Rincones Rojas LV, Ferrer Marcano AC, Mojica Muñoz JS, García AM, Celis LG. Leptin Gene and Receptor Mutations and its Association with Obesity and Overweight: A Mini Review. J Endocrinol Sci.2020;2(2):1-4

Journal of Endocrinological Science

Mini Review Open Access

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

Lorena V. Rincones Rojas, Amenaida C. Ferrer Marcano, Juan S. Mojica Muñoz, Angelica M. García, Luis G. Celis*

Faculty of Medicine – Universidad de la Sabana, Bogotá, Colombia

Article Info

Article Notes
Received: March 04, 2020
Accepted: October 05, 2020

***Correspondence:**
*Dr. Luis G. Celis, Faculty of Medicine – Universidad de la Sabana, Bogotá, Colombia; Email: luis.celis@unisabana.edu.co.

©2020 Celis LG. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License.

Keywords
Obesity
Leptin
Mutation
Gene
Hormone
Replacement therapy

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 stablishing 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[1]. 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[1-5].

Many factors are related to the origin of this disease, among them environmental agents and biological susceptibility[1,6]. 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[1,7,8]. 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[9] which leads to a decrease in the desire to eat and an increase in thermogenesis[7,10].

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[11].

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 anorexic 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[17].

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[18]. 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 anorexic 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

Mutation	Country	Findings
AC> T substitution at codon 105	Turkey	Patient with hyperphagia, BMI 55.8 and very low serum leptin concentration 0.9 ng / mL, with a finding of AC> T substitution, which led to a change in Arg> Trp in the protein. Homozygous for the mutation[22].
Substitution c.422 C> G	Karaul Village	Study carried out to estimate the prevalence, identifying 27 likely harmful variants in the leptin gene from 58 heterozygous subjects[23].
Substitution of asparagine for lysine at codon 103	Egypt	Patient with very low serum leptin levels and severe early obesity[24].
TTA to TCA in exon 3 of the LEP gene	Austria	14-year-old patient, daughter of non-obese parents, with BMI of 31.5 kg / m2 and undetectable levels of serum leptin[25].
c.398delG, c.104_106delTCA and c.481_482delCT	Pakistan	Mutations associated with early obesity in a study of 25 children[26].
Nonsense mutation c.163 C> T in codon 55 of exon 3 of the LEP gene	India	8-year-old patient with hyperphagia, morbid obesity, serum leptin levels <0.6 ng / mL consanguineous parents, studies with a homocytogous mutation in the LEP gene that leads to codon stop.C[27]
Mutation in exon 3 of the LEP gene [H118L]	China	Associated with a patient with severe obesity (BMI 46.0 kg / m2) in a study of 35 patients[28].
C.309C> A mutation that translates into non-functional leptin	Germany	Two siblings homozygous for the same mutation, who present with severe early obesity and hyperphagia[29].
C.350G> T mutation	First case reported in North and South America	Two sisters with undetectable leptin levels and severe obesity[18].
Mutation c.298C <T	Turkey	Patient with high levels of serum leptin and morbid obesity[30].

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[1,31]. 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[15].

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[32,33]. 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[32,34]. 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[34]. 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[35]. Amylin could act with leptin to induce weight reduction. In a clinical trial, the combination of leptin and pramlintide produced significant weight loss[36]. 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[37].

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[34].

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[38].

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[38].

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[9,19].

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[13,33,34]. 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

1. Uccioli L, Monticone G, Russo F, et al. OBESITY: PREVENTING AND MANAGING THE GLOBAL EPIDEMIC. WHO Tech Rep Ser. 1994; 37(10): 1051–5.
2. Kitahara CM, Flint AJ, Berrington de Gonzalez A, et al. Association between Class III Obesity (BMI of 40-59 kg/m2) and Mortality: A Pooled Analysis of 20 Prospective Studies. PLoS Med. 2014; 11(7): 1–14.
3. Qasim A, Turcotte M, de Souza RJ, et al. On the origin of obesity: identifying the biological, environmental and cultural drivers of genetic risk among human populations. Obes Rev. 2018; 19(2): 121–49.
4. Engin A. The Definition and Prevalence of Obesity and Metabolic Syndrome. 2017; 960. Available from: http://link.springer.com/10.1007/978-3-319-48382-5
5. Zarrati M, Abou N, Cheshmaz E. The asso ociation of o obesit ty and se erum lep ptin level s with complet te blood count an nd some serum biochemi b ical paramet ters in Ira anian ov verweigh ht and ob bese indi viduals. 2019.
6. Calva AP, Gonzalez IA, Bujaidar EM, et al. Review of the main genes involved in the development of obesity. Rev Mex Ciencias Farm. 2011; 42(4): 26–38.
7. Crujeiras AB, Carreira MC, Cabia B, et al. Leptin resistance in obesity: An epigenetic landscape. Life Sci [Internet]. 2015; 140: 57–63. Available from: http://dx.doi.org/10.1016/j.lfs.2015.05.003
8. Fairbrother U, Kidd E, Malagamuwa T, et al. Genetics of Severe Obesity. Curr Diab Rep. 2018; 18(10).
9. Morales Clavijo M, Carvajal Garces C. Obesidad y resistencia a la leptina. Gac méd Boliv. 2010; 33(1): 63–8.
10. Fernández-Formoso G, Pérez-Sieira S, González-Touceda D, et

al. Leptin, 20 years of searching for glucose homeostasis. Life Sci [Internet]. 2015; 140: 4–9. Available from: http://dx.doi.org/10.1016/j.lfs.2015.02.008

11. Ulloa ME, Armeno ML, Mazza CS. Obesidad Monogenica. Med Infant. 2017; XXIV Nº3: 294–302.
12. Duan DM, Jhang JY, Wu S, et al. Modification effect of sex and obesity on the correlation of LEP polymorphisms with leptin levels in Taiwanese obese women. Mol Genet Genomic Med. 2020; 8(3): 1–10.
13. Izquierdo AG, Crujeiras AB, Casanueva FF, et al. Leptin, obesity, and leptin resistance: where are we 25 years later? Nutrients. 2019; 11(11): 1–11.
14. Wasim M, Awan FR, Najam SS, et al. Role of Leptin Deficiency, Inefficiency, and Leptin Receptors in Obesity. Biochem Genet. 2016; 54(5): 565–72.
15. Paolacci S, Borrelli A, Stuppia L, et al. Mendelian obesity, molecular pathways and pharmacological therapies: A review. Eur Rev Med Pharmacol Sci. 2019; 23(3): 1357–78.
16. Engin AB, Engin A. Obesity and Lipotoxicity. 2017; 960. Available from: http://link.springer.com/10.1007/978-3-319-48382-5
17. Baxter J, Armijo PR, Flores L, et al. Updates on Monogenic Obesity in a Multifactorial Disease. Obes Surg. 2019; 29(12): 4077–83.
18. Yupanqui-Lozno H, Bastarrachea RA, Yupanqui-Velazco ME, et al. Congenital leptin deficiency and leptin gene missense mutation found in two colombian sisters with severe obesity. Genes (Basel). 2019; 10(5).
19. Rosado EL, Monteiro VCMF do L JB. Efecto de la leptina en el tratamiento de la obesidad e influencia de la dieta en la secreción y acción de la hormona. Nutr Hosp. 2006.
20. Illangasekera YA, Kumarasiri PVR, Fernando DJ, et al. Association of the leptin receptor Q223R (rs1137101) polymorphism with obesity measures in Sri Lankans. BMC Res Notes [Internet]. 2020; 13(1): 5–8. Available from: https://doi.org/10.1186/s13104-020-4898-4
21. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997; 387(6636): 903–8.
22. Larsson NG, Wang J, Wilhelmsson H, et al. 1998 Nature Publishing Group http://www.nature.com/naturegenetics. Nat Genet [Internet]. 1998; 18(3): 231–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9500544
23. Chekhranova MK, Karpova SK, Yatsyshina SB, et al. A New Mutation c.422C>G (p.S141C) in Homo- and Heterozygous Forms of theHuman Leptin Gene. Russ J Bioorganic Chem. 2008; 34(6): 768–70.
24. Mazen I, El-Gammal M, Abdel-Hamid M, et al. A novel homozygous missense mutation of the leptin gene (N103K) in an obese Egyptian patient. Mol Genet Metab [Internet]. 2009; 97(4): 305–8. Available from: http://dx.doi.org/10.1016/j.ymgme.2009.04.002
25. Fischer-Posovszky P, Von Schnurbein J, Moepps B, et al. A new missense mutation in the leptin gene causes mild obesity and hypogonadism without affecting T cell responsiveness. J Clin Endocrinol Metab. 2010; 95(6): 2836–40.
26. Fatima W, Shahid A, Imran M, et al. Leptin deficiency and leptin gene mutations in obese children from Pakistan. Int J Pediatr Obes. 2011; 6(5–6): 419–27.
27. Thakur S, Kumar A, Dubey S, et al. A novel mutation of the leptin gene in an Indian patient. Clin Genet. 2014; 86(4): 391–3.
28. Zhao Y, Hong N, Liu X, et al. A novel mutation in Leptin gene is associated with severe obesity in Chinese individuals. Biomed Res Int. 2014; 2014: 10–3.
29. Wabitsch M, Funcke JB, Von Schnurbein J, et al. Severe early-onset obesity due to bioinactive leptin caused by a p.N103K mutation in the leptin gene. J Clin Endocrinol Metab. 2015; 100(9): 3227–30.
30. Wabitsch M, Funcke JB, Lennerz B, et al. Biologically inactive leptin and early-onset extreme obesity. N Engl J Med. 2015; 372(1): 48–54.
31. Palhinha L, Liechocki S, Hottz ED, et al. Leptin Induces Proadipogenic and Proinflammatory Signaling in Adipocytes. Front Endocrinol (Lausanne). 2019; 10(December).
32. Paz-Filho G, Mastronardi CA, Licinio J. Leptin treatment: Facts and expectations. Metabolism [Internet]. 2015; 64(1): 146–56. Available from: http://dx.doi.org/10.1016/j.metabol.2014.07.014
33. Quarta C, Sánchez-Garrido MA, Tschöp MH, et al. Renaissance of leptin for obesity therapy. Diabetologia. 2016; 59(5): 920–7.
34. Roberto Coppari CB. The Potential of Leptin for Treating Diabetes and Its Mechanism of Action Roberto. Bone [Internet]. 2008; 23(1): 1–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf
35. Moon HS, Dalamaga M, Kim SY, et al. Leptin's role in lipodystrophic and nonlipodystrophic insulin-resistant and diabetic individuals. Endocr Rev. 2013; 34(3): 377–412.
36. Ravussin E, Smith SR, Mitchell JA, et al. Enhanced weight loss with pramlintide/metreleptin: An integrated neurohormonal approach to obesity pharmacotherapy. Obesity [Internet]. 2009; 17(9): 1736–43. Available from: http://dx.doi.org/10.1038/oby.2009.184
37. Araújo-Vilar D, Guillín-Amarelle C, Sánchez-Iglesias S, et al. Uso terapéutico de la leptina recombinante humana. Rev Española Endocrinol Pediátrica [Internet]. 2014; 5(1): 27–42. Available from: www.fda.gov/newsevents/newsroom/pres-
38. Mussini M, Temporelli KL. Obesidad: Un desafio para las politicas publicas. (Obesity: A Challenge for Public Policy. With English summary.). Estud Soc. 2013; 21(41): 165–84.