RESEARCH PAPER

Genetic Association Of Leptin G2548A Gene (Legpa G258A) Polymorphism With Periodontitis

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Abstract

Introduction: Obesity And Periodontitis Are Interlinked And Researchers Have Observed That There Is An Association Between Bmi Overweight And Obesity And Periodontitis Although The Magnitude Is Unclear. Also, It Was Reported That The Relationship Between Cardiovascular Disease And Periodontitis Should Be Considered, Since Abdominal Adiposity Or Visceral Fat Can Be Related To Both Diseases. From The Above Mentioned Articles, It Is Clear That There Is A Relationship Between Obesity And Periodontitis.

Aim: To Genetically Associate Leptin G2548A Polymorphism With Periodontitis.

Materials And Method: The Subjects Were Divided Into A Control Group A (N =25) And Cp Group B (N =25) Based On The Clinical Examination Of Probing Pocket Depth, Clinical Attachment Loss And Bleeding On Probing. The Periodontitis Group Contained 25 Patients With A Mean Age Of 39.02 ± 8.22 Years. A Volume Of 5 Ml Of Venous Blood Was Collected From The Antecubital Fossa And Dispersed In A Sterile Tube Containing A Pinch Of Ethylenediaminetetraacetic Acid. It Was Mixed Thoroughly To Avoid Clot Formation. Dna Isolation Was Performed According To The Modified Miller Et Al 1998 Protocol. Leptin G2548A Polymorphisms Were Assessed By Polymerase Chain Reaction (Pcr) Amplification And Restriction Digestion. The Primers Forward 5'- Taagccaaggcaaaattgag - 3' Reverse: 5'- Ctcaaaaatttatgttcctctgc - 3' Were Used For Amplification Of Dna Spanning The Leptin Polymorphic Site. The Digested Product Was Visualized On 2% Agarose Gel And The Results Were Documented.

Results: The Genotype Frequencies Of Lep G2548A Gene Polymorphism (Rs7799039) Among The Cases And Controls Is Shown In Table 1. The Genotype Frequency Of Cases And Controls Do Not Differ Significantly X 2Df (P = 0.690). The Overall Genotype Distribution Of The Lep G2548A Gene Polymorphism (Rs7799039) In Cases And Controls Are Shown In Table 2. Figure 1 Shows Agarose Gel Electrophoretogram Showing Partial Amplification Of Lep Gene Spanning G2548A Polymorphic Site (Rs7799039) Run Along With Standard Dna Ladder. Figure 2 Shows The Agarose Gel Electrophoretogram Showing Hhai Digested Amplicon Of Lep Gene At G2548A Site.

GENETIC ASSOCIATION OF LEPTIN G2548A GENE (LEGPA G258A) POLYMORPHISM WITH PERIODONTITIS.

Conclusion: Our Study Concludes That The Leptin G2548A Gene Polymorphism Had No Significant Association In Periodontitis. Further Studies Are Needed To Achieve A Better Understanding Of Leptin Gene Polymorphism Among Various Populations.

Keywords: Gene, Obesity, Polymorphism, Periodontitis, Inflammation.

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INTRODUCTION

Periodontal disease is a broad term for the spectrum of inflammatory diseases affecting the periodontium which comprises a set of structures that support the teeth, which include the gingiva, cementum, periodontal ligament, and alveolar bone [1]. Various classifications can be made and one of them is periodontitis, which refers to the progression of the disease over time without treatment. It is characterized by both dysbiosis of oral microbiota and proinflammatory events involving both cells and mediators from innate and adaptive immunity [2][3].For the identification of the bacterial pathogens responsible for periodontitis, many investigations targeting known species have been conducted with the use of both cultivation and molecular identification methods [4] *[5]. Tannerella forsythensis* (Bacteroides forsythus) and *Porphyromonas gingivalis* are widely regarded as major periodontal pathogens, and evidence has implicated several other species in disease etiology. However, no single pathogen or group of pathogens has been clearly identified as the cause of periodontitis [6–8]. Recent evidence also suggests a significant role for viruses in the initiation and progression of the disease. Periodontal bacteria and viruses may act synergistically to cause periodontitis [9][10].

The phenotype of periodontitis is determined by both genetic and the environmental factors that affect the individual [11]. Although pathogenic bacteria, viruses and various other environmental factors like smoking and stress [12] are involved in pathogenesis of periodontitis, genetic factors are also evidenced in the etiology of periodontitis [13,14]. There are a large number of scientific papers searching for the role of genes and their variants (polymorphisms) in host responses in periodontitis, and in the progression of the disease [15]. The genetic polymorphisms may in some situations cause a change in the protein or its expression possibly resulting in alterations in innate and adaptive immunity and may thus be deterministic in disease outcome [16] [17]. Complex diseases are typically polygenic [18]. The disease genes in complex diseases are therefore considered modifying disease genes [19] [20].

Although microorganisms are implicated as the etiologic agent that induces inflammation, it is the chemical mediators of inflammation that play a pivotal role in the loss of connective tissue, as well as supporting alveolar bone [21]. Cytokines such as interleukin-1b, tumor necrosis factor-a, prostaglandin E2, and, recently, leptin, have been shown to orchestrate the host response to infectious and inflammatory stimuli [22]

Leptin, a product of the ob (obese) gene, is a 16-kDa non-glycosylated peptide hormone, synthesized mainly in adipose cells to regulate weight control via its cognate receptor in hypothalamus centrally. It has been classified as a cytokine because it shows structural similarities to the long-chain helical cytokine family, which includes IL-2, IL-12, and growth hormone [23]. Leptin also stimulates the immune system by enhancing proinflammatory cytokine production and phagocytosis by macrophages. Therefore, during infection and inflammation, leptin expression is modulated in a manner similar to the cytokine response to infection and injury [24].

Two common functional DNA polymorphisms in the genes of leptin G2548A and leptin receptor A668G affect the amount of circulating cytokine-type hormone leptin with risk for development of oral squamous cell carcinoma (OSCC). Apart from OSCC, leptin G2548A is also involved in obesity. In a study conducted among Tunisian volunteers, the relationship between leptin G2548A polymorphism and obesity was studied. Although the results were controversial, it was observed that there is a link between the two [25]. In another similar study conducted among a Malaysian suburban population, it was noted that LEP G2548A contributes

to minor but significant variation in obesity-related phenotypes and is mainly associated with ethnicity [26].

It is important to know that obesity and periodontitis are interlinked. A study conducted in 2011 observed that there is an association between BMI overweight and obesity and periodontitis although the magnitude is unclear [27]. In another study, it was reported that the relationship between cardiovascular disease and periodontitis should be considered, since abdominal adiposity or visceral fat can be related to both diseases [28]. From the above mentioned articles, it is clear that there is a relationship between obesity and periodontitis. Thus, the aim of this study is to genetically associate leptin G2548A polymorphism with periodontitis.

MATERIALS AND METHODS

This study employed a cross-sectional design involving individuals from Chennai, Tamil Nadu, India. A total of 100 individuals who reported to the Department of Periodontics, Saveetha Dental College, Chennai, were included in this study. The subjects were divided into a control group A (N =25) and CP group B (N =25) based on the clinical examination of probing pocket depth, clinical attachment loss and bleeding on probing. The periodontitis group contained 25 patients with a mean age of 39.02 ± 8.22 years. The patients were chosen based on the 2018 classification of American Academy of Periodontology stage II and above . The control group contained 25 periodontally healthy subjects with mean age of 41.34 ± 7.49 years.

A detailed history of dental treatment, family history of periodontal diseases, smoking habits as well as general health concerns were obtained from the subjects. Except for the presence of periodontitis, the patients included in this study were systemically healthy. Smokers, pregnant or lactating mothers, immunocompromised individuals and subjects who had undergone periodontal therapy within the past 6 months were excluded from this study.

i) Sample collection

A volume of 5 mL of venous blood was collected from the antecubital fossa and dispersed in a sterile tube containing a pinch of ethylenediaminetetraacetic acid. It was mixed thoroughly to avoid clot formation. DNA isolation was performed according to the modified Miller et al 1998 protocol.

ii) Polymerase chain reaction and restriction endonuclease digestion

Leptin G2548A polymorphisms were assessed by polymerase chain reaction (PCR) amplification and restriction digestion. The primers forward 5'-TAAGCCAAGGCAAAATTGAG - 3' Reverse: 5'-CTTCAAAATTTATGTTCCTCTGC - 3' were used for amplification of DNA spanning the leptin polymorphic site. The amplification of DNA was performed in 20-µL volumes using 10 ng of genomic DNA, 5 pmol/µL each of the forward and reverse primers along with PCR Master Mix (Takara, Shiga, Japan). The cycling conditions were as follows: initial denaturation at 94°C for 5 minutes, denaturation at 94°C for 35 seconds, annealing at 54°C for 30 seconds, extension at 72°C for 35 seconds and a final extension at 72°C for 5 minutes. A 5-µL volume of PCR product was checked on a 1% agarose gel, and 15 µL of PCR product was digested using a HhaI restriction enzyme (New England Biolabs, Hitchin, UK). Digestion was carried out at 37°C for 2 hours. The digested product was visualized on 2% agarose gel and the results were documented.

iii) Statistical analysis

All statistical analyses were performed using SPSS version 23.0 for Windows (SPSS, Chicago, IL, USA). The distribution of genotypes and allele frequencies in the chronic periodontitis and control groups were compared using the $\chi 2$-test. The risk associated with individual alleles or genotypes was calculated as the odds ratio (OR) with 95% confidence intervals. Statistical significance in all tests was set at $P < .05$.

RESULTS

The genotype frequencies of LEP G2548A gene polymorphism (rs7799039) among the cases and controls is shown in Table 1. The genotype frequency of cases and controls do not differ significantly χ 2df (P = 0.690). The overall genotype distribution of the LEP G2548A gene polymorphism (rs7799039) in cases and controls are shown in Table 2. Figure 1 shows agarose gel electrophoretogram showing partial amplification of LEP gene spanning G2548A polymorphic site (rs7799039) run along with standard DNA ladder. Figure 2 shows the Agarose gel electrophoretogram showing HhaI digested amplicon of LEP gene at G2548A site.

Table 1 Genotype frequencies of LEP G2548A gene polymorphism (rs7799039) among the cases and controls

Groups	GG	GA	AA	G	A	HWE (p value)*
Case (N=25)	12	8	5	0.64	0.36	0.1265
Control (N=25)	9	10	6	0.56	0.44	0.3464

Table 2 Overall genotype distribution of the LEP G2548A gene polymorphism (rs7799039) in cases and controls

Dominant				
Genotypes	**Case**	**Control**	**Unadjusted OR [95% CI]**	**P value**
GG	12	9	1.6410 [0.5288 - 5.0928]	0.3913
GA + AA	13	16		
Recessive				
GA + GG	20	19	1.2632 [0.3299 - 4.8371]	0.7331
AA	5	6		
Allele				
G	32	18	1.3968 [0.6256 - 3.1190]	0.4148
A	28	22		

Figure 1 Agarose gel electrophoretogram showing partial amplification of LEP genespanning G2548A polymorphic site (rs7799039) run along with standard DNA ladder [Lane M = 100 bp DNA marker].

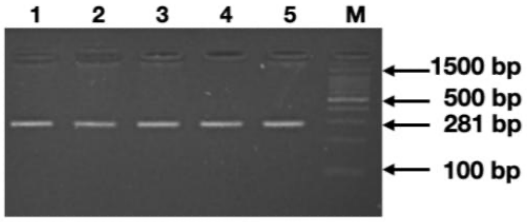
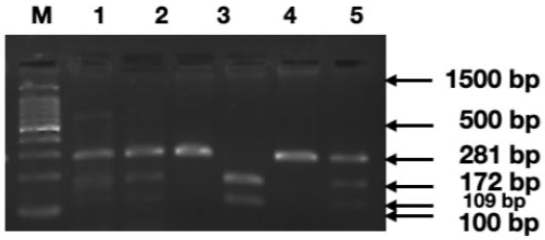
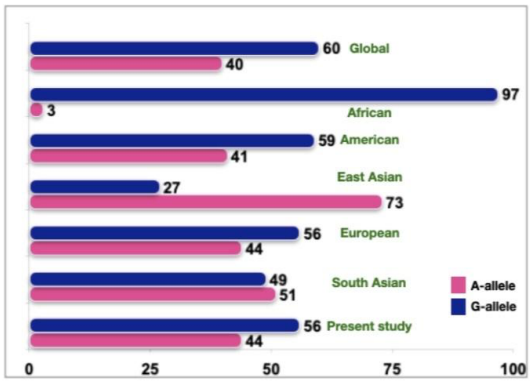


Figure 2 Agarose gel electrophoretogram showing HhaI digested amplicon of LEP gene at G2548A site (Homozygous GG - 172+109 bp; Heterozygous AG-281+172+109 bp; Homozygous AA - 281 bp) [Lane M = 100 bp DNA marker]



Graph 1 The graph depicts the allele frequency of LEP G2548A polymorphism in different population [Data acquired from Ensembl database]



DISCUSSION

The gene LEPTIN G2548A has an effect in our body by leading to the contribution of obesity and metabolic syndrome risk [25]. Apart from this, other types of the leptin gene also have a role in cardiovascular diseases [29]. In a study conducted in 2021, it was concluded that increased levels of leptin concentration might lead to movement of the teeth, especially in obese patients [30].

To the extent of our knowledge, the current study conducted is the first study to explore the association between leptin G2548A gene polymorphism with periodontitis. The polymorphism falls in line with the Hardy Weinberg Equilibrium. The p-value for statistical significance is 0.6, indicating that the association between the two is insignificant.

According to Carlson et al [31], greater levels of leptin in gingival crevicular fluid (GCF) from patients with periodontitis may act as a protective factor in the periodontal pocket. Leptin receptor expression on endothelial cells may be impacted by the cytopathic alterations that occur during inflammation. Increased

leptin receptor expression led to lower GCF level production, which may have enabled greater leptin-leptin receptor complex formation in the gingival tissue [32]. This difference was attributed to potential mechanisms and individual host responses against inflammation. In the absence of adipose tissue in the gingiva, protective mechanism could not be explained [33].

In a similar study, gingival leptin concentration was evaluated in both healthy and diseased gingiva. It was reported that the leptin levels decreased in gingiva, but the PD values increased and that GCF leptin levels and periodontal PD were inversely correlated [34]. When leptin concentrations decreased (> or =3 mm sulcus), VEGF concentrations increased, suggesting that leptin could be released from gingiva coincident to vascular expansion [35].

In a study that investigated the possible role of leptin by examining its relationship with OPG and RANKL in human gingival tissues obtained from patients with periodontitis, it was concluded that leptin was widely and significantly expressed in the control group with healthy individuals and went on to conclude that leptin can regulate OPG and RANKL expression in gingival fibroblasts and may play a role in the development of periodontitis by modulating the *OPG/RANKL* ratio [36] [37].

From other studies conducted, it can also be said that leptin might have an association with cardiovascular diseases such as myocardial infarction. It was noted that positive association was seen between increased serum leptin levels and progression of periodontitis and elevated serum leptin concentration is associated with increased BMI, GCP, and AMI. The rise in serum leptin in GCP and increased BMI may be considered as risk markers for acute myocardial infarction [31]**.**

In a similar study, elevated serum leptin concentration was correlated with the amount of periodontal destruction, whereas GCF leptin concentration was decreased with increasing severity of periodontitis, leading us to believe that the rise in serum leptin concentration attributable to periodontitis could be a risk marker for cardiovascular disease and as the periodontal disease progressed, serum leptin concentration increased [38].

It is important to note that apart from periodontitis and obesity, leptin G2548A gene is also associated with other inflammatory diseases such as atherosclerosis, renal inflammation, COPD, pelvic endometriosis, etc [39]. Among the inflammatory conditions which lead to chronicity, leptin has been considered an inflammatory marker of airway inflammation and a possible contributor to increased severity of COPD, a chronic inflammatory disease of the lung [40].

Apart from having an effect on the lungs, the kidney is another organ that is mostly affected by leptin as its clearance occurs in the said organ [41]. The kidney is subject to effects such as natriuresis, increased sympathetic nervous activity, and the stimulation of reactive oxygen species [42]. Leptin also triggers the development of glomerulosclerosis through a paracrine TGF-β pathway (between glomerular endothelial and mesangial cells) that promotes deposition of extracellular matrix and proteinuria [43]**.**

In addition to this, leptin promotes atherosclerosis by having an effect on atherogenesis. This occurs by increasing the amount of monocytes in the intima, leading to production of foam cells. This eventually leads to secretion of proinflammatory and atherogenic cytokines [44,45]**.**

CONCLUSION

Thus, our study concludes that the leptin G2548A gene polymorphism had no significant association in periodontitis. Further studies are needed to achieve a better understanding of leptin gene polymorphism among various populations.

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