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REVIEW ARTICLE

Hyperleptinemia associated with ischemic stroke

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Abstract

Introduction: *The major risk factors for stroke are obesity, diabetes mellitus, systemic arterial hypertension (SAH) and dyslipidemia. In 1994 leptin was identifies as adipokine produced by adipose tissue. Its main action is the regulation of energy balance. Currently, hyperleptinemia is associated with cardiovascular disease.* ***Objective:*** *To determine the association between serum leptin and stroke in patients with SAH.* ***Methods:*** *We determined serum leptin in subjects with stroke and SAH, and compared this with patients with SAH without stroke. We calculated Student t, c^2, and odds ratio (OR) for quantitative and qualitative variables.* ***Results:*** *60 subjects were recruited, 30 subjects per group. Considering a value > 3.93 ng/ml as hyperleptinemia, it also was found a t = 2.8 (p = 0.007), and c^2 with one degree of freedom of 10.82 (p = 0.001), obtaining an OR of 3.05 for the development of stroke in the presence of elevated leptin (95% CI: 0.9-9.6; p = 0.05).* ***Conclusions:*** *Hyperleptinemia is more common in patients with stroke than in those without this condition. But the question remains whether hyperleptinemia is a stroke risk factor or protective factor.* (Gac Med Mex. 2016;152:68-75)

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Introduction

Stroke encompasses a series of clinical disorders, most of the times with sudden manifestations; the main cause of stroke is lack or insufficient supply of blood to the brain[1]. Strokes are classified as ischemic and hemorrhagic.

In the USA, stroke causes for approximately 200,000 persons to die every year and is one of the main causes of disability[2]. Stroke represents the third cause of death in industrialized countries. Its worldwide incidence is 1.5-4 cases for each 1,000 inhabitants, and its prevalence, 8-20 cases for each 1,000 inhabitants.

This condition involves substantial financial expenses. Approximately 20% of survivors are estimated to require special care during the three months following the event and almost 30% are left with permanent serious disability.

In the year 2003, in Mexico, stroke was the sixth cause of death in men and the fourth in women. In the

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period from March to April 2008, the epidemiology of stroke in hospitals of the Distrito Federal was reported, and its prevalence was 11.15%. Cabrera et al. found that the main risk factors for stroke were systemic arterial hypertension (SAH) (56.65%), type 2 diabetes mellitus (DM), atrial fibrillation (15.24%) and smoking (4.33%).

Obesity is the main risk factor for the development of type 2 DM, cardiovascular diseases, high blood pressure, dyslipidemias, osteoarticular conditions and certain types of cancer[3].

In 2006, Goldstein et al., in a guideline for the prevention of ischemic stroke, reported different risk factors, which they classified as modifiable or non-modifiable. Modifiable factors include cardiovascular conditions. One of them, coronary heart disease, increases relative risk (RR) for ischemic stroke up to 1.73 among men and 1.55 among women, with a 95% confidence interval (CI) of 1.68-1.78 and 1.17-2.07, respectively. SAH increases RR depending on age, with a 4.0 RR being found in 50-year-old patients, which is decreased down to 1.0 in 90-year-old patients. This SAH-attributable risk decreases up to 38% with treatment. DM increases the RR for stroke from 1.8 to 6.0, and smoking increases RR up to 1.8. In occasions, dyslipidemia is associated with SAH and DM, and increases up to 2.0 the RR for ischemic stroke among men and women younger than 55 years. On the other hand, obesity increases the RR for ischemic stroke from 1.73 to 2.37[4].

Since obesity is the main risk factor for metabolic syndrome, multiple studies have been conducted to determine the etiology of this disease. So far, multiple biologic substances have been found, such as adipose tissue-released cytokines, which are subsumed under the term adipokines and are involved in energy homeostasis. Leptin is one of the main cytokines involved in the body's energy balance[15].

Body weight is controlled by both the endocrine and neurological components, which ultimately influence on the energy intake and expenditure effects.

A major regulator of these adaptive responses is leptin, a hormone that is synthesized in adipocytes[2]. Harvey et al., in 1988, detected this circulating factor that regulated the magnitude of body fat deposits. Coleman, in 1978, suggested that OB/OB obese mice lacked this factor, but also resistance to its effect. In 1994, Friedman cloned the *OB* gene in the mouse and its homologue in the human, and identified the protein product, which was termed leptin[6]. This hormone acts through brain circuits, predominantly in the hypothalamus, to influence on appetite, on energy expenditure and on the neuroendocrine function, regulating the energy balance[2]. Its name comes from the Greek *leptos*, which means "thin"[2,6].

The human leptin gene is found in chromosome 7q31; its DNA has more than 15,000 base pairs and three exons. Leptin is mainly produced in white adipose tissue and it is found at very small concentrations in brown adipose tissue. Its metabolic effects are mediated by interaction with specific receptors located at the central nervous system and peripheral nerves.

The receptor transmits the leptin signal through the Janus kinase 2 pathway, transducing three signals and activating their transcription (STATS 3, 5 and 6), a STAT subset known as fat-STATS.

One of the effector molecules resulting from this stimulus is the hypothalamic neuropeptide Y, a potent food-intake stimulator, the synthesis of which is inhibited by leptin. Some leptin receptor isoforms are expressed in peripheral tissues, and their deep biology responds to leptin in hepatocyte, adipocyte, hematipoietic cell and pancreatic islets' cultures, supporting a peripheral action. Leptin directly inhibits intracellular lipid concentrations by reducing the synthesis of fatty acids and triglycerides, and concomitantly increases lipid oxidation. Levels of leptin have been shown to directly associate with the quantity of adipose tissue[7]. The higher the body mass index (BMI) or waist circumference, the higher the levels of serum leptin[8].

In the first studies conducted in Latin American (Uruguayan) population, a correlation of 0.57 ($p = 0.0001$) was found between BMI and leptin levels. Higher levels were predominantly found in women for any BMI value. Gender is one of the significant variables in the determination of leptin serum levels ($p < 0.05$)[6]. It has also been implicated with the macrophage function and with hematopoiesis[5].

In addition to being synthesized in the adipose tissue, leptin is also produced in other tissues, such as primary and secondary lymphoid organs, bone marrow, mammary gland epithelium, ovaries, skeletal muscle and placenta, just to mention some.

Leptin exerts its effects by binding to and activating leptin-specific receptors; these receptors, in addition to the hypothalamus, have been found in the kidneys, lungs, lymphocytes, adipose tissue, the prostate, ovaries, the liver, the short bowel and the heart[6,7].

Several actions of leptin are currently known at the cardiovascular level: on blood pressure, sympathetic activation, insulin resistance, platelet aggregation, arterial thrombosis, angiogenesis and vascular inflammatory

responses, suggesting that leptin can play an important role in the development of cardiovascular diseases[9].

Leptin increases sympathetic activity on the kidneys and adrenal glands, indicating an obesity-associated sympathetic nervous system activity increase, partially caused by the effects of leptin. Leptin is selective, thus preserving renal sympathetic effects, in spite of the loss of its metabolic actions.

The wide distribution of leptin receptors on vascular cells suggests that leptin can play an important role in vascular physiology.

Leptin has angiogenic activity, which up-regulates the production of endothelin 1 in umbilical vein cells and promotes vascular calcification and smooth muscle cell proliferation and migration. Leptin is an independent risk factor for coronary events. The kidney has abundant presence of a leptin receptor truncated isoform. The direct or indirect effects of leptin on the kidney include an activation of transforming growth factor b, which contributes to glomerulosclerosis and proteinuria[10].

In addition, this hormone is involved with immunomodulating activities and, hence, adipokines have been proposed to be able to provide a relationship between the immune response and atherosclerosis[11].

Sierra-Johnson et al., in 2007, assessed the association between leptin levels and individual cardiovascular risk factors, and associated leptin levels with individual risk scores. For the male gender, an odds ratio (OR) of 2.41 was obtained with leptin determinations higher than 7.5 ng/ml, and for the female gender, an OR of 4.26 was found with serum leptin figures higher than 23.5 ng/ml, with a p-value < 0.01[9]. For metabolic syndrome, an OR of 6.14 associated with leptin higher concentrations has been found in the male gender, with a p-value < 0.001 (95% CI: 3.70-10.19), whereas in women, an OR of 2.94 was found (95% CI: 1.36-6.37), both adjusted for age[8].

The Study Heart Jackson, a stroke population-based study in an African American cohort, found that high serum leptin levels were significantly associated with ischemic stroke in women, with a p-value of 0.001 (OR: 1.68; 95% CI: 1.28-2.38)[12].

In Mexico, the relationship between the levels of leptin and cardiometabolic risk factors has been analyzed, but there are no statistics so far on the existing relationship between leptin levels and cardiovascular conditions such as stroke. In studies carried out by the Universidad Nacional Autónoma de México (UNAM – *National Autonomous University of Mexico*), serum leptin levels have been observed to be higher in diabetic elderly patients than in healthy subjects, but the results have not demonstrated a statistically significant difference[13]. Another study found statistical significance in the correlation between the serum leptin levels and insulin resistance, with an r-value of 0.575 and a p-value < 0.001[14].

In view of all this, studies so far conducted suggest a significant association of leptin levels with cardiovascular diseases.

Presentation of the problem

Given the findings that currently have been observed in recent studies, it is of interest to assess this hormone as a risk factor for multiple metabolic and cardiovascular conditions, such as ischemic stroke, a condition with high incidence and prevalence in our Latin population. Due to the increased incidence of ischemic stroke, it is highly important to determine if serum leptin at high concentrations represents a risk factor for ischemic stroke; subsequently, it could become a therapeutic target for the prevention of this condition, as well as for the management of dyslipidemia and other cardiovascular risk factors.

Objective

The objective of the study was to determine the association between leptin serum levels and ischemic stroke, as well as with other cardiometabolic risk factors, in patients with SAH.

Material and methods

A descriptive, observational, case-control study was designed. It was carried out from August 2013 to April 2014 at the Ticomán General Hospital of the Distrito Federal Ministry of Health. Male and female patients older than 18 years of age with a SAH diagnosis presenting with ischemic-type stroke were included. A group of patients older than 18 years of age, diagnosed with SAH and without any kind of stroke were used as controls. Patients with hemorrhagic stroke, history of valvular heart disease on treatment, history of coagulation disorders, hospitalization with suspected coagulopathy secondary to other underlying disease, history of stroke and/or acute myocardial infarction (AIM) within the previous 3 months, with previous diagnosis of carotid angiopathy or previous endarterectomy surgery were not included. Patients whose cranial control plain computed tomography (CT)-scan at

72 h indicated absence of stroke, those with no clinical data consistent with pyramidal or lacunar syndrome and patients with transient ischemic attack were withdrawn from the study.

Owing to the universe of patients to obtain the sample, and to satisfy the characteristics required to participate in the study, a consecutive case series non-probabilistic-type sampling was carried out.

A 60-patient sample was obtained, with 2 paired groups: there were 30 patients with ischemic stroke plus SAH and 30 with SAH and no ischemic stroke (controls).

Patients were recruited at the hospitalization area of the Distrito Federal Department Ticomán General Hospital of the Ministry of Health, and had to have been diagnosed with apoplectic syndrome, with plain or contrasted CT brain-scan demonstrating the presence of ischemic stroke, either in the initial or the control CT-scan at 48-72 h, corroborated by an imaging-specialized physician. Patients who met the inclusion criteria were included in the control group.

After admission, both cases and controls were taken a blood sample after an 8-h fasting. The sample was centrifuged to obtain the serum, which was extracted by decantation and kept frozen at –30 °C. At admission, the serum lipid profile was determined, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides, with an 8-h fasting.

The healthcare staff applied a questionnaire that included past medical history, especially chronic degenerative and metabolic conditions. A value of fasting glucose higher than or equal to 126 mg/dl, previous diagnosis of DM by a physician or being on treatment for this condition were regarded as a DM diagnosis. Systolic blood pressure values ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg were regarded as a SAH diagnosis for patients younger than 60 years, and systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 90 mmHg for subjects older than 60 years, according to the new definitions of the Joint National Committee, version 8, the arterial hypertension guidelines (JNC 8), as well as a previous history of SAH diagnosis or anti-hypertensive drugs consumption. Dyslipidemia was defined as the presence of hypertriglyceridemia with values higher than 150 mg/dl, as well as hypercholesterolemia with total cholesterol > 200 mg/dl, or LDL-C values higher than 100 mg/dl or HDL-C < 50 mg/dl in women and < 40 mg/dl in men[15].

Weight and height of the patients were obtained as anthropometric measurements and, according to the Mexican Official Standard (NOM-008-SSA3-2010), a value of 25.0 to 29.9 kg/m^2 was considered as overweight, and a value higher than 30 kg/m^2 as obesity.

For the determination of leptin serum levels, the serum sample was thawed and serum leptin was determined using the MILLPLEX MAG Human Adipokine Magnetic Bead panel 2 kit, which used fluorescence-labelled microsphere beads. An immunoassay procedure was carried out, and then the sample was processed in a Luminex 200 equipment by means of the xPONENT software at the biomedicine laboratory of the Center of Research and Advanced Studies (CINVESTAV – *Centro de Investigación y Estudios Avanzados*).

Descriptive statistics were used with central tendency and dispersion measures for the description of baseline demographics and study variables. Student's t-test was used to assess the difference of both means. The chi-square test was used for qualitative variables, comparing the presence of hyperleptinemia between patients with SAH and stroke and patients with SAH an no stroke.

To establish the OR of leptin with the different variables, 2 x 2 tables were created and the 95% CI was established.

All calculations were manually performed using the statistical pack SPSS, version 19. A p-value < 0.05 was considered to be statistically significant.

The sample size for this study was calculated based on the attainment of a p-value of 0.005 with a 95% CI and the stroke prevalence in our country reported in the literature. By using formulas for the difference of proportions, a number (n) of 30 patients per group was obtained.

Results

A total of 60 hypertensive subjects were studied, which were divided in two groups of 30. The data collected in the performed survey are found in the corresponding demographics table (Table 1).

Following the t-test, a value < 3.93 ng/ml was considered to be hyperleptinemia. A t-value of 2.80 was obtained, with a p-value of 0.007 (95% CI: 1.09-6.7). Based on this, 13 (43.3%) ischemic stroke patients were found to have leptin levels higher than 3.93 ng/ml, whereas among the controls there were only 6 (20%) subjects with hyperleptinemia. A χ^2 value with 1 χ^2 degree of 10.82 was obtained, with a statistically significant p-value (p = 0.001). An OR of 3.05 was calculated, with a p-value of 0.05 (95% CI: 0.9-9.6).

Table 1. Subjects baseline characteristics found in cases and controls*

Characteristic	Cases (stroke) (n = 30)	Controls (n = 30)	p < 0.05
Questionnaire-based			
Age (years)	70.6 (13.8)	66.5 (13.9)	
History of DM, n (%)	11 (36.6%)	14 (46.6%)	
Men, n (%)	14 (46.6%)	18 (60%)	
Women, n (%)	16 (53.3%)	12 (40%)	
Anthropometrics			
BMI (kg/m^2)	26.7 (3.56)	24.4 (2.92)	
Blood tests			
Leptin (ng/ml)	6.33 (7.06)	2.4 (3.02)	0.007†
Triglycerides (mg/dl)‡	112 (42)	169 (94)	
Total cholesterol (mg/dl)‡	141 (39.5)	143 (38.1)	
HDL-C (mg/dl)‡	39.7 (9.3)	36.5 (10.9)	
LDL-C (mg/dl)‡	81.2 (33)	78.9 (29)	

*Variable means are presented with the corresponding standard deviation, as well as the number of subjects in the cases and controls groups with the corresponding percentage.
†For leptin, the p-value obtained after the t calculation is mentioned. Means difference is 3.93 mg/ml, with a t = 2.8.
‡For lipids, the five different variables were only measured in 15 subjects with stroke and in 21 of all controls, since lipid profile was not available for all 60 subjects.

Higher serum leptin concentrations were found in the control group (Fig. 1). Women had higher leptin concentrations than men. However, when the group of women was separately analyzed, with regard to leptin levels, an OR = 2.57 was calculated, with a p-value of 0.23 (95% CI: 0.5-12.16) (Fig. 2 and 3).

With regard to obesity and hyperleptinemia, 36 subjects (60%) with BMI ≥ 25 kg/m^2 were found among cases and controls: 23 (38.3%) in the stroke group and 13 (21.6%) in the control group. There were no obese subjects without hyperleptinemia (Fig. 4).

Of the 60 studied patients, 25 had a DM diagnosis (41.6%); 6 patients with DM had hyperleptinemia and 19 diabetic subjects had serum leptin values lower than 3.93 ng/ml. The OR was calculated for diabetic subjects in relation with the leptin levels, and an OR of 0.53 was found, with a p-value of 0.28 (95% CI: 0.16-1.68) (Fig. 5).

On the other hand, the lipid profile was only measured in 15 subjects of the stroke and 21 of the control groups, with 40% (6 subjects) of stroke and hyperleptinemia subjects being found to have low levels of

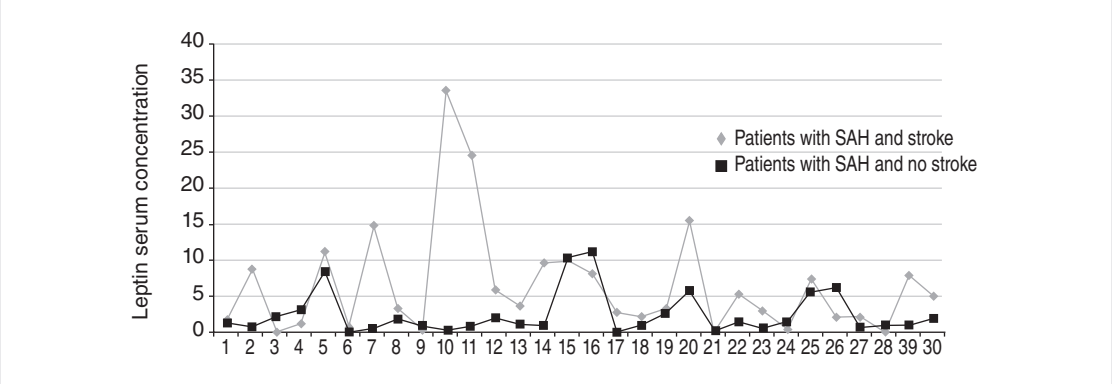

Figure 1. *Leptin serum concentrations in patients with and without stroke.*

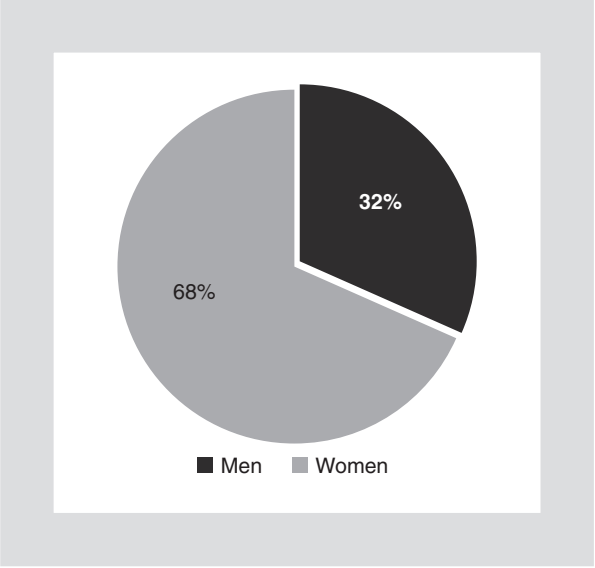

Figure 2. *Hyperleptinemia in men and women.*

HDL-C. The results on the relationship between hyperleptinemia and HDL-C levels did not yield statistically significant figures; in the ischemic stroke group, an OR of 4 was found, with a p-value of 0.27 (95% IC: 0.33-47.11). Seven subjects with hypertriglyceridemia were associated with hyperleptinemia, whereas the number of subjects with triglyceride values lower than 150 mg/dl and leptin higher than 3.93 ng/ml was five. In the subjects with hyperleptinemia-associated hypertriglyceridemia, an OR = 3.4 was obtained (p = 0.09; 95% CI: 0.8-14.4), whereas for leptin level-associated LDL-C, OR was 0.22 (p = 0.18; 95% CI: 0.02-2.04).

Discussion

Stroke is a condition found among the main causes of death and the primary causes of disability and func-

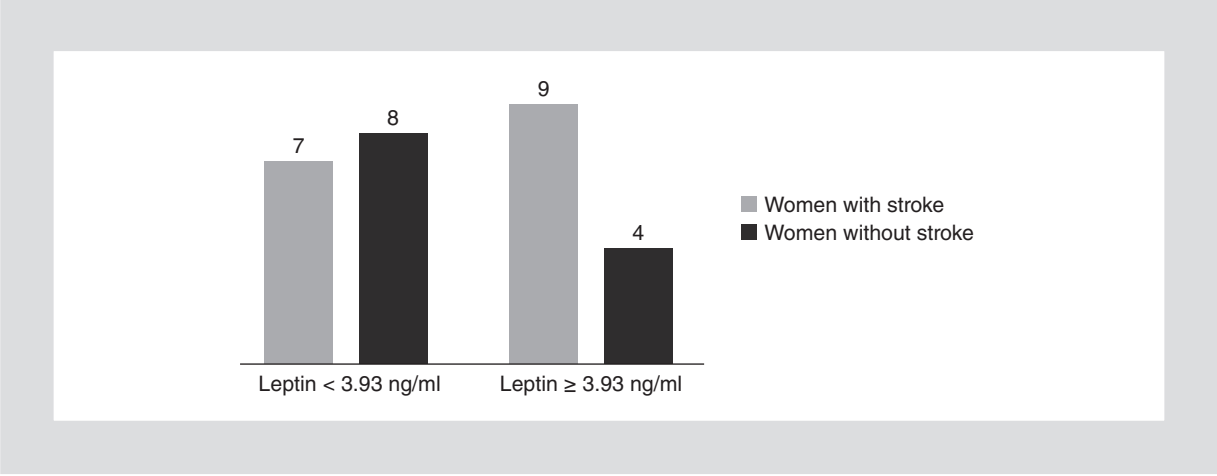

Figure 3. *Women with hyperleptinemia.*

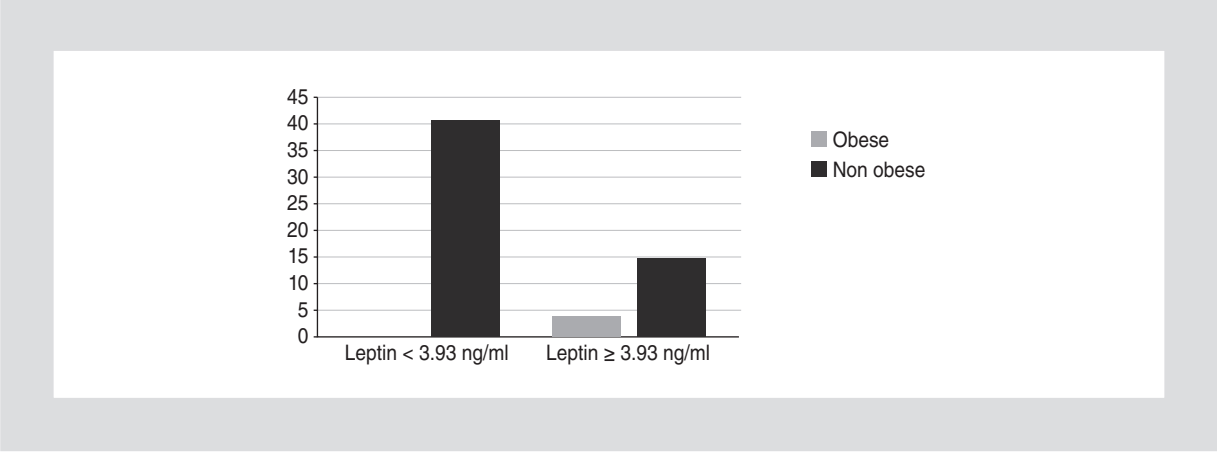

Figure 4. *Hyperleptinemia and obesity.*

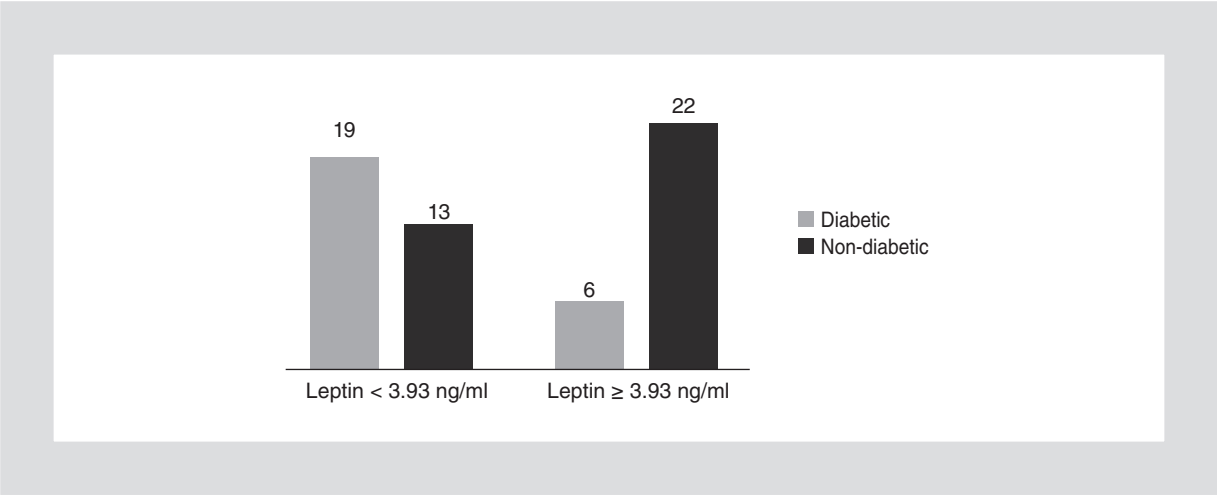

Figure 5. *Diabetic subjects and hyperleptinemia.*

tionality disturbances of people. However, it is a preventable condition. In order to implement primary prevention, risk factors involving this disease need to be withdrawn, which are all those cardiovascular factors associated with other chronic degenerative diseases, with obesity at first place. Currently, obesity has led to the development of multiple studies directed to the search of its causes and therapeutic targets. A multifactorial etiology has been established, with multiple systems involved, including the endocrine, neuroendocrine and immune systems.

This study assessed the existing relationship between the levels of leptin, one of the main hormones associated with obesity, and the presence of ischemic stroke. In many studies conducted in other countries, especially in the USA and European countries, an association has been observed between hypelerptinemia and cardiovascular conditions such as stroke and acute myocardial infarction, but few Latin statistical data are available.

The study arose based on the hypothesis that there would not be statistically significant differences between the levels of leptin and ischemic stroke in patients with SAH. The results allow concluding that there is a statistically significant difference between the levels of leptin in patients with SAH and ischemic stroke and subjects with SAH without ischemic stroke, with higher serum concentrations of leptin found in patients with cerebral infarction. Thus, the alternate hypothesis is accepted, since there is statistically significant difference between both studied groups. Hyperleptinemia occurs more in patients with cerebral infarction with SAH than in those who don't develop stroke.

With regard to the OR, it is suggested that hyperleptinemia increases the risk for developing ischemic stroke in patients with SAH, up to 2.05 times more than in hypertensive patients without hyperleptinemia, but statistical significance is borderline, with confidence interval that cross the unit, which leaves this increased risk unclear.

When analyzing the remaining results, it is concluded that women tend to show more hyperleptinemia than men; however, the OR for developing ischemic stroke in the presence of hyperleptinemia in the group of women suggests a 1.57-fold increase, which is not statistically significant ($p = 0.23$).

In the group of patients with diabetes, no association was found between leptin levels and the presence of DM; even a larger number of diabetic patients with leptin values below the mean were observed than diabetic subjects with leptin levels above the mean. This study concludes that, in this studied population, hyperleptinemia is not associated with the presence of DM.

Similarly, it is concluded that hyperleptinemia increases the risk for dyslipidemia, by hypertriglyceridemia, up to 2.4-fold, bit without statistical significance. With regard to total cholesterol, LDL-C and HDL-C, no hyperleptinemia-associated increase in the risk for developing dyslipidemia was observed.

Finally, it is concluded that there are higher concentrations of serum leptin in patients with overweight and obesity, but a correlation analysis was not performed to determine this association between leptin and BMI.

All this directs our scientific thought to be interested on developing cause and effect studies in our Latin

population, in order establish if leptin is really an independent risk factor for ischemic stroke. In this studio, the found OR suggests that hyperleptinemia can range from being a protective factor to being a risk factor; hence, the next step is to carry out studies to determine the RR.

Another of the reasons that led to the development of this study was the search for the relationship between hyperleptinemia and other cardiometabolic risk factors, such as DM and dyslipidemias. The results lacked statistical significance with regard to the relationship between leptin and DM or leptin and lipids. This is thught to be owing to the modest sample size, since very broad CIs were even found, which suggests the need to develop studies with larger samples that are significant to reduce biases. In our study, a larger number of subjects were observed with lipid alterations, such as hypetriglyceridemia, in the presence of hyperleptinemia.

As for the BMI values and their association with leptin levels, our study demonstrated what was previously observed in other countries: there are higher levels of leptin as BMI increases, which suggests that in our Latin population there is leptin resistance. Our thought leads towards genetic investigation in Mexicans, in order to establish the genes associated with leptin resistance.

The field of research in this area of neuroendocrinology needs to be broadened. We consider that this study leaves an open door for multiple works that guide investigation towards this field of great etiologic and, subsequently, therapeutic interest to enter.

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