Original Article / Özgün Araştırma

Serum Leptin Levels in Acute Ischemic Stroke Patients: Data From a Tertiary Care Institution From Kashmir Valley of Northern India

Akut İskemik İnmeli Hastalarda Serum Leptin Seviyeleri: Kuzey Hindistan'daki Keşmir Vadisinden Üçüncü Basamak Bir Hastaneden Alınan Veriler

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Abstract

Objective: Leptin has drawn the attention of experts for its role in a myriad of conditions including stroke. However, in the absence of credible evidence linking leptin to stroke, its role as a risk factor is still debatable. We aimed to determine the leptin levels and its relationship with other cardiometabolic risk factors in patients with ischemic stroke in our region.

Materials and Methods: It was a hospital based case-control observational study involving 100 patients and 100 age- and sex- matched healthy controls. Leptin levels were measured in both patients and controls in addition to estimation of lipid profile, insulin level and fasting blood glucose. Insulin resistance was calculated using the homeostasis model assessment for insulin resistance model. Carotid intima-media thickness (CIMT) was determined by high-resolution echo-colour Doppler system (GE LOGIQ S8). Neuroimaging was also performed. Student's t-test for continuous variables, chi-square test for categorical variables and Pearson correlation coefficient to determine the correlation of leptin levels with various parameters were used.

Results: The mean leptin levels were significantly higher in patients compared to control group (15.36±5.76 vs. 5.72±1.19 ng/ml; p<0.001). Leptin was found to have positive correlations with atherogenic lipid profile, inflammatory markers i.e, white blood cells and erythrocyte sedimentation rate, fasting plasma glucose and insulin resistance in patients with ischemic stroke whereas there was an inverse correlation between leptin and high density lipoproteins. Similarly leptin was found to have positive association with systolic blood pressure, body mass index and CIMT in patients.

Conclusion: Hyperleptinemia is a common finding in patients with ischemic stroke and is significantly associated with various cardiovascular risk factors known to predispose to ischemic stroke.

Keywords: Leptin, ischemic stroke, obesity, carotid intimal media thickness

Öz

Amaç: Leptin, inme de dahil olmak üzere sayısız koşuldaki rolü nedeniyle uzmanların dikkatini çekmiştir. Bununla birlikte, leptini inme ile ilişkilendiren güvenilir kanıtların yokluğunda, bir risk faktörü olarak rolü hala tartışmalıdır. Bölgemizdeki iskemik inme hastalarında leptin düzeylerini ve diğer kardiyometabolik risk faktörleri ile ilişkisini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu çalışma, 100 hasta ile yaş ve cinsiyet açısından eşleştirilmiş 100 sağlıklı kontrolü içeren hastane temelli gözlemsel bir olgu-kontrol çalışmasıdır. Lipid profili, insülin seviyesi ve açlık kan şekeri ölçümüne ek olarak hem hastalarda hem de kontrollerde leptin seviyeleri ölçüldü. İnsülin direnci insülin direncinin hemostatik modelle değerlendirilmesi modeli kullanılarak hesaplandı. Karotis intima-medya kalınlığı (KİMK), yüksek çözünürlüklü eko-renkli Doppler sistemi (GE LOGIQ S8) ile belirlendi. Nörogörüntülemede yapıldı. Sürekli değişkenler için Student's t-testi, kategorik değişkenler için ki-kare testi ve leptin düzeylerinin çeşitli parametrelerle korelasyonunu belirlemek için Pearson korelasyon katsayısı kullanıldı.

Bulgular: Ortalama leptin düzeyleri hastalarda kontrol grubuna göre anlamlı derecede yüksekti (15,36±5,76 vs. 5,72±1,19 ng/ml; p<0,001). Leptin ile iskemik inmeli hastalarda aterojenik lipid profili, enflamatuvar belirteçler yani beyaz kan hücreleri ve eritrosit sedimentasyon hızı, açlık plazma glukozu ve insülin direnci ile pozitif korelasyonlar bulunurken, leptin ile yüksek yoğunluklu lipoproteinler arasında ters bir korelasyon vardı. Benzer şekilde hastalarda leptinin sistolik kan basıncı, vücut kitle indeksi ve KİMK ile pozitif ilişkisi olduğu bulundu.

Sonuç: Hiperleptinemi iskemik inmeli hastalarda sık görülen bir bulgudur ve iskemik inmeye yatkınlık oluşturduğu bilinen çeşitli kardiyovasküler risk faktörleri ile anlamlı şekilde ilişkilidir.

Anahtar Kelimeler: Leptin, iskemik inme, obezite, karotis intimal medya kalınlığı

Introduction

Stroke is a heterogeneous and multifactorial disease that has emerged as the major global health problem on account of long-term burden on the society in terms of health-care costs and patient care and is the second leading cause of mortality after ischemic heart disease worldwide (1). It is estimated that the incidence of stroke has increased in low and middle income countries contrary to decreasing trend in the developed countries (2). The commonest mode of presentation of stroke is a focal neurological deficit of sudden onset as a result of either ischemia or hemorrhage (3). Of the various types of stroke, ischemic stroke accounts for 60-80% of all strokes and is due to occlusion of cerebral blood vessel which limits the blood supply to the brain and causes cerebral infarction. The combination of traditional risk factors including smoking, hypertension, diabetes mellitus, sedentary lifestyle, overweight or obesity, dyslipidemia and genetic factors are known to be associated with stroke (4). The modifiable risk factors provide the opportunity to introduce therapeutic interventions to mitigate the impact of the disease. However, despite the identification of some of the major risk factors, the complexity of the disease and lack of reliable biomarkers preclude the effective measures to prevent and early detection of stroke.

Adipose tissue stores act as an active endocrine organ, secreting numerous humoral factors including a number of adipokines. Of the numerous adipokines, leptin has drawn the maximum attention of experts for its role in a myriad of conditions including obesity induced hypertension, atherosclerosis, glucose regulation, insulin sensitivity, fatty acid catabolism, vascular and endothelial function. Furthermore, leptin has been invariably linked to the development of coronary heart disease and has lately come under scrutiny for its possible involvement in the underlying pathophysiological mechanism of stroke with studies reporting an association between leptin and stroke warranting further research to explore the relationship between the two.

Although higher leptin levels were associated with increased risk of vascular disease including stroke in some studies (5,6), this relationship was not found in other studies (7,8). In contrast, some of the other studies has reported a protective role of higher leptin levels vis a vis stroke (9,10). However, the role of hyperleptinemia in central sympathetic activation and renal renin angiotensin-aldosterone mechanisms involved in hypertensive response and the development of arterial hypertension can explain its association with stroke. Furthermore, the role of hyperleptinemia on influencing the atherothrombotic process may further explain the relationship between the two.

In the absence of credible evidence linking leptin to stroke, its role as a risk factor for stroke is still debatable. The current study was undertaken to determine the leptin levels and its relationship with various cardiometabolic risk factors including inflammatory markers and carotid intimal thickness in patients with ischemic stroke in our region.

Materials and Methods

The present study was a cross sectional, case-control observational study conducted over a period of 2 years in the Department of General Medicine, GMC Srinagar. The patients who were admitted with ischemic stroke and confirmed on magnetic resonance imaging within 24 hours after admission, and apparently healthy participants without risk factors for stroke were included in the study after taking proper informed consent from patients or their attendants and controls. The study was approved by the Institutional Ethical Committee of Government Medical College (decision no: 144/ETH/GMC).

Study Participants

A total of 100 patients admitted with acute ischemic stroke were included in the study; however, patients with haemorrhagic stroke and/or recurrent stroke were excluded from the study. One hundred apparently healthy age- and sex- matched individuals without risk factors for ischemic stroke were taken as controls.

Data Collection

All the enrolled participants were evaluated through general information and social history including their smoking habits and physical activity after obtaining written informed consent. Height, weight and waist circumference were measured and body mass index (BMI) was calculated for each participant.

Sample Collection and Laboratory Testing

Blood samples from all participants were collected within the first 24 hours of admission, and serum was separated and aliquots were frozen at -80 °C until analysis. Serum levels of high density lipoproteins (HDL), low density lipoproteins (LDL), triglycerides (TG), total cholesterol, fasting plasma glucose and serum leptin levels were assessed in both patients and controls. The biochemical analyses such as measurement of total cholesterol and TG concentrations were performed with a Technicon DAX-72 auto analyzer (Technicon, Bayer Corporation, Tarrytown, New York) in the Central Biochemistry Laboratory, Government Medical College, Srinagar. HDL cholesterol concentrations were measured using RAXT auto analyzer after phosphotungstic acid and magnesium chloride precipitation. LDL cholesterol was calculated by using Friedwald formula: LDL=Total cholesterol - (TG/5) - HDL. LDL-cholesterol was not calculated and reported as a missing value if the TG level was >400 mg/dl. Fasting plasma glucose was measured using a modified hexokinase enzymatic method (Roche Cobas Mira). Leptin levels were determined by a commercially available quantitative enzyme- linked immunosorbent assay kit (Abcam, China). The intra and inter-assay coefficients of variation (CV) were 5.2-8.3% and 5.8-9.2%, respectively.

Insulin resistance (IR) was estimated by the homeostasis model assessment using the homeostasis model assessment for IR (HOMA-IR). Carotid Doppler studies were performed and carotid intimal thickness was assessed in patients with ischemic stroke. The measurement of carotid intima-medial thickness was performed by using a high-resolution echo-colour Doppler system (LOGIQ S8; GE Healthcare, Chalfont St Giles, United Kingdom). The CV of the measurements were less than 3%. All scans were read by an independent physician, blinded to the clinical status of the subjects.

Statistical Analysis

The data were entered in a Microsoft Excel and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were summarized as percentages. Student's independent t-test was applied for comparing continuous variables. Comparison of categorical variables was carried out with

chi-square test or Fisher's Exact test, whichever was appropriate. Pearson correlation coefficient was employed to determine the correlation of leptin levels with various parameters. Two-sided p value ≤ 0.05 was considered statistically significant.

Results

A total of 200 participants were enrolled in this study comprising of 100 patients diagnosed as having ischemic stroke and 100 healthy participants in the control group. The mean ages of patients and controls were comparable (64±10 vs. 66±10 years; p=0.379). Of the patient group 47% were male and 53% were female. Of the control group 62% were male and 38% were female (p=0.083).

The mean (±SD) BMI was significantly higher in the patient group compared to the control group (27.9±3.6 vs. 23.2±2.9 kg/m2; p<0.001). Majority (49%) of the patients were overweight (25-29.9 kg/m^2) however, 30% and 21% were obese (>30 kg/m^2) and of normal weight (<18.5 kg/m^2), respectively. However, in the control group, majority (78%) of participants had normal BMI (<18.5 kg/m^2) compared to 16% and 2% classified as overweight and obese, respectively. The details of the biochemical profile in these subjects are given in Table 1.

The mean leptin levels were significantly higher in patients compared to control group (15.36±5.76 vs. 5.72±1.19 ng/ml; p<0.001). Gender wise comparison of leptin levels (ng/ml) revealed significantly (p<0.001) higher leptin levels in female patients (20.36±2.12 ng/ml) compared to male patients (9.72±2.18 ng/ml).

Patients with ischemic stroke had significantly higher mean TG (149.05+67.62 vs. 108.04+29.88 mg/dl; p<0.001), total cholesterol (207.05+76.37 vs. 130.08+26.43 mg/dl; p<0.001), LDL cholesterol (91.14+27.16 vs. 78.82+20.28 mg/dl; p=0.005) and fasting plasma glucose levels (124.61±52.86 vs. 93.96±9.12 mg/dl; p<0.001), and lower HDL cholesterol concentrations (42.78±8.21 vs. 50.02±7.29 mg/dl; p<0.001) compared to controls.

Leptin was found to have positive correlations with TG, fasting blood glucose, erythrocyte sedimentation rate (ESR) and HOMA-IR in both male and female patients whereas there was an inverse correlation between leptin and HDL cholesterol levels in both male and female patients (Table 2). Similarly, leptin was found to have positive association with systolic blood pressure (SBP), BMI and CIMT in both male and female patients.

Multivariate Analysis

There was a significant difference between subjects with and without stroke when considered jointly on the variables BMI and serum leptin levels [Wilk's Lambda: 0.480, F (2.147)=79.51, p<0.001, partial η2: 0.52]. A separate ANOVA was conducted for each dependent variable (BMI and Leptin), with each ANOVA evaluated at an alpha level of 0.025. There was a significant difference between patients and controls in terms of serum leptin levels] with stroke patients having higher leptin levels than controls [F (1.148)=137.3, p<0.001, partial η2: 0.48. There was also a significant difference between patients and controls in terms of BMI with stroke patients having higher BMI than controls [F (1.148)=63.90, p<0.001, partial η2: 0.30]. However, when adjusted for BMI, the difference in serum leptin levels was significantly higher in patients with normal BMI (<25)

(14.46±5.51 vs. 5.62±1.16; p<0.001) as well as in overweight or obese (BMI ≥25) subjects (15.60±5.82 vs. 6.19±1.26; p<0.001).

Discussion

The ubiquitous presence of leptin, a product of adipose tissue and its receptors in various tissues and studies reporting its pleiotropic effects on numerous biological functions including functions of the central and peripheral nervous systems (11,12) has generated a lot of interest to unravel its association with different disease processes including its' possible involvement in the underlying pathophysiological mechanism of stroke. The higher circulating leptin levels in patients with stroke have been associated with increased prevalence of various vascular risk factors including hypertension, IR, diabetes and dyslipidemia (13). Leptin has been found to have proinflammatory effects including induction of endothelial dysfunction, oxidative stress, enhancing platelet aggregation and besides promoting vascular calcification, smooth muscle cell proliferation and arterial stiffness. It has further been associated with development and vulnerability of atherosclerotic plaques (14,15) and is known to mediate proatherogenic response (16). Studies have revealed that leptin-induced local inflammation in vascular endothelium is likely to be involved in the development of advanced atherosclerotic lesions and subsequent vascular events (17). Leptin has now been understood to have a role in atherosclerosis hence; determining the plasma or serum levels of leptin may serve as reliable prognostic biomarker for inflammation and atherosclerosis in stroke.

The present study was designed to study the relationship between leptin levels and ischemic stroke in the background of conflicting results from earlier studies vis a vis the relationship between the two. Our study demonstrated that patients with ischemic stroke had significantly higher levels of leptin compared to healthy control population; furthermore levels were higher in female patients compared to male patients. These observations are in agreement with results from an earlier study (18). The presence of higher levels of leptin in females compared to males has been suggested to mediate, in part, by effects of sex steroids in addition to the possible influence of higher adiposity seen among the females. The demonstration of significant hyperleptinemia in our patient cohort and its association with an increased prevalence of various cardiometabolic risk factors which are known to predispose to higher risk of ischemic stroke reinforce the observation of possible link between the two.

One of the observations of the study was the significantly higher levels of inflammatory markers like ESR and white blood cell in the patient cohort and further it was observed that these markers were positively associated with hyperleptinemia seen in patients with ischemic stroke. The fact that inflammation being a hallmark of ischemic stroke is presumed to be mediated by release of cytokines, particularly leptin, and demonstration of association of leptin with the markers of inflammation in our study supports the possible role of leptin in inflammatory response seen in patients with ischemic stroke.

There were increased levels of atherogenic lipid profile comprising of elevated TG, LDL and total cholesterol and reduced levels of HDL cholesterol in the patients with ischemic stroke in addition to having higher levels of markers of inflammation such as leukocyte count, and ESR. Our study further revealed that leptin had a positive correlation with proatherogenic lipid

Table 1. Comparative analysis of clinical and biochemical parameters in patients and controls			
Variables	Patients (n=100) 95% CI	Controls (n=100) 95% CI	Total (n=200) 95% CI	Significance
BMI (kg/m²)	27.93±3.58 (27.22-28.64)	23.28±2.86 (22.46-24.09)	26.38±4.0 (25.73-27.03)	0.000*
Age (years)	64.43±9.71 (62.50-66.35)	65.94±10.18 (63.04-68.83)	64.93±9.86 (63.34-66.52)	0.379
Waist hip ratio	0.86±0.04 (0.85-0.87)	0.87±0.02 (0.87-0.88)	0.87±0.03 (0.86-0.87)	0.188
TLC (mg/dl)	8.07±3.99 (7.28-8.86)	5.34 ±9.12 (5.08-5.60)	7.17 ±3.54 (6.59-7.73)	0.000*
ESR	25.03±14.89	7.03±6.03	16.08±12.03	0.000*
BSF (mg/dl)	125±53 (114-135)	94±9 (91-96)	114±46 (107-121)	0.000*
Urea (mg/dl)	47.58±19.81 (44-51)	26.14±7.94 (24-28)	40.43±19.60 (37-43)	0.000*
Creatinine (mg/dl)	1.16±0.53 (1.05-1.27)	0.89±0.14 (0.85-0.94)	1.07±0.46 (1.00-1.15)	0.001*
HDL (mg/dl)	42.78±8.2 (41-44)	50.02±7.29 (48-52)	45.19±8.60 (44-46)	0.000*
LDL (mg/dl)	91.14±27.15 (86-96)	78.82±20.28 (73-84)	87.03±25.67 (83-91)	0.005*
TG (mg/dl)	149.05±67.6 (136-162)	108.04±29.8 (99-116)	135.38±60.89 (125-145)	0.000*
Cholesterol (mg/dl)	207.05±76.37 (192-222)	130.08±26.43 (122-137)	181.39±73.69 (169-193)	0.000*
Leptin (ng/ml)	15.36±5.75 (14.22-16.50)	5.72±1.18 (5.38-6.06)	12.14±6.57 (11.09-13.21)	0.000*

*Significant, BMI: Body mass index, HDL: High-density cholesterol, LDL: Low-density cholesterol, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, TG: Triglycerides, CI: Confidence interval, TLC: Total leucocyte count, BSF: Blood sugar fasting

Table 2. Correlation analysis of leptin levels with risk factors				
Variables	Male		Female	
	Pearson correlation	Significance	Pearson correlation	Significance
BMI	0.714	0.000	0.681	0.000*
HDL	-0.437	0.002	-0.397	0.003*
TG	0.541	0.000	0.459	0.000*
FPG	0.289	0.038	0.312	0.024*
HOMA-IR	0.591	0.000	0.508	0.000*
ESR	0.415	0.008	0.391	0.005*
IMT	0.563	0.000	0.475	0.000*
SBP	0.283	0.041	0.319	0.017*

*Significant, BMI: Body mass index, HDL: High-density cholesterol, ESR: Erythrocyte sedimentation rate, TG: Triglycerides, IMT: Intima media thickness, SBP: Systolic blood pressure, FPG: Fasting blood glucose, HOMA-IR: Homeostasis model assessment for insulin resistance model

profile including TG, LDL, cholesterol, and inflammatory markers like ESR whereas there was an inverse correlation between leptin and HDL levels in both male and female patients with ischemic stroke. Leptin levels also had a positive association with fasting blood glucose and HOMA-IR, a marker of IR. These findings are in accordance with the results from earlier studies (19,20). The positive correlation between leptin and atherogenic dyslipidemia and markers of inflammation support the causal relationship

between hyperleptinemia and atherosclerosis possibly via proinflammatory response mediated by leptin, thus increasing the predisposition to possibility of higher risk of ischemic stroke.

Carotid artery intima-media has been recognized as an independent non-invasive diagnostic tool for the identification of atherosclerosis and it has been found that leptin has been found to correlate with markers of subclinical atherosclerosis such as CIMT and coronary artery calcifications in a number of studies. Studies have revealed that leptin-induced local inflammation in vascular endothelium is likely to be involved in the development of advanced atherosclerotic lesions (17). An earlier study investigating the relationship between leptin and CIMT concluded that leptin was independently associated with CIMT; however, the association was dependent on obesity (21). Similarly a study from South India demonstrated the presence of high serum leptin levels and its association with CIMT in acute ischemic stroke (19). In our study leptin was found to be independently associated with CIMT. This relation was found in both male and female patients independently of age and other vascular risks. However, relationship between leptin and markers of preclinical atherosclerosis is still controversial with few studies demonstrating absence of a relationship between leptin and CIMT (22,23).

Leptin is currently considered to play a vital role in the development of hypertension and is involved in the promotion of increased arterial pressure via multiple physiological processes like sympathetic nervous system activation, activation of the renin-angiotensin system, IR and hyperinsulinemia (24). Hypertension is one of the strongest risk factors for stroke in general population and risk of stroke increases linearly when blood pressure level rises. In the current study, we observed a significantly positive correlation of leptin levels with SBP in both male and female patients with ischemic stroke. This was in accordance with the results from an earlier study in which the high leptin levels were associated with ischemic stroke both in men [Odds ratio (OR): 4.89; 95% confidence interval (CI): 1.89-12.62] and in women (OR: 4.10; 95% CI: 1.45-11.62) (6).

Leptin levels have been shown to directly associate with the quantity of adipose tissue. Thus, increased BMI or waist circumference, is associated with the higher levels of serum leptin (25). Our study demonstrated that leptin levels strongly correlated with BMI in both male and female patients with ischemic stroke with females having higher BMI and leptin compared to males. These results are in agreement with the observations from earlier studies (18,20).The higher level of leptin with increase in BMI, a measure of obesity, suggests the possibility of leptin resistance which demands further investigation including a genetic one, in order to establish the genes associated with leptin resistance.

The presence of higher levels of leptin in patients with stroke and its significant association with a number of important risk factors known to predispose to stroke including atherogenic lipids, proinflammatory markers, markers of IR and CIMT in patients with ischemic stroke gives credence to the observation that it may have a possible involvement in the underlying pathophysiological mechanism of stroke. The study results provide rationale for large well designed studies evaluating in depth clinical relationship between leptin and ischemic stroke.

Study Limitations

1. Leptin levels were determined in a single measurement, which might not capture a diurnal variation in leptin levels.

2. Observational nature of the study prevented the establishment of causal relationship between serum leptin levels and ischemic stroke.

Conclusion

This study demonstrated the presence of significantly higher levels of leptin in patients with ischemic stroke, independent of BMI, compared to age- and sex- matched healthy controls. Higher leptin levels were observed in female patients compared to males. Furthermore, there was a positive association between leptin and various traditional risk factors associated with stroke including hypertension, overweight or obesity, atherogenic lipids, inflammatory markers, and CIMT in patients indicating possible involvement of leptin in the underlying pathophysiological mechanism culminating in stroke.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethical Committee of Government Medical College (decision no: 144/ETH/GMC).

Informed Consent: Obtained written informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.H.B., J.A.B., P.A.S., Design: M.H.B., J.A.B., P.A.S., Data Collection or Processing: N.K., Analysis or Interpretation: M.H.B., N.K., J.A.B., P.A.S., Literature Search: M.H.B., N.K., J.A.B., Writing: M.H.B., J.A.B.

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References

1. Murray CJL, Lopez AD. Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions. In: Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions. 1996. p. 906.

2. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355-369.

3. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25-e146.

4. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circ Res 2017;120:472-495.

5. Söderberg S, Stegmayr B, Stenlund H, et al. Leptin, but not adiponectin, predicts stroke in males. J Intern Med 2004;256:128-136.

6. Söderberg S, Stegmayr B, Ahlbeck-Glader C, et al. High leptin levels are associated with stroke. Cerebrovasc Dis 2003;15:63-69.

7. Rajpathak SN, Kaplan RC, Wassertheil-Smoller S, et al. Resistin, but not adiponectin and leptin, is associated with the risk of ischemic stroke among postmenopausal women: results from the Women's Health Initiative. Stroke 2011;42:1813-1820.

8. Stott DJ, Welsh P, Rumley A, et al. Adipocytokines and risk of stroke in older people: a nested case-control study. Int J Epidemiol 2009;38:253-261.

9. Ku IA, Farzaneh-Far R, Vittinghoff E, et al. Association of low leptin with cardiovascular events and mortality in patients with stable coronary artery disease: the Heart and Soul Study. Atherosclerosis 2011;217:503-508.

10. Scholze A, Rattensperger D, Zidek W, Tepel M. Low serum leptin predicts mortality in patients with chronic kidney disease stage 5. Obesity (Silver Spring) 2007;15:1617-1622.

11. Münzberg H, Flier JS, Bjørbaek C. Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. Endocrinology 2004;145:4880-4889.

12. Correia ML, Haynes WG, Rahmouni K, et al. The concept of selective leptin resistance: evidence from agouti yellow obese mice. Diabetes 2002;51:439-442.

13. Saber H, Himali JJ, Shoamanesh A, et al. Serum leptin levels and the risk of stroke: the framingham study. Stroke 2015;46:2881-2885.

14. Pérez-Pérez A, Vilariño-García T, Fernández-Riejos P, et al. Role of leptin as a link between metabolism and the immune system. Cytokine Growth Factor Rev 2017;35:71-84.

15. Beltowski J. Leptin and atherosclerosis. Atherosclerosis 2006;189:47-60.

16. Konstantinides S, Schäfer K, Koschnick S, Loskutoff DJ. Leptin-dependent platelet aggregation and arterial thrombosis suggests a mechanism for atherothrombotic disease in obesity. J Clin Invest 2001;108:1533-1540.

17. Bouloumie A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. FASEB J 1999;13:1231-1238.

18. García-Sánchez JL, Jiménez-Saab NG, Guerrero-González J, et al. Hiperleptinemia asociada a evento vascular cerebral isquémico (EVCi) [Hyperleptinemia associated with ischemic stroke]. Gac Med Mex 2016;152:78-86.

19. Menon B, Krishnan R. Role of leptin in acute ischemic stroke. J Neurosci Rural Pract 2018;9:376-380.

20. Bidulescu A, Liu J, Chen Z, et al. Associations of adiponectin and leptin with incident coronary heart disease and ischemic stroke in african americans: the jackson heart study. Front Public Health 2013;1:16.

21. Ciccone M, Vettor R, Pannacciulli N, et al. Plasma leptin is independently associated with the intima-media thickness of the common carotid artery. Int J Obes Relat Metab Disord 2001;25:805-810.

22. Oflaz H, Ozbey N, Mantar F, et al. Determination of endothelial function and early atherosclerotic changes in healthy obese women. Diabetes Nutr Metab 2003;16:176-181.

23. van den Beld AW, Bots ML, Janssen JA, et al. Endogenous hormones and carotid atherosclerosis in elderly men. Am J Epidemiol 2003;157:25-31.

24. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res 2015;116:991-1006.

25. Li WC, Hsiao KY, Chen IC, et al. Serum leptin is associated with cardiometabolic risk and predicts metabolic syndrome in Taiwanese adults. Cardiovasc Diabetol 2011;10:36.