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Oxidative stress is related with obesity and the polymorphisms g-2548a of the leptin gene (lep) and q223r of the leptin receptor gene (lepr) in tepehuano and mestizo populations of Mexico

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Resumen

Objetivo: Determinar la correlación entre el estrés oxidativo y los polimorfismos de G-2548A de *LEP* y Q223R de *LEPR* en indígenas tepehuanos y mestizos de México.

Métodos: Identificamos y caracterizamos a 50 sujetos voluntarios clínicamente sanos sin obesidad y con 50 sujetos obesos sin patologías ni alteraciones clínicas. Determinamos la capaciad antioxidante total y la peroxidación lipídica en plasma. Genotipificamos utilizando el método de PCR y enzimas de restricción (PCR-RLP). Resultados: el análisis de frecuencia aletica del polimorfismo de G-2548A *LEP* en tepehuanos no obesos, mostró una frecuencia del 56% en el genotipo heterocigoto GA, mientras que el genotipo GG homocigoto, ocurrió en el 32%. Por otro lado, los mestizos presentaron una frecuencia del 64% en el genotipo GA heterocigoto y el 28% de frecuencia del tipo GG homocigoto. Si mismo, el alelo A mostro una frecuencia mayor (60%) comparado con la de los sujetos tepehuanos (54%). En grupos con sobrepeso/obesidad, la frecuencia del alelo A fue mayor en mestizos (45%) que en la población tepehuana (40%). Al evaluar la frecuencia aletica de polimorfismos en Q223R de LEPR en tepehuanos obesos, los genotipos heterocigotos QR, representaron el 56%, mientras que los no obesos tuvieron una frecuencia del 48%. Con respecto al polimorfismo G-2548A de LEP, en mestizos obesos, el alelo A mostro una frecuencia mayor (45%) comparado con los sujetos tepehuanos (40%). En el grupo de los no obesos, la frecuencia aletica de los sujetos tepehuanos fue mayor (46%) comparado con los sujetos mestizos (40%). Ni en sujetos mestizos ni en tepehuanos con sobrepeso/obesidad, la capacidad atioxidante se correlacionó con el genotipo Q223R del gen LEPR, sin embargo el genotipo heterocigoto de LEPR que mostro mayor frecuencia, tuvo relación con los niveles de peroxidación tanto en los poblaciones de tepehuanos como Mestizos no obesos.

Conclusiones: Probablemente el genotipo GG de LEP es un factor protector ante el daño oxidativo en sujetos Tepehuanos no obesos. Sin embargo en los sujetos tepehuanos con sobrepeso/obesidad, el daño es comparable con los sujetos no obesos mestizos, lo cual sugiere que la obesidad está determinada por el decremento de la expresión del polimorfismo GG del gen de LEP en Tepehuanos.

Palabras clave: estrés oxidativo, G-2548A *LEP*, Leptina, obesidad, Q223R *LEPR,* receptor de leptina

Abstract

Objective: To determine whether there is a correlation between oxidative stress and the polymorphisms G-2548A of *LEP* and Q223R of *LEPR* in the indigenous Tepehuano and Mestizo populations in Mexico.

Methods: We identified and characterized 50 obese subjects and 50 non-obese healthy volunteers in two study groups: Tepehuanos and Mestizos from the state of Durango in Mexico. Oxidative stress was determined by measuring the total antioxidant capacity and lipid peroxidation in the plasma. Genotyping was performed using the PCR-RFLP method. Results: Analysis of the allele frequency of G-2548A *LEP* polymorphism in non-obese Tepehuanos showed that the heterozygous GA genotype represented 56% and the wild GG homozygous accounted for 32%. Meanwhile, for the non-obese Mestizo subjects, the frequency of the GA heterozygous was 64% and the wild GG homozygous was 28%. In the non-obese Mestizo subjects the A allele showed a higher frequency (60%) compared to the Tepehuano subjects (54%). For the overweight/obese Mestizo, the A allele frequency was higher (45%) than in the overweight/obese Tepehuanos subjects (40%). In assessing the allele frequency of the Q223R polymorphism of *LEPR* in non-obese Tepehuanos, the QR heterozygous genotype accounted for 56%, whereas in non-obese Tepehuano subjects heterozygous had a frequency of 48%. With regard to the G-2548A polymorphism of *LEP*, in the obese Mestizo subjects, the A allele showed a higher frequency (45%) compared to Tepehuano subjects (40%). In the non-obese Tepehuano subjects, the A allele frequency was higher (46%) compared to overweight/obese Mestizo subjects (40%). Antioxidant capacity was not correlated with the heterozygous genotype of Q223R of *LEPR* gene in overweight/obese Mestizos nor in either group of Tepehuano subjects. The genotype of the *LEPR* heterozygote that was most frequent had a relation to the levels of lipid peroxidation in no-obese Mestizo and Tepehuano populations.

Conclusions: Carrying the wild GG homozigous genotype of *LEP* is a protection factor against oxidative damage for non-obese Tepehuano subjects. However, for overweight or obese members of this population, damage is observed that is comparable to non-obese Mestizos. These findings suggest that obesity is probably determined by a decrease in the expression of the wild AA *LEP* gene polymorphism in the Tepehuanos.

Key words: oxidative stress, G-2548A *LEP*, Leptin, obesity, Q223R *LEPR,* leptina receptor.

Introduction

In the last two decades, obesity has been identified as the principal risk factor for cardiovascular disease, musculoskeletal disorders, hypercholesterolemia, hyperinsulinemia, diabetes mellitus type 2, and various cancers [1-6]. The etiology of obesity is complex, because of the interactions among psychological, environmental, metabolic, and genetic factors [7-9]. Dietary changes influenced by the environment have been observed to play a major role in developing obesity. It has been suggested that nutrients generate epigenetic changes in the human genome, such as DNA methylation and histone modification, which subsequently lead to modifications in the expression of the genes involved in obesity [10]. Interestingly, studies assessing differences in dietary habits between indigenous and non-indigenous populations have found that non-indigenous populations are more likely to be obese [11,12]. In Mexico, studies have shown that the life styles of indigenous people, like the Tepehuanos and Yaqui in Mexico, do not promote obesity [12-14]. The Tepehuano Amerindians live in the mountains of the Sierra Madre Occidental, in the states of Durango and Nayarit, Mexico. Their ancestors are from Meso-

America, while the ancestors of the Mestizo population are the product of a cross between the descendents of Europeans and Africans with Amerindians [15-18]. The Tepehuanos cultivate their own food and live in villages far from urban areas, so they retain their traditional lifestyle and language [13,14,19].

As it looks, different correlations between nutrition, oxidative stress, and the genetic architecture of the non-indigenous population (Mestizos) are plausible, in comparison to the indigenous population (Tepehuanos), since these populations have different genetic backgrounds. Until now, there are no studies which show whether or not this affects the development of obesity.

In this regard, the search for genetic markers has identified candidate genes that favor the predisposition to obesity. Most of these genes encoding for the molecular components of the physiological systems that regulate energy balance [20]. The biological homeostasis of energy is regulated by hypothalamic leptin-melanocortin signaling in which the leptin hormone (*LEP*), bound to its receptor (*LEPR*), plays an essential role in the generation of satiety signals [21]. For this reason, the candidate genes commonly associated with obesity are leptin (*LEP*) and leptin receptor (*LEPR*) [6,22-24]. A nucleotide substitution of G for A located at -2548 of the initial codon of the *LEP* gene promoter (*LEP* G-2548A), has been associated with an increase in synthesis and secretion of leptin in adipocytes, although no association has been found in some populations [23-28]. Unlike polymorphism in the *LEP* gene, in the leptin receptor gene, potential polymorphisms involved in obesity have been identified [29-31]. However, only the polymorphisms *LEPR* Q223R, *LEPR* K109R, and *LEPR* K656N are associated with this etiology [3]. In particular, the polymorphism Q223R has been associated with increased body mass in different ethnic groups in several countries [3,23,32]. Additionally, leptin, as a hormonal peptide produced by the adipocytes in the adipose tissue, induces the production of reactive oxygen species (ROS), generating a state of oxidative stress (OS) in obese patients [33]. Data shows that adipose tissue, by secreting leptin and consequently producing ROS, is considered to be the predominant tissue for systemic oxidative stress in the obese persons. Also, it has been shown that hyperleptinemia is associated with oxidative stress and the inactivation of nitric oxide, by reducing the activity of nitric oxide synthase (NOS) [34]. ROS can damage any type of biomolecule, like nucleic acids (DNA), lipids, and proteins. To counteract the effect of ROS, the human body has very effective mechanisms, including antioxidant enzymes and non-enzymatic systems. The antioxidant systems that directly eliminate the radicals $O_2^{\bullet-}$ and H_2O_2 are the superoxide dismutase (Sod), catalase (Cat), and glutathione peroxidase (GPx). To protect against ROS, besides enzymatic systems, the organism has molecules which are not enzymes, but have the capacity to eliminate free radicals. These molecules are: glutathione, vitamins E and C, carotenoids, thiols, polyamines, and eritroascorbic acid [35-37]. There is also nitric oxide synthase (NOS), which is the enzyme responsible for synthesising nitric oxide. The biomarkers for oxidative stress more broadly found in obese patients are generally malondialdehyde (MDA), which is a product of the peroxidation of unsaturated fatty acids, as well as total antioxidant capacity, which provides important biological information about the health of the patient. This analysis examines the detoxification capacity of ROS, by the enzymes Sod, Cat, GPx, and molecules like ascorbic acid, α-tocopherol, β-carotene, reduced glutathione, uric acid, and bilirubin. The cooperation of all these antioxidant systems protects the patient from free radicals of oxygen and nitrogen, such that, if the antioxidant capacity is low, the patient is in a high level of oxidative stress.

In this work, we set out to assess whether a correlation exists between oxidative stress, overweight, and the polymorphisms *LEP* G-2548A and *LEPR* Q223R for both an indigenous population (Tepehuano) and a non-indigenous (Mestizo) population in Mexico.

Materials and Methods

Patients

In a cross-sectional study, comparing the relationship between two groups: Tepehuanos and Mestizos from the state of Durango, Mexico, 50 obese subjects and 50 healthy non-obese volunteers were indentified and characterized. The obese patients were selected according to their body mass index (BMI), based on the criteria of the World Health Organization (WHO), who define obesity as a BMI $\geq$ 30 kg/m^2 [38] . None of the patients included in the study showed any cardiovascular, renal, hepatic, muscular, gastrointestinal, neurological, endocrine, hematopoietic disease, or any type of anemia, asthma, mental illness, or other organic abnormalities. In addition, from 90 days prior to the study and during the study period, the subjects did not receive any medication or drugs known as enzyme inducers or inhibitors that could interfere with analytical measurements of oxidative stress like antioxidant capacity and lipid peroxidation. Anthropometric measurements like height, weight, and waist size were taken individually in underwear and without shoes. This study was approved by Local Research Ethics and Investigation Committee of the General Hospital of Durango, Durango (ID: R-2007-901-5). Mestizo individuals came from the urban área of Durango City and indigenous individuals were from El Mezquital, a region in the south of the state of Durango, inhabited by native ethnias. In accordance with the Helsinki Declaration, a voluntary written consent was obtained from each participant.

Biochemical parameters

Using intravenous puncture, 10 mL of blood was extracted. The blood was collected in heparinized polypropylene tubes (2 drops of heparin per 10 mL of blood), mixed by inversion, and centrifuged at 3,000 rpm and 0°C for 10 min. The resulting plasma was separated into two aliquots and stored frozen at -70°C until analysis. Measurements of glucose, cholesterol, triglycerides, HDL, and LDL were determined using routine diagnostic reagents and enzymatic and colorimetric methods.

Plasma total antioxidant capacity

Total antioxidant capacity was determined by colorimetric assay with the Antioxidant Assay Kit (Cayman Chemical Company, USA). The assay is based on the ability of antioxidant systems present in the patient's plasma to inhibit the oxidation of 2,2'-azino-bis[3-ethylbenzothiazoline-6-sulphonic acid] (ABTS). The quantity of $ABTS^{\cdot+}$ produced can be measured by reading absorbance between 405-450 nm. The absorbance is inversely proportional to the concentration of the antioxidants present in the patient´s plasma. The capacity of the blood antioxidants to prevent the oxidation of ABTS to $ABTS^{\cdot+}$ is compared with Trolox (a water soluble analog of tocopherol). The results were quantified as milliequivalent activity per milliliter of plasma. Generally, human plasma has an antioxidant capacity between 0.5-2.0 mM of Trolox equivalents [39,40].

Lipid peroxidation measurements

The determination of lipid peroxidation was based on the protocol specified in the TBARS (Thiobarbituric Acid Reactive Substances) Assay Kit (Cayman Chemical Company, USA). This method quantifies the reactive species of thiobarbituric acid (TBARS), which are produced by lipid peroxidation. These include malondialdehyde, which is the most abundant, stable, and most easily characterized. The maximum absorbance of these species is 532 nm and was determined using a spectrophotometer model UV/VIS OD 650 (Beckman). The results were expressed in nmol equivalents of MDA per milliliter of plasma. Typically normal human plasma has a lipid peroxidation expressed in MDA of 1.86-3.94 μM [41,42].

Genotyping

The genotyping of the polymorphisms *LEP* G-2548A and *LEPR* Q223R was determined from total blood treated by alkalyne lysis, followed by PCR, using the primer pairs described previously [23,27,28,43]. The individual PCR's were done in a final volume of 25 µL using 2 ul of blood lysate as template, 1X PCR buffer, 2.0 mM $MgCl_2$, 0.2-0.25 mM of each dNTP, 2.5 pmol of each primer, and 1.0 U Taq DNA polymerase. The reaction mix was denatured for 5 min at 95°C, annealing at 58.5 °C for *LEP* G-2548A, then at 72°C for 60 s for 55 cycles, and for *LEPR* Q223R, annealing at 50.0 °C, then at 72 °C for 30 s for 55 cycles. The amplified fragments were from 242 bp for *LEP* G-2548A and 80 bp for *LEPR* Q223R. These PCR products were digested with 1.0 U of *Hha*I and *Msp*I restriction enzymes (Promega, Madison, WI. USA) respectively, according to the manufacturer's protocol. The digested samples were separated by electrophoresis on agarose gels at 2.0% and stained with ethidium bromide. The generation of fragments at 61 and 181 bp correspond to the *LEP* G-2548A polymorphism, and at 22 and 58 bp they correspond to the *LEPR* Q223R polymorphism in the studied populations.

Statistical analysis

For the analysis of variance, we used version 18 of SPSS statistical software. The ANOVA and Kruskal Wallis tests were used to evaluate the comparison between ethnic groups, while the Friedman test was used for comparison of the ethnic subgroups. For the analysis of simple correlation, we used the Kendall and Spearman for categorical variables and Pearson for quantitative variables. The differences between the means were compared with the LSD and TUKEY tests. Levels of significance were set at $P< 0.05$.

Results

The clinical and biochemical characteristics of the two study groups (Tepehuanos and Mestizos) are shown in Table 1. The body mass index in the group of obese individuals was 26.7 ± 7.76; 28.9 ± 3.3, whereas in the non-obese group was (22.5 ± 1.69; 20.2 ± 1.77). The value for mean arterial pressure (MAP) of the overweight Tepehuano subjects was lower (82.9 ± 8.6) than it was for the Mestizo subjects (87.6 ± 9.4). It is worth mentioning that the MAP value for the Mestizo subjects was not expected, since normal weight subjects showed values (88.2 ±7.6) that were similar to the overweight subjects (87.6 ± 9.4). Interestingly, the obese Tepehuano patients also had a similar MAP (82.9 ± 8.6) to the non-obese Tepehuanos (82.6 ± 9.5) and did not show a statistically significant difference among this ethnic group. Total cholesterol values did not show a statistically significant difference among the four study groups. But, surprisingly, the triglyceride values were higher in non-obese Mestizo subjects (153 ± 65.4) than in obese Mestizos (85.4 ± 111.4). This result is in contrast to the Tepehuano groups, where obese Tepehuanos patients had higher triglyceride levels (165.3 ± 103.3) than the non-obese (99.0 ± 41.0). These triglyceride values were higher in the overweight Tepehuano group. HDL values did not show a statistically significantly difference in the Mestizo groups, whereas the non-obese Tepehuanos had a higher concentration of HDL (40.63±12.1) than the obese (31.8 ± 5.9). LDL levels were significantly different in the Mestizo groups, while among the Tepehuanos there was no difference. The overweight Tepehuanos had a higher concentration of plasma VLDL (34.1 ± 18.7) than the non-obese subjects (19.9 ± 8.2), while the healthy Mestizos had a higher value of VLDL than the obese. Comparing the levels of VLDL between the two groups of obese patients, the Tepehuanos had the highest amount of plasma lipoproteins.

Comparison of genetic characteristics

The genotypic distribution of the alleles of the polymorphism G-2548A of *LEP* was in Hardy-Weinberg equilibrium, both for the Tepehuanos and for the Mestizos. For the polymorphism

Q223R of *LEPR* , for both the Mestizos and for the Tepehuanos the distribution was also in equilibrium.

G-2548A *LEP* polymorphism

The analysis of allele frequency in non-obese Tepehuanos showed that the heterozygous GA genotype accounted for 56%, while the wild homozygous GG was only 32%, with the lowest relative frequency for the mutated homozygous AA genotype at 12%. Meanwhile, Mestizo subjects had higher heterozygote GA frequencies with a value of 64%, and the wild GG homozygote was 28%. The lowest relative frequency was the mutated AA homozygous genotype at 8%. In the non-obese Tepehuano subjects, the A allele had a higher frequency (45%) than it did for the Mestizo subjects (40%). Interestingly, however, in the overweight/obese Mestizo individuals, the A allele frequency was higher (45%) than it was in the overweight/obese Tepehuano subjects (40%).

The distribution of allelic frequencies and genotypic frequencies for the polymorphism of G-2548A of *LEP* are show in Table 2.

Q223R *LEPR* polymorphism

The analysis of allele frequency in non-obese Mestizos showed that the heterozygous QR genotype accounted for 47%, while the Tepehuano subjects had also values of 56% in heterozygote frequency and 32% in the wild QQ homozygous. The lowest relative frequency was the mutated homozygous RR genotype which was only 12%. In obese Mestizo subjects, the A allele showed a higher frequency (60%), compared to the Tepehuano subjects (56%). In the non-obese Tepehuano individuals, the frequency of the A allele was higher (60%) than in overweight/obese Mestizo subjects (50%). The distribution of allelic frequencies and genotypic frequencies for the polymorphism of Q223R of *LEPR* are show in Table 3.

Association of genetic polymorphisms to clinical and biochemical characteristics and oxidative stress in Tepehuanos and Mestizos

BMI (body mass index)

Pearson correlation analysis showed a positive correlation of 0.5 for *LEPR* polymorphism to BMI in overweight/obese Tepehuan, while a negative correlation of -0.6 was found between *LEP* polymorphism and BMI in non-obese Mestizos.

Antioxidant Capacity

Antioxidant capacity not showed a correlation to the Q223R heterozygous genotype of the *LEPR* gene and G-2548A of *LEP* in no- obese, neither in overweight/obese Mestizos nor in either group of the Tepehuano subjects.

Lipoperoxidation

Correlation analysis found a positive correlation (0.5 p (0.01)) between the presence of the heterozygous GA genotype of *LEP* and lipoperoxidation in non-obese Tepehuano subjects (C.I. 95%: 0.13-0.74), this correlation is shown in Figure 5. The heterozygous genotype of the *LEPR* that was most common had a relation to the lipoperoxidation level (0.13 p(0.05)) in no-obese Mestizo populations (C.I. 95%: 0.52-0.2) but not in the Tepehuano population.

Discussion and Conclusion

The correlation between BMI and *LEPR* gene polymorphism was positive (P 0.50) in overweight/obese Mestizo subjects, although no such correlation was found among the other groups.

There was a negative correlation (P -0.6) between the *LEP* gene polymorphism and non-obese Mestizo subjects, which suggests that, for this group, the polymorphism is a protective factor against body mass increase, since this correlation did not exist in clinically healthy overweight/obese Mestizo subjects.

Values for oxidative damage (MDA) were independent of ethnic group membership and dependent on BMI. Obese subjects showed an adaptive response to the insult generated by overweight and obesity, and this response has been sufficient to prevent more oxidative damage. In other oxidative stress conditions, such as systemic sclerosis and physical exercise, there is often an increase in oxidative damage accompanied by increased total antioxidant capacity [44,45].

Antioxidant capacity was higher in both the overweight/obese and the non-obese Tepehuanos than in the two groups of Mestizos. Lipoperoxidation was higher in non-obese Mestizos than in non-obese Tepehuanos. In both groups, other authors [46, 47] have reported that oxidative damage is higher when antioxidant capacity is lower and vice versa. However, in overweight/obese subjects this phenomenon is not observed, since overweight/obese Mestizo subjects have lower antioxidant capacity, which probably diminishes the use of antioxidant systems due to an increase in free radicals and ROS products from the physiopathology triggered by the gain in body mass at the expense of fatty tissues and deposits [48].

Carrying the wild genotype of the *LEP* gene is a protection factor against oxidative damage for non-obese Tepehuano subjects. However, when this population becomes overweight or obese, despite having a higher antioxidant capacity than overweight Mestizos, there is damage compared to the non-obese Mestizos. These findings suggest that obesity is probably conditioned to the decreased expression of the wild *LEP* genotype in Tepehuanos.

The populations studied did not show the characteristics reported above in terms of oxidative damage, which can be explained by the fact that all of the Mestizo and Tepehuano individuals were clinically healthy and the range of oxidative damage in the four groups was within normal values. However, we believe that it is still necessary to study other associations between genes and polymorphisms in order to characterize the relationship between antioxidant capacity and other antioxidant systems.

In summary, oxidative stress is related with the polymorphisms Q223R of the leptin gene (*LEPR*) negative in mestizos no obese and the obesity en tepehuan population, whereas G-2548A of the leptin receptor gene (*LEP*) is related with oxidative stress in no- obese tepehuan population.

Disclosure statement

The authors confirm that there is no conflict of interest associated with this manuscript.

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Aprovechamiento del hongo Matsutake tricholoma magnivelare (peck) redhead en Durango, México.

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Resumen

En México la colecta del hongo matsutake (*Tricholoma magnivelare)* que es el sustituto de *Tricholoma matsutake*, es realizado en varios estados del país, para atender la demanda del mercado japonés desde finales de los años 80´s. Su aprovechamiento se caracteriza por una alta presión extractiva motivada por el alto precio al que es pagado. Casos documentados se encuentran en el estado de Oaxaca. En el presente trabajo se analizo la problemática en torno al aprovechamiento de *T. magnivelare* en el municipio de Pueblo Nuevo, Durango a través de: a) análisis documental, b) estudio etnomicológico, c) estudio cuantitativo. En los ejidos La Campana y La Ciudad como áreas de estudio durante el periodo 2010-2012. Los resultados del estudio etnomicológico mostraron que *T. magnivelare* no es una especie tradicional y que prevalece un interés económico inmediato. Los resultados del análisis documental sugirieron que su aprovechamiento se realiza sin ningún esquema técnico, organizativo ni de planeación que determine aspectos clave como la tasa de aprovechamiento. La ausencia de estos esquemas se debe a la poca difusión entre los recolectores de los instrumentos jurídicos en materia de hongos silvestres y el aplazamiento de su implementación. La fase cuantitativa mostró un panorama restrictivo en cuanto a la biomasa disponible en términos pluviales y de distribución. Frente a dicha problemática, es valioso conservar la información que los recolectores han aprehendido respecto a esta especie y canalizarla a la elaboración de productos de valor agregado para su comercialización en el mercado