for resistin showed a limit of detection of 0.012 ng/ml, an interassay CV of 7.6% and an intra-assay CV of 5.9%.

Blood levels of fasting glucose, insulin, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), Erythrocyte sedimentation rate (ERS) and triglycerides were also determined (Table 2). Low-density lipoprotein-cholesterol (LDL-C) was estimated by Friedewald equation. HOMA-IR, an index of insulin sensitivity, was calculated as follows:  $\text{HOMA-IR} = \frac{\text{Fasting serum insulin (mIU/L)} \times \text{Fasting blood glucose (mmol/L)}}{22.5}$ . Patients and controls were comparable regarding BMI, smoking, sedentariness, and menopause. Resting blood pressure was also measured. The clinical characteristics of migraine were collected.

**Table 2.** Biochemical parameters of patients with chronic migraine and controls.

	Chronic migraine	Controls	p value
Total cholesterol (mg/dL)	199.28 ± 53.86	200.57 ± 26.27	0.95
HDL-cholesterol (mg/dL)	58.84 ± 17.52	64.00 ± 29.44	0.56
Triglycerides (mg/dL)	102.73 ± 40.60	127.57 ± 37.40	0.42
Glucose (mg/dL)	83.67 ± 9.38	82.71 ± 12.30	0.74
Erythrocyte sedimentation rate (mm/h)	11.04 ± 10.71	10.83 ± 7.49	0.97
Insulin (ng/mL)	3.80 ± 2.93	5.39 ± 4.49	0.11
Leptin (ng/mL)	20.34 ± 19.37	12.21 ± 9.90	0.08
Adiponectin (µg/mL)	12.08 ± 5.15	7.27 ± 3.63	0.001
Resistin (ng/mL)	12.98 ± 4.21	10.14 ± 4.85	0.032

## Statistics

Statistical analyses have been performed using SPSS – version 20 (SPSS Inc, Chicago, Illinois, USA). The statistical significance of differences among the groups was assessed by t-test, ANOVA Bonferroni test or MannWhitney U test, as appropriate. Baseline demographic, clinical and biochemical characteristics were summarized in the tables using means for continuous variables. The statistical models have been adjusted for possible confounders. Binary and multiple linear logistic regression and correlation analyses were done when necessary. A two-tailed p value of < 0.05 was considered as statistically significant in biochemical and clinical comparisons.

## Results

No difference in age, sex, BMI, education, marital status, fasting glucose, triglycerides, total cholesterol, HDL-C, LDL-C, insulin, ERS was found between cases and controls (Table 1 and 2). Crude total adiponectin levels were significantly increased in patients with chronic migraine in comparison with controls (12.08 5.15 mg/mL vs 7.27 3.63 mg/mL, p ¼ 0.001) (Figure 1), also after adjusting for BMI and age (p ¼ 0.018). In the bivariate analysis, the

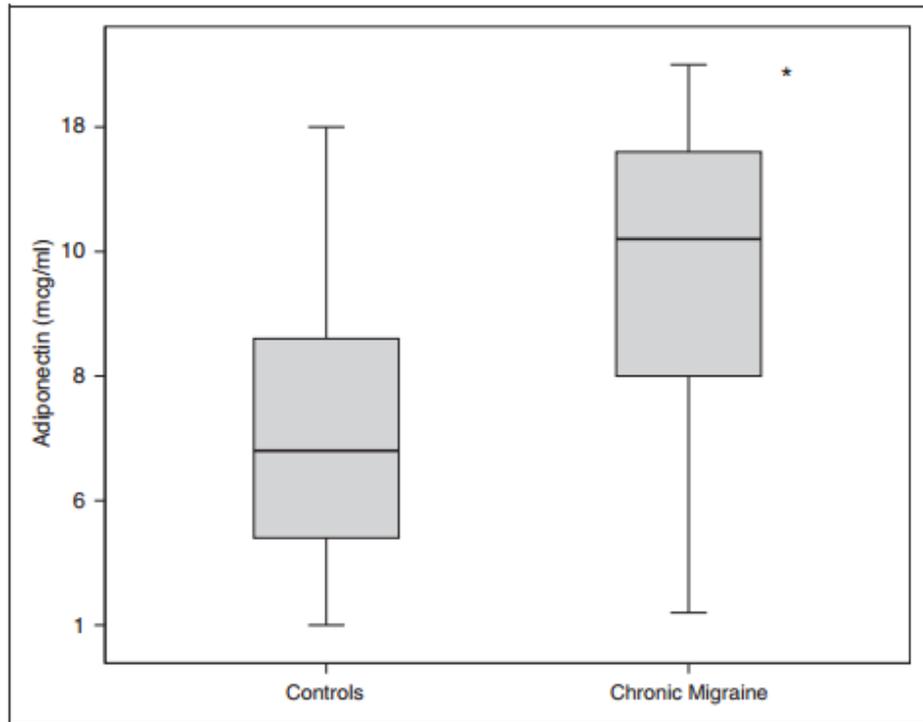


Figure 1. Adiponectin concentration in controls and patients with chronic migraine. Data are presented as a box plot. Adiponectin levels were significantly higher in patients with chronic migraine when compared with controls. \*p < 0.001.

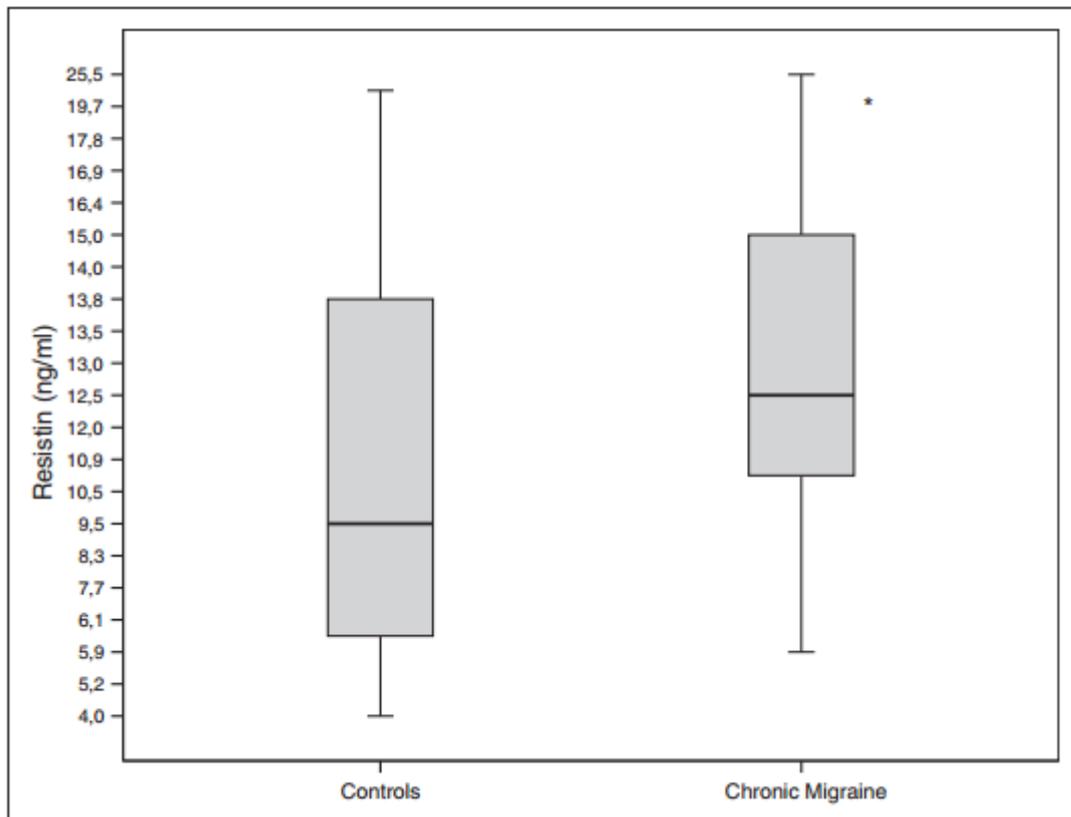


Figure 2. Resistin concentration in controls and patients with chronic migraine. Data are presented as a box plot. Resistin levels were significantly higher in patients with chronic migraine when compared with controls. \* $p < 0.05$ .

adiponectin levels were negatively associated with total cholesterol ( $r = -0.500$ ;  $p = 0.013$ ), and LDL cholesterol ( $r = -0.478$ ;  $p = 0.021$ ) levels.

Crude serum concentrations of resistin were significantly increased in patients with chronic migraine in comparison with controls (12.98  $\pm$  4.21 ng/mL vs 10.14  $\pm$  4.85 ng/mL respectively,  $p = 0.032$ ) (Figure 2), also after adjusting for BMI and age ( $p = 0.046$ ). No further correlations were found between resistin levels and the other biochemical parameters.

No significant difference in leptin levels was found between controls and migraineurs. However, after correction for BMI, sex and age, leptin levels were found to be significantly increased in chronic migraineurs ( $p = 0.007$ ). In addition, in chronic migraineurs we found a positive correlation between leptin and basal insulin ( $r = 0.557$ ,  $p = 0.004$ ), between leptin and glucose ( $r = 0.456$ ,  $p = 0.025$ ), and between leptin and HOMA-IR ( $r = 0.481$ ,  $p = 0.015$ ). Furthermore, a significant positive correlation between leptin and ERS was also found ( $r = 0.619$ ,  $p = 0.002$ ).

Finally, no correlations were found between total adiponectin, resistin and leptin levels and the collected clinical characteristics of migraine.

## Discussion

Our study investigated the involvement of adipokines in chronic migraine and provided two main findings. First, we found that plasma concentrations of both adiponectin and resistin were significantly increased in patients with chronic migraine. Our results are in accord with previous studies that found increased serum adiponectin concentrations in patients affected by EM and CM (16,18) and also in patients with CM with medication overuse headache (15). Then, in our CM patients, a significant correlation between leptin concentrations and both markers of insulin metabolism and inflammation was found. Taken together, these data confirm that, in addition to episodic migraine, adipokines are also significantly altered in patients with chronic migraine and may be involved in the pathogenic mechanisms of the disease.

In our study, we confirmed that chronic migraine is associated with increased adiponectin concentrations. It is of interest to note that receptors for adiponectin are expressed in key structures involved in migraine pathogenesis, including the hypothalamus and the cerebral microvasculature (21). The hypothalamus has long been considered to play a prominent role in migraine pathophysiology, as many of the features and symptoms associated with the clinical syndrome are related to dysfunction of several hypothalamic nuclei. In patients with chronic migraine, higher orexin-A levels have been found, probably as an expression of hypothalamic response to stress due to chronic pain (22). Intriguingly, orexin-A stimulates glucose uptake in adipocytes and the secretion of adiponectin (23). Thence, adiponectin could represent an interesting link between the orexinergic and endocrine systems. In addition, this adipokine may be considered as a potential migraine biomarker, since increased levels of adiponectin are found in both EM and CM patients, independently from medication overuse (15,16).

This is the first study investigating resistin concentrations in patients with chronic migraine. Therefore, our findings of increased resistin concentrations must be interpreted cautiously. In episodic migraine, a correlation between resistin concentrations and migraine pain severity has been shown (19). Resistin is secreted by macrophages, and to a lesser extent by adipocytes. Circulating resistin has been shown to contribute to insulin resistance by increasing production of hepatic glucose and promoting inflammation (24). Several studies have clearly showed that insulin resistance is significantly altered in migraine (7).

Resistin is also expressed in the hypothalamus and is a key immune mediator, directly stimulating NF- $\kappa$ B-mediated inflammation through the expression and secretion of TNF $\alpha$ , IL-6, and IL-12 (25,26). Intriguingly, central resistin, via hypothalamic Toll-like receptor 4, determines the overall inflammation and impairment of insulin responsiveness in a rat model (27). Therefore, therapies promoting a decrease of serum resistin levels could represent a promising strategy for migraine therapeutic intervention, reducing both insulin resistance and systemic inflammation.

Studies evaluating interictal leptin concentrations in migraineurs have been inconclusive so far (13,17,20). In our study, we found no significant alterations in crude plasma concentrations of leptin in patients with CM. However, correcting the statistical model for BMI, sex and age, we found that in female patients, serum leptin levels significantly increase with advancing age. In addition, leptin concentrations strongly correlated with both indices of insulin resistance and markers of inflammation. These findings suggest that leptin may have a significant role in the complex relationship between insulin resistance, inflammation, and frequency of migraine attacks that has been previously described (17). Leptin is produced by the adipose tissue, which regulates energy metabolism by inhibiting hunger and acts mainly in the hypothalamus, binding to specific receptors belonging to the cytokine receptor family (28). Interestingly, this adipokine antagonizes the activity of hypothalamic neurons expressing orexin and modulates the orexin-mediated stress responses (29). Several studies have demonstrated a direct correlation between the concentrations of leptin and C Reactive Protein (30). Notably, in our study, we also found a correlation with ERS in chronic migraineurs, suggesting a complex interplay between plasma leptin and markers of inflammation.

The production of leptin is higher in women than in men, and is positively related to the quantity of adipose tissue and total body fat (31,32). Recent studies have shown that higher levels of leptin stimulate insulin release, and this explains our findings regarding the correlation between leptin and insulin (33). In addition, a recent study reported in the subgroup of migraine patients that experienced weight loss with topiramate prophylaxis therapy, headache frequency and leptin concentrations were significantly decreased (34). Indeed, further studies are warranted to better elucidate the complex role of leptin in migraine.

There are some limitations in our study that deserve mention and suggest caution in the interpretation of the results. First of all, this is a study performed in a small sample of non-obese CM patients referring to a Headache Center. Additional, population-based studies are needed to further investigate adipokine involvement in migraine. Then, even if blood samples were drawn in a pain-free period, some of our patients had previously used non-steroidal anti-inflammatory drugs for the treatment of the attacks, which may influence adipokine secretion. In addition, we measured only total adiponectin plasma concentrations. Adiponectin oligomers (high, middle, and low molecular weight) are also present in human plasma with different pro- and antiinflammatory effects (15,35). Therefore, larger studies are warranted in order to investigate adiponectin oligomers in CM, evaluating if different oligomers may exert different roles in the disease. Finally, it is well known that weight, gender and body fat may significantly influence plasma adipokine concentrations. However, in our chronic migraine patients, the increase in adiponectin and resistin concentrations that we observed remained statistically significant even after adjusting for age, sex, and BMI.

In conclusion, our study shows that in patients with chronic migraine there is a complex dysfunction of plasma adipokine secretion. In addition, as previously suggested for episodic migraine, our data suggest that altered adipokine concentrations may become a biomarker of the disease as well as a new therapeutic target.

### **Clinical implications**

- The adipokines (adiponectin, leptin, and resistin) are peptides secreted from the adipose tissue with an important role in the modulation of endothelial function, weight, immune response, inflammation, and insulin resistance.
- We measured plasmatic levels of total adiponectin, leptin, and resistin as well as several parameters of insulin resistance and inflammation in a group of non-obese patients with chronic migraine and healthy controls.
- We found a significant increase in adiponectin and resistin concentrations in patients with chronic migraine. In addition, leptin concentrations showed a significant correlation with both indices of insulin resistance and markers of inflammation.
- Our study shows that adipokine concentrations are significantly altered in non-obese chronic migraineurs, suggesting that these peptides may be involved in the pathogenesis of the disease.

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### Declaration of conflicting interests

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