

Insulin Resistance and High Sensitivity C-Reactive Protein in Migraine

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ABSTRACT: Background: A relationship between migraine and vascular disorders such as hypertension, stroke, and coronary ischemia has been recently reported. Insulin resistance and endothelial dysfunction, which commonly underlies these disorders, have not been widely investigated in migraine patients. In this study, we aimed to investigate the existence of insulin resistance and endothelial dysfunction, and their relationship to vascular risk factors in patients with migraine. **Methods:** We evaluated insulin resistance and high-sensitivity C-reactive protein (hs-CRP), a marker of endothelial dysfunction, in 60 migraine patients and 25 healthy control subjects. Multiple analysis of covariance test was used to adjust for known confounding factors that can influence insulin metabolism and endothelial function, such as obesity, blood pressure, and lipid parameters. **Results:** Insulin resistance, as measured homeostasis model assessment (HOMA)-R levels, was significantly higher in the migraine group ($p < 0.001$). After adjustment for confounding variables, the relationship between migraine and the HOMA-R levels remained significant ($p < 0.001$). The hs-CRP levels did not differ between the migraine and control groups. **Conclusions:** Our data show that insulin resistance is present in migraine patients. Endothelial dysfunction is not found during the headache-free period. Further studies are needed to explain the role of insulin resistance in migraine pathogenesis.

RÉSUMÉ: Résistance à l'insuline et protéine C-réactive ultrasensible dans la migraine. Contexte : Selon la littérature récente, il existerait une relation entre la migraine et certains troubles vasculaires comme l'hypertension, l'accident vasculaire cérébral et l'ischémie coronarienne. La résistance à l'insuline et la dysfonction endothéliale, qui sont souvent des pathologies sous-jacentes à ces troubles vasculaires, ont été peu évaluées chez les patients migraineux. Nous avons recherché la présence de la résistance à l'insuline et la dysfonction endothéliale et leur relation aux facteurs de risque vasculaire chez les patients migraineux. **Méthodes :** Nous avons évalué la résistance à l'insuline et la protéine c-réactive ultrasensible (hs-CRP), un marqueur de la dysfonction endothéliale, chez 60 patients migraineux et 25 sujets témoins normaux. L'analyse de covariance a été utilisée pour tenir compte des variables confondantes connues qui peuvent influencer le métabolisme de l'insuline et la fonction endothéliale, telles l'obésité, la tension artérielle et les valeurs de lipides. **Résultats :** La résistance à l'insuline mesurée par le HOMA-R était significativement plus élevée dans le groupe de patients migraineux ($p < 0,001$). Après avoir tenu compte des variables confondantes, la relation entre la migraine et le HOMA-R est demeurée significative ($p < 0,001$). Il n'existait pas de différence entre les niveaux de hs-CRP du groupe de patients migraineux et du groupe témoin. **Conclusions :** Cette étude démontre que la résistance à l'insuline est présente chez les patients migraineux. Quant à la dysfonction endothéliale, elle n'est pas présente pendant la période sans céphalée. Le rôle de la résistance à l'insuline dans la pathogénèse de la migraine devra faire l'objet d'études plus poussées.

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Migraine is a chronic neurological disease with disabling headache attacks and autonomic symptoms. Although the pathogenesis of migraine is still unclear, vascular and neuronal dysfunctions are held responsible. It has been demonstrated that altered vasomotor function and inflammation of cerebral vessels contribute to the development of migraine attacks.^{1,2} Whether these pathophysiologic alterations have also contributed to the endothelial dysfunction seen in vascular and metabolic diseases such as hypertension, dyslipidemia, obesity, coronary ischemia, and stroke, whose risks were reported to be high in migraine,³⁻⁶ is unclear. The high incidence of migraine among morbidly obese women and the effect of obesity on the transformation of episodic migraine to the chronic form suggest that similar factors probably act in the pathogenesis of migraine and metabolic disorders such as obesity.⁷⁻⁹

Insulin resistance appears if there is insufficient physiological response in spite of normal insulin secretion, and plays a central pathogenic role in the development of the metabolic syndrome. In addition, insulin resistance causes endothelial dysfunction and the tendency to develop cardiovascular diseases while triggering

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mediators such as high-sensitivity C-reactive protein (hs-CRP), which is a marker of chronic low-grade inflammation.^{10,11}

In this study, we aimed to investigate the existence of insulin resistance and endothelial dysfunction, determined by the homeostasis model assessment (HOMA) score and hs-CRP, respectively, and their relationship to vascular risk factors in patients with migraine.

MATERIAL AND METHODS

Sixty consecutive newly diagnosed migraine patients who presented to the Neurology Department due to headache were enrolled in the study. Patients using medications that alter glucose metabolism, such as β -blockers, valproic acid, etc., and suffering from any cardiovascular or metabolic diseases were excluded. Differential diagnosis of cardiovascular and metabolic diseases (such as coronary artery disease, stroke, diabetes, thyroid diseases, etc.) and any intercurrent illness (such as respiratory or urinary infections) was made according to the anamnesis of patients, physical examination findings, and related laboratory analyses and investigation. The patients had normal neurological examinations; migraine with or without aura was diagnosed according to the International Classification of Headache Disorders (ICHD)-II criteria.¹² Blood pressure, weight, height, and waist circumference (WC) were recorded for all patients. Waist circumference was measured midway between the lower rib margin and the iliac crest. Body mass index (BMI) was calculated on the basis of World Health Organization (WHO) recommendations.¹³ Twenty-five age- and gender-matched healthy subjects, who had no history of any type of headache, any vascular or metabolic disease, and any medication use interfering in insulin metabolism, were enrolled as the control group. The study was approved by the local Ethics

Committee, and all patients gave their informed consent to participate in the study.

Serum samples were collected from an antecubital vein without using a tourniquet, between 08:30 and 09:00 a.m. after overnight fasting. Fasting glucose and lipid parameters were measured immediately. For hs-CRP and insulin, venous blood samples were centrifuged within 15 minutes at 3000 rpm for 10 minutes, and the supernatant serum samples were transferred into polypropylene tubes at -80°C until the assays were performed. The participants' serum fasting glucose levels were measured using the glucose oxidase technique (Konelab 60, Finland). Cholesterol esterase enzymatic assays (Konelab 60, Finland) were used to measure total cholesterol and high-density lipoprotein-cholesterol (HDL-C). The participants' triglyceride levels were measured by the lipase technique (Konelab 60, Finland). Low-density lipoprotein-cholesterol (LDL-C) levels were calculated according to Friedewald's formula. Serum insulin levels were determined by chemiluminescent enzyme immunoassay (Immulate DPC 2000, CA, USA). Insulin resistance was calculated according to HOMA-insulin resistance ($\text{HOMA-R} = \text{fasting serum glucose mmol/L} \times \text{insulin } \mu\text{IU/mL} / 22.5$).¹⁴ Quantitative determination of hs-CRP (DRG Inc., USA) was performed using an enzyme-linked immunosorbent (ELISA) according to the manufacturer's instructions. The intra-assay coefficient of variance was less than 5% for hs-CRP.

STATISTICAL ANALYSIS

All statistical analyses were performed by using SPSS 11.5 software for Windows. Data were expressed as mean \pm standard deviation. The normality of the distribution of all variables was assessed by the Kolmogorov-Smirnov test. Student's t-test and Pearson correlation analyses were used for normally distributed

Table: The clinical and laboratory characteristics of all participants

| | <i>Migraine group (n= 60)</i> | <i>Control group (n= 25)</i> | <i>P</i> |
|---------------------------|-----------------------------------|----------------------------------|----------|
| Female/Male, n | 46/14 | 17/8 | Ns |
| Age (year) | 38.3 \pm 10.2 | 35.3 \pm 8.8 | Ns |
| BMI (kg/m ²) | 26.1 \pm 5.6 | 25.1 \pm 3.7 | Ns |
| WC (cm) | 85.4 \pm 15.4 | 83.8 \pm 11.2 | Ns |
| SBP (mmHg) | 124.6 \pm 19.6 | 116.7 \pm 20.1 | Ns |
| DBP (mmHg) | 78.9 \pm 14.1 | 76.5 \pm 11.5 | Ns |
| Fasting glucose (mg/dL) | 88.1 \pm 9.1 | 83.8 \pm 9.0 | Ns |
| HOMA-R | 2.7 \pm 1.5 | 1.8 \pm 0.65 | <0.01 |
| Total cholesterol (mg/dL) | 184.1 \pm 40.2 | 185.6 \pm 35.1 | Ns |
| Triglyceride (mg/dL) | 136.7 \pm 127.7 | 107.7 \pm 60.0 | Ns |
| LDL-C (mg/dL) | 114.6 \pm 36 | 112.2 \pm 30.4 | Ns |
| HDL-C (mg/dL) | 52.2 \pm 12.8 | 54.3 \pm 19.8 | Ns |
| hs-CRP (mg/L) | 0.063 \pm 0.024 | 0.053 \pm 0.02 | Ns |

BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-R: homeostasis model assessment-insulin resistance, LDL-C: low density lipoprotein-cholesterol, HDL-C: high density lipoprotein-cholesterol, hs-CRP: high-sensitivity C-reactive protein, Ns: not significant.

variables. The Mann-Whitney U test and Spearman rank correlation test were used for non-parametric variables. Regarding the variables correlating with HOMA-R and hs-CRP, the association was tested using the multiple analysis of covariance test to adjust for the confounding variables affecting the association. Possible confounds included BMI, WC, age, and blood pressure and lipid parameters. *P* values <0.05 were considered statistically significant.

RESULTS

The characteristics of the migraine patients and the control subjects are shown in the Table. The HOMA-R levels of the migraine patients were significantly higher than those of the control subjects ($p < 0.001$). The levels of hs-CRP were higher in the migraine group than in the control group, but did not reach any significant value. Twenty-three percent of patients had migraine with aura, and their hs-CRP levels did not differ from those of the patients who had migraine without aura (0.076 ± 0.015 mg/L, 0.062 ± 0.024 mg/L, $p > 0.05$). Also, the HOMA-R levels did not show any significant difference among the aura groups (2.84 ± 1.02 , 2.83 ± 1.62 , $p > 0.05$). Age, gender, anthropometric values, blood pressure, serum fasting glucose, and lipid levels did not differ between the two groups.

The WC and BMI were significantly correlated with HOMA-R and hs-CRP levels in the migraine group ($p < 0.01$, $p < 0.05$; $p < 0.001$, $p < 0.05$, respectively). After adjustment for potential confounding variables, the relationship with the HOMA-R levels and migraine still remained significant ($p < 0.001$).

DISCUSSION

The main finding of our study is that migraine patients have insulin resistance irrespective of other confounding factors that can be related to insulin resistance, such as obesity, hypertension, and hyperlipidemia. Our findings confirm a previous study that demonstrated insulin resistance in non-obese migraine patients.¹⁵ It is well-known that insulin resistance is present in many diseases such as hypertension, central obesity, dyslipidemia, and type 2 diabetes mellitus, and those patients have increased risk of cardio- and cerebrovascular diseases.^{16,17} Similarly, migraine patients have a greater risk of vascular diseases, as reported in previous studies. In this regard, it can be speculated that one of the shared underlying mechanisms between migraine and vascular disorders might be insulin resistance. Enhanced platelet aggregation and high levels of von Willebrand factor that promote atherothrombosis were reported in migraine and the insulin-resistant state.¹⁸⁻²⁰

Disorders of the hypothalamic-pituitary axis have been implicated in the pathogenesis of primary headache syndromes. Cavestro et al²¹ found higher insulin levels in migraine in comparison to other headache types, and the researchers speculated that high levels of insulin may play a role in the pathogenesis of migraine with the probable action of excessive insulin on insulin receptors in hypothalamic and brainstem regions. The frequent worsening of migraine in patients taking estrogen-progestin drugs, which induce hyperinsulinism and hypoglycemia, supports their hypothesis.²² Polyuria, polydipsia, food-craving, and mood disturbance, seen in migraine as premonitory symptoms, also suggest transient hypothalamic dysfunction in migraine patients.^{23,24}

Another finding of the present study is that the hs-CRP levels in patients with migraine were not significantly different from those of the control cases. Our aim in measuring the hs-CRP levels in migraine was to investigate if there was an endothelial dysfunction with a probable insulin resistance in migraine. The hs-CRP levels are known to be higher in patients with vascular disorders such as coronary artery disease and stroke^{25,26} and are the markers of subclinical inflammation and endothelial dysfunction in these patients. Regarding the insulin resistance and the evidence of association with these vascular disorders, it was not speculation to expect high hs-CRP levels in migraine. Supporting this expectation, two previous studies found high hs-CRP levels during the headache-free period in migraine,^{27,28} but these studies had some serious limitations. The first study²⁷ had a retrospective design and recruited no control cases, only highly selected migraine patients who had complex clinical features. Possible confounding factors that could affect CRP levels such as coexisting disease and classical cardiovascular risk factors were not eliminated. In the study by Vanmolkot and de Hoon,²⁸ confounding factors were eliminated by appropriate statistical analysis, but the high proportion of migraine with aura in the study (unusual in the general migraine population) was remarkable.²⁹ Another interesting point was that migraine patients without aura had higher hs-CRP levels, although association with vascular diseases was demonstrated particularly in migraine patients with aura. In contrast to these studies, we found no difference in hs-CRP levels either in the general migraine group compared with the control group or in the migraine subgroups. Further studies with larger patient and control groups are needed to support the present findings.

The results of the present study showed that migraine patients have insulin resistance but not endothelial dysfunction, at least during the headache-free period. The relatively small sample size, case-control design, and absence of smoking among the vascular risk factors in the study are considered to be the limitations. Whether insulin resistance contributes to the increased vascular risk in migraine patients needs further large prospective studies.

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