Leptin Gene and Receptor Mutations and its Association with Obesity and Overweight: A Mini Review

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Abstract

Overweight and obesity are considered a global epidemic in the twenty-first century, it is a multifactorial disease due, in part, to a genetic component. The most common genetic alteration is one that affects the neuroregulatory pathway of Leptin, a fundamental hormone for appetite regulation. Mutations that affect the LEP gene are present in the different exons of this gene and have been described for many years. Although obesity due to a genetic mutation is not the most common cause, its diagnosis is of paramount importance since it can affect the quality of life and life expectancy of the patients suffering from this condition.

The purpose of this mini review is to present up-to-date evidence regarding Leptin gene mutations, possible treatment strategies such as Leptin Replacement Therapy (LRT), leptin sensitizers and anti-inflammatory drugs, and discuss the importance of establishing health policies worldwide to achieve a timely and successful approach to this disease.

Introduction

Obesity is a multifactorial pathology defined by the World Health Organization (WHO) as the excessive accumulation of fat. It is considered a global public health problem due to its association with multiple non-infectious comorbidities such as diabetes, cardiovascular disease, cancer, osteoarthritis, depression, and reduction in life expectancy.

Many factors are related to the origin of this disease, among them environmental agents and biological susceptibility. There are different genetic variants that can cause moderate to severe obesity; however, the literature illustrates that most of these presentations are produced by mutations in the leptin gene (LEP) or its receptor, which are associated with poor appetite control leading to obesity. Leptin is a hormone secreted and synthesized by the adipocyte in response to food in order to suppress appetite by altering the hypothalamic pathway, once in the hypothalamus it reaches the arcuate nucleus, the ventromedial nucleus, the dorsomedial nucleus and other areas of the brain related to energy balance by initiating a cascade of specific signals that inhibit multiple orexigenic neuropeptides which leads to a decrease in the desire to eat and an increase in thermogenesis.

The foregoing highlights the importance of detecting these rare forms of genetic obesity, which allows progress in understanding the disease, since its management requires special therapies and a multidisciplinary team.
The purpose of this mini review is to present up-to-date evidence regarding Leptin gene mutations, their management and their relationship with obesity and overweight, since multiple cases have been reported.

**Discussion**

Leptin is a peptide protein composed of 167 amino acids, secreted mainly by adipocytes; therefore, its levels are directly proportional to the adipose tissue of a person’s body\(^{10,12,13}\). The leptin receptor is part of the glycoprotein 130 (gp130) family and has six defined isoforms from A to F (a-f LEPR)\(^8\). Since 1994, leptin and its gene mutations have been associated with obesity and it has taken many years to understand their role in regulating the metabolic system\(^8\).

Leptin is considered important for metabolic homeostasis and glucose regulation, regardless of the person’s diet and weight\(^14\). It acts in the arcuate nucleus, where it activates neurons that express anorexigenic peptides such as proopiomelanocortin (POMC)\(^15\). It is also responsible for inhibiting orexigenic peptides such as neuropeptide Y (NPY) to reduce hunger\(^15\). Both pathways connect in the hypothalamic nucleus to inhibit feeding and promote energy expenditure\(^15,16\). However, there is an inversely proportional relationship between leptin sensitivity and body mass index (BMI); This means that if a person has an increased BMI, their sensitivity to leptin will decrease, resulting in an inadequate hunger-suppressing effect\(^15\).

In the article “Congenital Leptin Deficiency and Leptin Gene Missense Mutation Found in Two Colombian Sisters with severe obesity”, published in 2019, describes the first case of morbid obesity due to a LEP gene mutation in North and South America. The article exposes a case of congenital leptin deficiency (CLD), a treatable monogenic form of obesity that begins with a normal birth weight followed by a rapid development of severe obesity that has symptoms such as severe hyperphagia, decreased satiety, and accelerated increase in weight\(^16\). It has been established that obesity in childhood can be of monogenic, as well as polygenic and of multifactorial origin. And it is mainly due to alterations in the leptin/melanocortin pathway in the hypothalamus, which lead to the absence of anorexigenic factors and, therefore, to early-onset obesity, with a prevalence of 1/1,000,000\(^6,15\). Regarding obesity of monogenic origin, mutations can occur mainly in the LEP gene or in hormone receptors located mostly in the hypothalamus\(^6\). Early-onset obesity secondary to a leptin receptor mutation is less prevalent, and is generally associated with normal or high plasma leptin levels, non-metabolic symptoms such as compromised immune system\(^15\), and other disorders such as no pubertal development and decreased secretion of growth hormone and thyrotropin\(^19\). The first case was reported in 1998 due to a c.2598 + 1G > A mutation in North Africa\(^15\). More recently, in a study conducted in Sri Lanka with 530 subjects, the presence of the G allele of the LEPR polymorphism Q223R was found to be associated with obesity\(^20\).

Regarding LEP gene mutations, the first case reported was in 1997 in a family of Pakistani origin and with a high degree of consanguinity in which the deletion of a guanine nucleotide at codon 133 was described, which resulted in a premature codon stop\(^21\). Multiple mutations that have effects on the hormone leptin have been reported in the literature. The following table 1 makes a compilation of the mutations found in different populations and that have been linked as a cause of obesity and overweight.

### Table 1: Summary of mutations affecting leptin hormone associated with obesity

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Country</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>AC&gt; T substitution at codon 105</td>
<td>Turkey</td>
<td>Patient with hyperphagia, BMI 55.8 and very low serum leptin concentration 0.9 ng / mL, with a finding of AC&gt; T substitution, which led to a change in Arg&gt; Trp in the protein. Homozygous for the mutation(^22).</td>
</tr>
<tr>
<td>Substitution c.422 C&gt; G</td>
<td>Karaul Village</td>
<td>Study carried out to estimate the prevalence, identifying 27 likely harmful variants in the leptin gene from 58 heterozygous subjects(^22).</td>
</tr>
<tr>
<td>Substitution of asparagine for lysine at codon 103</td>
<td>Egypt</td>
<td>Patient with very low serum leptin levels and severe early obesity(^24).</td>
</tr>
<tr>
<td>TTA to TCA in exon 3 of the LEP gene</td>
<td>Austria</td>
<td>14-year-old patient, daughter of non-obese parents, with BMI of 31.5 kg / m2 and undetectable levels of serum leptin(^25).</td>
</tr>
<tr>
<td>c.398delG, c.104_106delTCA and c.481_482delCT</td>
<td>Pakistan</td>
<td>Mutations associated with early obesity in a study of 25 children(^26).</td>
</tr>
<tr>
<td>Nonsense mutation c.163 C&gt; T in codon 55 of exon 3 of the LEP gene</td>
<td>India</td>
<td>8-year-old patient with hyperphagia, morbid obesity, serum leptin levels &lt;0.6 ng / mL consanguineous parents, studies with a homoyzygous mutation in the LEP gene that leads to codon stop.C(^27).</td>
</tr>
<tr>
<td>Mutation in exon 3 of the LEP gene [H118L]</td>
<td>China</td>
<td>Associated with a patient with severe obesity (BMI 46.0 kg / m2) in a study of 35 patients(^28).</td>
</tr>
<tr>
<td>C.309C&gt; A mutation that translates into non-functional leptin</td>
<td>Germany</td>
<td>Two siblings homozygous for the same mutation, who present with severe early obesity and hyperphagia(^29).</td>
</tr>
<tr>
<td>C.350G&gt; T mutation</td>
<td>First case reported in North and South America</td>
<td>Two sisters with undetectable leptin levels and severe obesity(^28).</td>
</tr>
<tr>
<td>Mutation c.298C &lt;T</td>
<td>Turkey</td>
<td>Patient with high levels of serum leptin and morbid obesity(^29).</td>
</tr>
</tbody>
</table>
Treating obesity should be a priority worldwide since it is considered the main risk factor for many chronic non-communicable diseases such as cardiovascular disorders, insulin resistance, and cancer. Adipose tissue is considered an endocrine organ that affects many physiological parameters of the body, such as the immune system response, appetite, fertility, angiogenesis, and the inflammatory response.

All these diseases create high costs expenses for any health system; therefore, early diagnosis and specific treatment are of the utmost importance.

Leptin replacement therapy (LRT) has been indicated and approved by the Food and Drug Administration (FDA) as a treatment for patients suffering from leptin deficiency and patients with lipodystrophy. LRT consists of the subcutaneous administration of recombinant human methionyl leptin (Metreleptin) once or twice a day; it has been associated with better glycemic control, insulin sensitivity, weight loss, appetite control, and prevention of reduced metabolic rate. Because its effects are potentially useful, it can be used in patients with other diseases associated with low, normal or high levels of serum leptin such as common obesity, type 1 and 2 diabetes mellitus, or neurodegenerative disorders. For those patients with resistance, combining leptin with leptin sensitizers could be a reasonably feasible way to overcome such resistance. Based on animal experiments, it has been suggested that amylin would be one of these sensitizers. Amylin could act with leptin to induce weight reduction. In a clinical trial, the combination of leptin and pramlintide produced significant weight loss. This effect was accompanied by a trend towards improvement in metabolic parameters such as total cholesterol, LDL, blood glucose and insulin levels, and insulin resistance.

However, interventions with anti-inflammatory drugs, combined with administration of leptin and hormones that help reduce weight, should be further investigated as an alternative treatment.

A good number of the treatment measures analyzed are very expensive, not only in economic terms, but also in political terms, which shows the need for a strong commitment on the part of governments to reach the proposed objectives regarding the prevention of obesity.

To get closer to the reality that each country presents, the need to generate reliable statistics and multidisciplinary studies is highlighted, which reflect the complexity and local characteristics of the problem. Visualizing both the magnitude of the problem and its evolution over time is what allows us to glimpse the cultural and socioeconomic differences of the committed population so that the implemented policies are in accordance with their needs.

Conclusions

Serum leptin levels must be interpreted and related individually. And they cannot be a fundamental part of the diagnosis since these levels can be normal, high or low, and this depends on the form of presentation; if it is the classic or functional form, which is the case in which resistance to leptin is present and although it is rare, it should be taken into account at the time of diagnosis and initiation of treatment.

Recent studies in animals have developed new strategies for the treatment of obesity and resistance to leptin, associating hormone replacement therapy with “leptin sensitizers” such as metformin, flurbiprofen or pramlintide acetate; These agents act on the neuroendocrine system, reversing leptin resistance. More studies should be done on this new pharmaceutical approach as a possible treatment for genetic obesity, but also metabolic obesity.

Severe monogenic obesity is a treatable disease; however, due to its low prevalence, many countries do not have a health system that can provide early diagnosis and effective treatment, so new health policies are needed to achieve a timely and successful approach to this disease and, in turn, reduce many associated comorbidities.

References

5. Zarrati M, Abou N, Cheshmaz E. The asso ciation of o besity and se rum lep tin level s with complet e blood count an nd some serum bioch emi cal paramet ers in I ra ni an ov erweight and obese individua ls. 2019.


