REVIEW ARTICLE

# Association Between Leptin Receptor Gene (*LEPR*) Polymorphism and Obesity: A Review

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**ABSTRACT**

Polymorphisms of the leptin receptor gene (*LEPR*) are known to occur at several sites of this gene and are thought to play a role in leptin resistance which causes obesity. The most extensively researched single nucleotide polymorphism is found in codon 223, which results in the conversion of glutamine (CAG) to arginine (CGG) by changing adenine (A) to guanine (G). However, its relationship with anthropometric and metabolic parameters of obesity is still unclear. The genetic variant on the *LEPR* may alter the receptor's structure and function which affects fat accumulation in obesity. However, it might provide diverse outcomes among individuals of different ages, sexes, and ethnicities. This review aims to determine the association between Gln223Arg *LEPR* polymorphisms and obesity in several populations in the world, and the insight into oral health, especially the inflammatory underlying oral diseases. As the result of this review article, the relationship between *LEPR* polymorphisms and obesity including its metabolic alteration varies between populations, possibly due to gene-to-gene communication or gene interaction with the environment.
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**Keywords:** *LEPR*, Gene polymorphism, Leptin receptor, Obesity, Oral health

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## INTRODUCTION

Worldwide, both in developed and developing countries, obesity has reached pandemic proportions. According to WHO statistics from 2016, there are more than 1 billion obese persons in the globe, including 650 million adults, 340 million adolescents between the ages of 5 and 19, and 39 million young children. From 2020 to 2035, there is expected to be a 100% increase in the prevalence of obesity among children and adolescents (1). Obesity negatively affects health due to its role as a risk factor for cardiovascular complications, such as hypertension, stroke, and coronary artery disease (2). On the other hand, excessive fat accumulation in obesity leads to metabolic alteration including insulin resistance and dyslipidemia (3). Obesity and overweight significantly impact societal costs and health-related quality of life, and cause the largest portion of overall costs in the healthcare system. Intensive preventive and treatment strategies are serious to reduce the burden of obesity on the health services (4).

Obesity is a state characterized by increasing body weight due to excessive fat accumulation in the body. The neurohormonal regulates the balance of caloric intake and energy expenditure in normal conditions, but it is lacking in obese individuals (5). Obesity is a

chronic multifactorial disease resulting from complex interactions among many genes and environmental factors, such as a sedentary lifestyle and changes in dietary patterns including cigarette exposure, fast food consumption, larger portions of meals, sugary drinks, and high-caloric ingredients in a meal (6,7).

Importantly, the considerable interindividual variance in body weight, which determines how they respond to this obesogenic environment, has a major genetic component, interactions among genes, and epigenetics involvement (8,9). There are many mechanisms involved in the control of energy balance, but the leptin-melanocortin pathway has received the most attention. Mutations of the genes that regulate this pathway such as leptin (*LEP*) and leptin receptor (*LEPR*) cause a deficiency protein produced by the genes that alter the regulation of body weight and are associated with obesity (10,11). In the case of common obesity, the existence of polymorphisms in genes associated with body weight becomes intriguing to examine because the incidence of obesity caused by mutations in a gene is quite rare. In the form of polygenic obesity, polymorphism in candidate genes has been evaluated (12). The emergence of the hypothesis that leptin resistance occurs in obesity opens up research opportunities that focus on polymorphism in the *LEP* and *LEPR* and its association with anthropometric as well as biological markers in the obesity (13,14).

Recent studies also considered that obesity has a link with oral health due to the shared risk factors, especially for non-healthy dietary patterns. Obesity and oral disorders, such as periodontitis, dental caries, and tooth loss, have been linked, according to a Korean longitudinal study. Compared to patients with lower body mass indexes (BMI), those with higher BMI had a significantly higher frequency of these disorders (15). Furthermore, based on the result of a systematic review including 66 articles conducted in 2023, oral health indicators including dental caries, periodontitis, and tooth loss may be associated with obesity. One of the potential explanations for this relationship is thought to be the existence of systemic inflammation in obesity (16). Just as the systemic inflammatory effects on obesity involve the role of leptin, similar concepts can be applied to any oral disease based on inflammation including periodontitis and dental caries. It has been shown that human tooth pulp tissues contain leptin receptors. Inflammatory and local immune responses in human dental pulp may be influenced by leptin, as evidenced by the up-regulation of leptin receptor expression in inflammatory pulp samples (17). In inflammatory periodontal tissues, there was a significant overexpression of leptin and leptin receptors. This upregulation was presented in periodontal cells and was linked positively with the degree of inflammatory infiltration (18).

In this review, we attempted to provide an explanation based on many investigations of the association between the most common *LEPR* single nucleotide polymorphism/SNP, Gln223Arg, and obesity phenotype including the metabolic complications that have been conducted in diverse populations. Additionally, because obesity, inflammation, and oral diseases are closely related, we are attempting to investigate the association between this polymorphism and obesity-related diseases in the field of oral health.

The study featured a search of the scientific literature for various original research, systemic reviews, and literature reviews that addressed the relationship between obesity and the *LEPR* gene polymorphism, including disorders of oral health related to obesity. The terms "obesity," "*LEPR* polymorphism," and "oral diseases" were used as keywords for searching. The databases used were NCBI, Science Direct, PubMed, Google Scholar, and other reliable online resources.

## *LEPR* POLYMORPHISM AND OBESITY

LEPR with gene ID (HGNC: 6554, Entrez Gene: 3953, Ensembl: ENSG00000116678, OMIM: 601007, UniProtKB: P48357), is located in the short arm of chromosome 1 (1p31.3) (Fig.1).


**Fig 1. Location of *LEPR* on human chromosome 1- with permission from the GeneCards (19)**

The locus starts from 65,420,652 bp to 65,641,559 bp terminal end of the short arm (pter). The gene has 220,908 bp in size based on sequence from NCBI Reference Sequence: NC_060925.1 (19). The *LEPR* consists of 24 exons and has six variants of transcription that encode four isoforms of the leptin receptor protein (20). The protein produced is called the leptin receptor, a group of cytokine gp 130 receptors, which can stimulate gene transcription by activating the protein signal transducer and activating transcription (STAT) in the cytosol. This protein is a receptor for leptin, a hormone produced by adipocytes that plays a role in regulating energy and weight balance, regulating fat metabolism, and is involved in the hematopoietic pathway to the formation of lymphocytes. The protein of the *LEPR* has a molecular weight of 132,494 Daltons, which consists of 1165 amino acids (19).

Polymorphism of *LEPR* can be found in any sites along the gene, from the untranslated region such as 3′ UTRDel/Ins of CTTTA-pentanucleotide (21,22), intronic sequence (23,24), and in the exon, especially in Lys109Arg (rs1137100), Gln223Arg (rs1137101), Ser334Ser (rs1805134), Lys656Asn (rs8179183), and Pro1019Pro (rs1805096) (21,23,25–28). Polymorphism in the intronic sequence has been reported to occur

in rs2025804 (24) and other sites of intron such as in rs11208659, rs11804091, rs10157275, rs9436303, rs1627238, and rs1327118 (23). Results from a meta-analysis study revealed that the most often examined SNP was Gln223Arg (Q223R), followed by Lys109Arg (K109R) and Lys656Asn (K656N) (29). The codon 109 in exon 4 is one of the polymorphic sites, that contain the two types of nucleotides, A or G, in position 326 (A326G). As a result, this causes the substitution of AAG-encoded lysine to become an AGG-encoded arginine (28). Position 668 in codon 223 of exon 6 (CAG to CGG) contains the non-conservative alteration that changes glutamine to an arginine (Gln/Q to Arg/R) due to the polymorphism (28). Nucleotide position 1,968 in codon 656 is located in exon 14 and is a G to C transition giving the changes of AAG (lysine/K) to become AAC (asparagine/Asn/N) (30). In addition to non-synonymous polymorphism, *LEPR* also has two of the most common synonymous SNP that do not change the amino acid, which are Ser334Ser (T of AGT alternates C to AGC) and Pro1019Pro (A of CCA alternates G to CCG) (30). Studies on *LEPR* polymorphism and its association with obesity in different populations around the world showed varying results. The American, European, and Asian populations have been explored to study the association between *LEPR* polymorphism and obesity phenotypes and clinical variables. We present the summary of the studies on the three most common polymorphisms that showed the significant impact of this polymorphism and obesity in Table I.

**Table I. Studies on the three most common *LEPR* polymorphisms associated with obesity phenotypes and clinical biomarkers**

| SNP | Population/ Country | Sample Category | Association with anthropometric variables | Association with clinical variables | References |
|---|---|---|---|---|---|
| Lys109Arg (K109R) | Japanese/Japan | Children and adolescents | The weight was higher in Arg109Arg homozygotes | Lys109Arg polymorphism was associated with total cholesterol and LDL | (26) |
| | Javanese/Indonesia | Adults | K109R polymorphism was correlated with obesity traits (body weight, BMI, and waist circumference) | K109R polymorphism was correlated with leptin level | (27) |
| | Malay, China, India/Malaysia | Adults | Population with the K allele was significantly higher in body weight, BMI, WC, WHR, total body fat, subcutaneous fat, visceral fat level, and skeletal muscle than those who have the R allele | The K allele was a risk allele for increasing blood pressure, leptin level, and resting metabolism | (28) |
| | Sweden/Swedia | Adults | The Arg109 homozygotes showed lower BMI and sagittal abdominal diameter compared to Lys109 homozygotes | The Arg109 homozygotes have lower blood pressure and HDL cholesterol | (31) |
| Gln223Arg (Q223R) | Brazilia | Children | The R allele in heterozygotes or homozygotes has higher energy intake compared to the QQ homozygous in prospective cohort study | R/R genotype carriers had significantly higher fasting glucose levels in relation to QQ | (32) |
| | Hungaria | Children | The RR genotypes exhibit a higher BMI and percent of body fat | The RR genotypes showed lower binding capacity of leptin and leptin receptor | (33) |
| | Romania/Romania | Adults | Q223R polymorphism was not associated with obesity | The 223R allele has higher triglyceride, HDL, fasting glucose, and blood pressure, indicated it as a contributor for developing metabolic alterations | (34) |
| | Caucasian/United States | Adults | Arg223 homozygotes have higher levels of BMI, waist circumference, and waist-to-hip ratio | Arg223 homozygotes has higher leptin levels | (35) |
| | Austronesian-speaking/ Pacific Island | Adults | The Q allele had a significantly higher body weight and BMI | Not evaluated | (25) |
| | India | Adults | QR and RR genotype has higher BMI and WHR compared to QQ | QR and RR genotype has higher leptin, insulin levels, and increasing the risk of T2DM | (36) |

CONTINUE

**Table I. Studies on the three most common *LEPR* polymorphisms associated with obesity phenotypes and clinical biomarkers cont.**

| SNP | Population/ Country | Sample Category | Association with anthropometric variables | Association with clinical variables | References |
|---|---|---|---|---|---|
| Gln223Arg (Q223R) | Turkish/Turkey | Adults | The waist and hip circumference were higher in the RR genotypes | The RR genotype showed an increase in total cholesterol and LDL compared to the QR and QQ genotypes | (37) |
| | Malay, China, India/Malaysia | Adults | Based on ethnicity, subjects with Q223 alleles had significantly greater BMI and adiposity indices (total body fat and subcutaneous, lower muscle percentage) | The higher systolic blood pressure can be found in Q223 individuals | (28) |
| | Javanese/Indonesia | Adults | The RR genotypes has significantly higher in body weight, BMI, and waist | RR genotypes have significantly higher leptin levels | (27) |
| Lys656Asn (K656N) | Caucasian/United States | Adults | Carriers of Asn656 homozygotes has higher levels of BMI, WC, and WHR | The leptin levels is higher in career Asn656 | (35) |
| | Mexican Mestizo/Mexico | Children and adolescents | Reductions in skinfolds and body circumference were associated with the N allele | The N allele was associated with higher HDL levels | (38) |
| | Spain | Adults | The K656N polymorphism contribute to the response of weight loss | Carriers of Asn656 allele have a different response than wild-type obese, with a lack of decrease in insulin levels, leptin levels, and HOMA-IR | (39) |

BMI: Body Mass Index; HDL: High-Density Lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance; LDL: Low-Density Lipoprotein; T2DM: Type 2 Diabetes Mellitus; WC: Waist Circumference; WHR: Waist-to-Hip Ratio

Other studies' findings indicated no association between *LEPR* polymorphism with obesity traits and metabolic parameters (31–33). Despite the high frequency of *LEPR* polymorphism in the population under study, no statistically significant correlation between the *LEPR* polymorphism, anthropometric, and metabolic parameters in children was suggested because of a recessive weak influence on body mass index/BMI (32). K109R and Q223R polymorphisms are not associated with obesity phenotypes and markers of metabolic abnormalities between groups (genotypes K/K vs. K/R and R/R for K-109R SNP, and Q/Q vs. Q/R & R for Q-223R) in Mexican children and adolescents. However, the same analysis for K656N showed the positive effect of this polymorphism on BMI, skinfold thickness, and waist circumference, as well as for lipid profile (34). Another study in the Mexican adult population stated that Q223R polymorphism was not significantly associated with BMI and leptin concentration (35,36). Studies in Asia populations presented similar results. In the Japanese population, there were no apparent relationships between the Gln223Arg or Lys109Arg *LEPR* polymorphism and BMI or clinical variables from fasting insulin, homeostasis model assessment-insulin resistance /HOMA-IR, serum leptin, and soluble leptin receptor (sOB-R) (37). Furthermore, the Q223R polymorphism also was not associated with obesity traits and metabolic markers including leptin, insulin, and lipid profiles in Turkish children (38). Even though leptin is implicated in the development of obesity, a study carried out in a large Korean population revealed that leptin is not linked to metabolic complications associated with obesity, such as type 2 diabetes mellitus (39).

**Polymorphism of Gln223Arg (Q223R) *LEPR* and the effect on obesity traits and clinical biomarkers**

The meta-analysis study indicated that the most frequently researched *LEPR* polymorphism is Q223R (29). Codon 223 of *LEPR* is a part of the leptin receptor immunoglobulin-like domain (ObR-Ig/IGD), located in the extracellular domain of this receptor, and has a role in receptor activation (40). A mutation of the A of wild-type allele to G of the mutant allele at this codon will change a neutral amino acid to a positively charged one, potentially altering the signaling capacity of the leptin receptor and suspected leading to leptin resistance (41). The consequence of this condition causes a change in leptin transport across the blood-brain barrier, dysregulation of leptin expression, hypothalamic inflammation, and gene mutation, which alter eating behavior and result in obesity (14). Molecular dynamic simulation using computational analysis showed that the mutant form of Gln223Arg *LEPR* changes conformational behavior that leads to malfunction of the receptor. The substitution of Gln at the 223rd position by Arg causes a rigid conformation of the receptor. At the atomic level, when compared to the native structure, the mutant has a higher tendency to produce intramolecular h-bonds and less capacity to form intermolecular h-bonds. The mutant's predisposition for the development of bonds revealed further confirmation that it was more stiff and

compact than the natural structure (42).

As listed in Table I, the LEPR polymorphism of Gln223Arg showed a significant association with anthropometric indicators of obesity. Individuals with the mutant 223R allele, both in heterozygous and homozygous stages, have significantly increased body weight, BMI, and adiposity indicators in numerous populations, including Hungarians, Caucasians in the United States, Indians, Turks, and Javanese in Indonesia (27,43–46). Another study in the Tunisia population revealed that the individuals with RR genotypes have significantly higher BMI, waist circumference, and daily energy intake (47). Interestingly, other populations such as in Pacific Island and multi-ethnic Malaysian suburbs (Malay, Chinese, and Indians), demonstrate the opposite results. The individuals with the Q223 allele perform higher in BMI and other fat accumulation indicators (25,28). The Gln223Arg *LEPR* polymorphism also affects developing obesity in children. A case-control study on Romanian children revealed that *LEPR* 223GG genotypes have significantly higher indicators of adiposity (MUAC – middle upper arm circumference, and TST - tricipital skinfold thickness), compared to the 223AA genotypes. Generally, the G allele carriers have a 1.67 higher risk for developing obesity (48).

Despite the effect on obesity phenotype, the Q223R *LEPR* polymorphism also affects the biological marker of obesity. According to two investigations on children in Brazilia and Hungary, the homozygous RR genotype carriers exhibited decreased binding capacity between leptin and leptin receptors, considerably increased caloric intake, and fasting blood glucose levels (43,49). In Romanian children, the *LEPR* 223GG genotypes significantly increased leptin levels, and markers of inflammation such as TNF alfa and Il-8, but decreased the adiponectin (48). On metabolic parameters, this is found that the RR genotype of Q223R *LEPR* has significantly increased the total cholesterol, blood glucose, insulin levels, and HOMA-IR (47).

Consistent with these findings, other studies on adult populations in Javanese, Indians, and Caucasians revealed that people with the 223R allele both heterozygous and homozygous have higher leptin levels as a consequence of reduced leptin binding capacity (27,44,45). The Q223R *LEPR* polymorphism is also associated with the clinical biomarkers for metabolic alteration of obesity. The individuals who have the 223R allele tend to have fasting blood glucose, insulin levels, higher triglyceride, total cholesterol, LDL, and blood pressure, which indicate the development of metabolic and cardiovascular complications of obesity (46,50). Another study in Thailand stated that leptin and blood glucose levels are significantly higher in metabolic syndrome patients and associated with the *LEPR* Q223R polymorphism (51).

**Combined genotypes Analysis of Gln223Arg LEPR Polymorphism**

In several previous studies, the association between *LEPR* polymorphism and obesity appears more significant after a combined genotype or haplotype analysis was conducted. In a study in the Tunisian population, the *LEPR* 223RR genotype was associated with obesity (OR=1.74; p=0.037). Furthermore, the combined genotype model of Q223R *LEPR* and G2548A *LEP* was associated with obesity, in which AR (2548A + 223R) dan AQ (2548A + 223Q) increased the risk of obesity in (OR=3.36; p <0.001; OR= 2.56; p=0.01, respectively) (47). A similar study conducted in the Turkish population demonstrated that the combination of *LEP*/*LEPR* GG/GG increased the risk of obesity based on statistically significant variations in genotype frequency between the obese and control groups (p<0.05) (52). Subjects with homozygous mutated genotypes for the four SNPs: GG for *LEP* A19G, AA for *LEP* G2548A, and RR for both *LEPR* K109R and *LEPR* Q223R had higher subcutaneous fat and leptin levels. These findings indicate the synergies effect between *LEP* and *LEPR* on adiposity in the Malaysian suburban population (28).

Analysis of Q223R LEPR polymorphism also showed an association with body composition after lifestyle intervention in Caucasian pre-pubertal children. In this study, response to dietary intervention, physical activity modifications, and behavioral therapy over three months, was influenced by the genetic determinant. In comparison to wild-type homozygotes (AA), carriers with minor allele (G) both in heterozygotes and homozygotes revealed significantly greater in changes body mass index and fat mass. After the completion of the genotype combination analysis between Q223R and K656N, this change became considerably more prominent (53).

The Q223R *LEPR* haplotype analysis was carried out between genes and the loci that make up the same gene. The results of a study carried out in Brazilia on individuals with Caucasian and European history, the *LEPR* 223Arg considerably increased leptin levels and waist circumference. The *LEPR* 223GG genotype in a single analysis was associated with the risk of obesity (OR=2.14; p=0.047). However, after analysis of 3 haplotypes of *LEPR* polymorphism (AGG: 109Lys/233Arg/656Lys) the risk for obesity was increased (OR: 2.56, 95% CI: 1.19-5.49, p = 0.017) (54). Another study showed that the combination analysis between *LEPR* Q223R and the other loci of the gene. The combination of genotype frequency *LEPR* 223/492/1019 showed that the AG/GG/GA combined genotypes was found more frequent in obese groups compared to the control, indicating that the 223G allele contributes to the development of adiposity in children (48). Considering the previous studies, it seems probable that a leptin receptor gene does not cause obesity; instead, a combination of factors involving ethnicity, pleitropic genotype effects, lifestyle

choices, and nutritional status may all contribute to an individual's ability to maintain energy homeostasis (46).

## SEX DIFFERENCES AS A MODIFIER OF GLN223ARG *LEPR* POLYMORPHISM

Sex differences have contributed to the association of *LEPR* polymorphism and obesity or its metabolic and cardiovascular complications. After analyzing the Q223R *LEPR* polymorphism, the girls-only carriers of the RR genotype had substantially higher mean BMI values (22.5 vs. 21.3 Kg /$m^2$ p = 0.032) and plasma leptin levels (18.2 vs. 15.1 ng /mL p = 0.016) in comparison to QR carriers. It has been suggested that the Q223R polymorphism in *LEPR* has a sex-specific influence on Spanish pubertal children, as the study demonstrates that this polymorphism is only significantly associated with leptin levels and BMI in girls (55). The different results appear in other studies conducted on Saudi children and adults. Based on genotype distribution, there was no different result between obese and non-obese groups. After adjusting the sex and class of age, there was a significant increase of GG genotype only in male obese children and teenagers (6 – 17 years old), but it was not found in adult males or female subjects (56). Another study on adult Saudis demonstrated the GG genotypes have higher BMI, waist, and hip circumference both in obese and obese women, and higher in leptin, insulin, fasting glucose, and HOMA-IR in the obese group (42). A study in Caucasian male subjects showed that the Q223R *LEPR* polymorphism was related to the incidence of obesity. The overweight and obese males with the homozygous R genotype have significantly higher BMI, waist circumference, waist-to-hip ratio, and leptin levels, but considerably decrease the whole norepinephrine spillover compared to both the lean and overweight-obese males with the Q allele. The primary conclusion obtained from this study reveals that lowered thermogenesis mediated by the Q223R *LEPR* polymorphism may contribute to the continued development of obesity (44).

## ROLE OF ENVIRONMENT ON GLN223ARG *LEPR* POLYMORPHISM

Genotype and allele frequency of Q223R *LEPR* are different among populations depending on geographical circumstances, indicating that there is a role of environment in this polymorphism. Previous studies conducted on Portuguese and Romanian showed that the genotype distribution of this polymorphism is significantly different, with the RR genotype being found less frequently in this population (32,50). In the American such as Brazilian and Mexican populations, the same results from the European countries were found. In the two populations, the RR genotype was found as the minor genotype (30,36). A similar result was found in the Spanish children population which the genotypes distribution were QQ 32.5%, QR 47.9%, and RR 19.6%, with an R allele prevalence of 43.6% (55). A study in Caucasian males also revealed that the minor genotype was the RR (44). Likewise, in the Turkish population, the RR genotype is also found in the lowest numbers compared to the heterozygous and wild-type homozygous (46). The genotype frequency in a country in Africa, Tunisia, showed a similar result, which is the lowest number of genotypes is RR and the highest frequency is the wild-type QQ genotype (47).

The opposite results were found in several studies on Asian populations. The mutant R allele was found in higher frequency in Asians including the Pacific Islands and Malaysia (25,28). A study in the Japanese population revealed that the Arg/Arg (RR) genotype was found the highest frequency both in males and females (77.2% and 72.2%, respectively) (37). Another study conducted in the Japanese population also demonstrates a similar result, in which the Arg/Arg genotype was found in 67% (26). Meanwhile, in the Korean population, the RR genotype was found in 75.9% of studied subjects (39). The difference in allele frequency of Q223R *LEPR* polymorphism between Asians and populations on other continents indicates the shift in allele frequency occurred in Asians. This phenomenon indicated the adaption process that occurred was influenced by the difference in ecological regions, subsistence, and main dietary component (57). Asians have significantly higher derived allele frequencies for 223R (80.56–95.00%) than Caucasians have (30.18–56.67%) (29). This event demonstrates the effect of evolution's natural positive selection theory. It indicates that in such populations, the derived or mutant allele has a protective effect (29). Another explanation of the environmental influence on polymorphism is on the side of how the variants affect phenotypes differently. The influence of environment on genetic polymorphism can also be explained using the nutrigenetics approach. For Q223R *LEPR* polymorphism, a study in the Finnish population demonstrates that a lifestyle intervention including diet regulation and exercise reduces the body weight in certain genotypes compared to the others. A kind of dietary composition consisting of a combination of reduced saturated fat and increased fiber intake is more effective in reducing the weight in homozygous Q genotype in individuals with impaired glucose tolerance (21). Based on the concept of genotype-phenotype interaction, it is well-known that the trait, especially the complex trait not only influenced by the single gene but also involves other elements such as other related genes, the cellular environment, mechanical forces, external molecules, temperatures, and epigenetic imprinting (58). The variability of genes in an individual was inherited from the ancestors and the expression of the genes into different phenotypes depends on specific ethnicities (58,59). A trait's influence from genes may also be explained by variations in age, genetic background, and environmental circumstances.

Alternatively, a trait's influence from genes may increase with development or at different developmental stages (32).

## *LEPR* POLYMORPHISM AND OBESITY-RELATED ORAL DISEASES: A NEW INSIGHT IN ORAL HEALTH

The findings indicating a strong association between obesity and dental disorders demonstrated a reciprocal connection between oral and systemic health. Previous studies conducted on adolescents revealed a significant frequency of dental caries and a favorable link between dental caries and both general and central obesity based on multiple markers, such as decaying, missing, and filled teeth (60,61). Another retrospective cohort study showed that increased risk for particular metabolic abnormalities, such as BMI ≥ 30 kg/m2, high waist circumference, and elevated serum leptin, was associated with a higher caries experience at age 5. In comparison to individuals who had been caries-free, those with high caries experience at age 5 were aging more quickly by age 45 (62). A study conducted on Indonesian adults revealed that more than 50% of patients with severe periodontitis have a BMI of 25 kg/$m^2$, indicating that obese persons are more susceptible to developing periodontitis (63). A large study in the United States also revealed a consistent result regarding the association between both BMI and waist circumference and periodontitis, even after controlling for numerous factors (64).

It was established that low-grade systemic inflammation occurring in obesity, and could impair other chronic inflammatory diseases like periodontitis, although the mechanism remains unclear. Patients with chronic periodontitis had significantly higher serum leptin concentrations than healthy volunteers, and there was a strong correlation between serum leptin and probing depth (65). After adjusting with BMI, the result of another study showed that the serum leptin concentration was significantly higher in obese patients with chronic periodontitis compared to non-obese. Serum leptin also significantly correlated with clinical parameters including plaque index, gingival index, probing depth, and clinical attachment loss (66). Evidence that leptin and its receptors are expressed by periodontal tissue and the dental pulp prompted the hypothesis that leptin has a role in this chronic inflammatory oral diseases (17,18). As with other multifactorial diseases, the presence of gene polymorphisms determines the genetic susceptibility to dental caries and periodontitis. Nevertheless, according to our knowledge, only two studies examined the association between periodontitis and the *LEPR* polymorphism that have been conducted. The first study was conducted in the Czech population, and the result showed that the genotype frequency of *LEPR* P1019P (rs1805096) polymorphism was not significantly different between chronic periodontitis patients and healthy controls (67). The second study in the Chinese population examined the relationship between moderate/severe periodontitis and the risk of type 2 diabetes mellitus (T2DM) by analyzing the gene-gene or gene-environment interactions between *ADIPOQ* (rs1501299) and *LEPR* (rs1137100/K109R). In contrast to individuals with none or mild periodontitis who had rs1501299-TT/GT and rs1137100-AA/GA, the results indicated that patients with moderate/severe periodontitis who had the GG rs1137100 genotype and the rs1501299 GG genotype had the highest risk of T2DM (68).

## CONCLUSIONS

Polymorphism of *LEPR* was interesting to be studied in different populations in the world, due to its possible role in developing obesity. Even though the polymorphism can be found in many sites of the gene, the Q223R polymorphism is the more frequent site to be analyzed, with contrasting results. The different results are possibly due to gene-to-gene communication or gene interaction with the natural environment. Future studies regarding this polymorphism are still interesting due to the complexity of the interaction between genes and the environment in obesity and obesity-related diseases including the inflammatory underlying oral disorders.

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