

Relationship between Leptin and Migraine

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ABSTRACT

Objective: to assess the relationship and association between levels of leptin in serum and the risk of migraine.

Study Type: cross-sectional study

Study Place and Duration: from 1st January 2021 to 1st January 2022, at Sharif Medical and Dental College, Lahore.

Material and methods: Total 626 individuals were randomly selected aged between 35-75 years, during the period of 2021-2022. After minimum fasting of 8 hours the blood samples are obtained along with calculation of body weight and height are calculated. At 8°C samples were stored and transported to laboratory on dry ice. Leptin and adiponectin levels (serum) are calculated using ELISA (enzyme-linked immunosorbent assay) Using GDA (glucose dehydrogenase assay). The relation between the migraine diagnosis and the leptin levels was calculated by the usage of BLRA (binary logistic regression analysis). < 0.05 (p-value) was taken to be important. With the help of SPSS v.21 the statistical analyses were undertaken.

Results: There were no statistical difference was found in age, gender, BMI, glucose status and adiponectin in both the groups. Lifetime, major depressive disorder was higher in migraine group than controls as 197 (62.9%) and 141 (45.0%), respectively, (p=0.000). Regular intake of antidepressants was also higher in migraine group 53 (16.9%) and lower in controls 35 (11.1%), (p=0.038). Similarly, the average leptin was higher than that of control group as 13.23±2.66ng/mL and 15.07±4.21ng/mL, respectively, (p=0.000). (Table. I).

Conclusion: The results of this study suggest that high levels of leptin are associated with risk of migraine.

Keywords: relationship, association, leptin, increases, migraine, aura, major depressive disorder, headache, serum

INTRODUCTION

In women migraine is three times more common as compared to men and it is a primary headache of disabling nature and neurovascular origin¹, with a domination worldwide of about 1 billion people². It is now quite serious disorder worldwide for it is being ranked 3rd most dominant and 7 main specific cause of debility², deep personal, social and economic impact can be found in migraine affected person. The most common form of migraine is MWOA (migraine without aura) which is characterized with related symptoms by the repeated unilateral, severe headaches prolonging from 4 to 72 hours³. On the other hand in case of MWA (migraine with aura) which lasts for less than an hour and is associated with rescindable focal nervous symptoms³ there is a connection between obesity and migraine is advocated through latest findings⁴. Endothelial function and inflammation mediated by adipokines (adipose tissue secreted cytokines) could be the processes which play main role in pathophysiology of migraine. This could be the relationship between migraine and obesity⁵. Leptin (16kDa peptide hormone), a type of adipokines, can cause anorexia and due to anorexigenic elements escalation in energy resource depletion. More importantly, leptin can be inflammatory cytokine and thus control immune response⁶. A 30-kDa protein, adiponectin can cause and prevent inflammatory responses⁶, and is involved in glucose production and fatty acid oxidation^{6,7}. However, in case of obesity leptin concentration is usually increased⁸ and adiponectin concentration is lowered⁹. Conflicting results were provided by the teams that calculated the concentration of these adipokines in patients with migraine^{5,10-17}. Migraine's is heterogeneity could be one of the reason of conflicting results. The adipokines could be differentially linked to the two subtypes of migraine – Migraine without aura and Migraine with a Though the subtypes of migraine were partially taken in consideration during the last study done to access the relation between migraine and adipokines MDD (major depressive disorder) could also be playing major role in relation between migraine and obesity, as it is usually presented to be related to migraine and obesity. To be sure, there is 2-4 times higher risk of major depressive disorder (MDI) in patients suffering from migraine^{18,19}, and many meta-analyses and reviews has shown depression in related to obesity²⁰⁻²². Major depressive disorder can

act as a mediator of the relationship between migraine and obesity and could also be inclining toward both the conditions (such that obesity can incline towards MDD, which inclines toward migraine, or the contrary). In this study. We intended to find the relationship between migraine and serum leptin. Under consideration of depression status to assess the relationship between leptin and migraine analyses were in synced for MDD for lifetime.

MATERIAL AND METHOD

From the residents of Lahore (city of Pakistan), according to the civil register, 626 individuals were randomly selected aged between 35-75 years, during the period of 2021-2022. After informing all members, their written consent were taken. Through authorized French version of DIHS (Diagnostic Interview for Headache Syndromes), the lifelong dominance of migraine under ICHD-II's (International Classification of Headache Disorders) criteria are assessed. However the prevalence of the MDD was calculated using DIGS (Diagnostic Interview for Genetic Studies) using its French translation. Interviews were reviewed by senior and well experienced psychologist which were taken by well-trained psychologists or psychiatrists. After minimum fasting of 8 hours the blood samples are obtained along with calculation of body weight and height are calculated. At 8°C samples were stored and transported to laboratory on dry ice. Leptin and adiponectin levels (serum) are calculated using ELISA (enzyme-linked immunosorbent assay) Using GDA (glucose dehydrogenase assay).

With the help of Pearson chi-square and Mann-Whitney U tests in individuals with controls and migraine the differences in categorical or continuous variables were calculated respectively. Using Spearman correlation, analysis was done on inter-relation between continuous variables and leptin levels. The relation between the migraine diagnosis and the leptin levels was calculated by the usage of BLRA (binary logistic regression analysis). < 0.05 (p-value) was taken to be important. With the help of SPSS v.21 the statistical analyses were undertaken.

RESULTS

Six hundred and twenty six patients were enrolled in our study. The patients were randomized into two groups as control 313

(50.0%) and migraine 313 (50.0%). There were no statistical difference was found in age, gender, BMI, glucose status and adiponectin in both the groups. Lifetime, major depressive disorder was higher in migraine group than controls as 197 (62.9%) and 141 (45.0%), respectively, ($p=0.000$). Regular intake of antidepressants was also higher in migraine group 53 (16.9%) and lower in controls 35 (11.1%), ($p=0.038$). Similarly, the average leptin was higher than that of control group as 13.23 ± 2.66 ng/mL and 15.07 ± 4.21 ng/mL, respectively, ($p=0.000$). (Table. I).

Table I: Demographic and clinical characteristics of both the groups

Characteristic	Control N (%)	Migraine N (%)	P-value
Age (years)	44.96±7.66	45.85±7.41	0.141
BMI (kg/m ²)	25.28±2.04	25.05±2.24	0.177
Gender			
Male	202 (64.5)	215 (68.7)	0.271
Female	111 (35.5)	98 (31.3)	
Glucose (mmol/L)	5.62±0.55	5.59±0.54	0.754
Lifetime major depressive disorder			
Yes	141 (45.0)	197 (62.9)	0.000
No	172 (55.0)	116 (37.1)	
Regular intake of antidepressants			
Yes	35 (11.1)	53 (16.9)	0.038
No	278 (88.8)	260 (83.1)	
Leptin (ng/mL)	13.23±2.66	15.07±4.21	0.000
Adiponectin (mg/mL)	11.02±3.69	11.05±1.44	0.870

DISCUSSION

The current study showed evaluation of 626 patients of migraine and its association with serum leptin levels. By adjusting for the comprehensive variables which are reported to influence the serum leptin levels such as BMI, demographic variables, fasting blood sugar levels etc., a strong association between diagnosis of migraine and high serum leptin levels was found. Even though known history of major depressive disorder was highly associated with the diagnosis of migraine, the relationship between high serum levels of leptin and diagnosis of migraine was not fully explained by the depression. Literature review doesn't show any consistent results regarding the association of high levels of serum leptin and diagnosis of migraine. Even though our study proves high association between leptin levels in serum and diagnosis of migraine, the contrasting previous studies prove that there might be variance in the subtype of the migraine being studied. For instance, in a previously conducted study they found low levels of serum leptin in patients with history of episodic migraine as compared to normal controls without adjusting for BMI¹¹. In another study however, it was documented that higher crude levels of serum leptin were found in non-obese female patients of migraine as compared to the 40 control female subjects (all migraine patients had symptoms of aura)¹².

In another previously conducted study which assessed the association of migraine subtypes and serum leptin levels suggested negative results in 72 of the patients with migraine off which 59 had probable migraine and there were 850 control subjects¹⁴. Nonetheless, only 23 migraine patients and 12 with the diagnosis of probable migraine had known history of aura i.e. an experience of visual aura previously.

In another study association between migraine without aura and serum leptin levels was observed specifically. These results were consistent with the preclinical study proving that high serum levels of leptin is potentially the causative factor for the increase in the cortex susceptibility to the cortical spreading depression (CSD) i.e. a proposed mechanism which explains the induction of aura before or during migraines. Cortical spreading depression consists of slow and propagating glial and neuronal depolarization wave form which is followed by hyperpolarization³⁰. In an experimental rat model study, chronic high levels of leptin in serum has been found to be associated with increase in CSD²³ and in fat Zucker rats which is a model of obesity with intrinsic high levels of leptin in

serum, there was significant higher frequency of KCl-induced cortical spreading depression as compared to lean rats²⁴.

As far as the underlying mechanism is considered, the higher serum levels of leptin in patients with migraine without aura could also be because of a feedback response to prolonged hypothalamic-pituitary-adrenal axis activation and stress. In lean rat, upon administration of leptin, it was shown that it prevented the induction of corticotrophin-releasing hormone production in paraventricular nucleus and also lowered the corticosteroids levels²⁵. In addition, photo stimulation of orexin neurons in lateral hypothalamus in vivo was also found to induce stress via regulations of corticotrophin releasing hormone. Upon administration of leptin activation of orexin neurons was inhibited via leptin-receptor-b-expressing inhibitory neurons thus suppressing the HPA axis²⁶. A previously conducted meta-analysis found lack of association between high levels of adiponectin and migraine as also reported by previous studies^{13,16}. However these findings are in contrast to with another study which revealed that higher adiponectin levels were observed in migraine suffering patients i.e. $n=68$, in comparison to controls i.e. 65, after ruling out the presence of psychiatric illnesses, allodynia and impact of migraine¹⁵. Similarly another study did find an association between high levels and migraine but only in men aged 50 years or higher, but failed to report any association in women with migraine¹⁴.

There were several limitations in current study and therefore results must be interpreted in light of these limitations. The rate of participation in this study was very low, most probably because of the very comprehensive and detailed psychiatric and physical evaluations. Moreover, this was a cross sectional study and thus the data of this study did not allow to evaluate the temporal sequence between the onset of migraine and the increase in levels of leptin and all the included participants apart from one had a diagnosis of episodic migraine. Thus, evaluation of association of chronic migraine with high levels of leptin/adiponectin could not be done specifically as has been previously observed¹⁰.

CONCLUSION

The results of this study suggest that high levels of leptin are associated with risk of migraine. In future, prospective study which can provide evidence of temporal sequence among the increase in levels of leptin and the onset of the migraine must be conducted in order to confirm the results of the current study and to further evaluate the role of leptin levels in pathogenesis of migraine. Furthermore, subtypes of leptin i.e. high and low molecular weight oligomers should be studied as well in order to disentangle the probable differential effect of these subtypes on the risk of the migraine.

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