**Cwalina Izabela, Komarowska Marta, Dargiewicz Ewelina, Hermanowicz Adam. The study of leptin concentration in saliva during orthodontic treatment, periodontal diseases and wound healing in the oral mucosa-review. Review article. Journal of Education, Health and Sport. 2018;8(12):743-750. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2529172**
**http://ojs.ukw.edu.pl/index.php/johs/article/view/6433**

**The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).**
**1223 Journal of Education, Health and Sport eISSN 2391-8306 7**



**The authors declare that there is no conflict of interests regarding the publication of this paper.**

**Received: 20.11.2018. Revised: 20.12.2018. Accepted: 31.12.2018.**

# The study of leptin concentration in saliva during orthodontic treatment, periodontal diseases and wound healing in the oral mucosa-review

**Izabela Cwalina[1], Marta Komarowska[2], Ewelina Dargiewicz[3], Adam Hermanowicz[2]**

[1]Ortho-Dent Private Dental Practice, Bialystok, Poland
[2] Pediatric Surgery Department; Medical University of Bialystok; Bialystok; Poland
[3] Department of Orthodontics; Medical University of Bialystok; Bialystok; Poland
Corresponding author: Izabela Cwalina, email: izabela.cwalina20@gmail.com

## Abstract

### Background

The oral cavity is a very complex environment characterized by numerous interactions between different tissues, secretions from various glands, foods, air and microorganisms. Leptin is a hormone-like protein, which plays an important role in protection of host against inflammation and infection. It exhibits many physiological properties. Some studies have reported changes in leptin levels during orthodontic treatment, wound healing, periodontal disease. The aim of the paper was to review the salivary leptin role in each of these cases.

### Methods

Articles published before November 2018 were obtained from PubMed, Dentistry & Oral Sciences Source. Inclusion criteria were: a) empirically based b) peer-reviewed.

**Discussion and results**
Salivary leptin levels significantly decrease during orthodontic tooth movement and periodontal diseases. However, it increases while wound healing in the oral mucosa.
**Conclusion**
There is a correlation between tooth movement and leptin level. Obese patients could have lesser tooth movement. This hormone promotes wound healing and angiogenesis in oral cavity. Leptin concentration in saliva increases in patients with periodontitis.

**Keywords:** saliva, leptin, healing, orthodontic tooth movement, periodontitis

## Introduction

The oral cavity is a very complex environment characterised by numerous interactions between different tissues, secretions from various glands, foods, glands, air and microorganisms. Saliva is the most important fluid in the oral cavity and salivary markers could reflect the condition of the oral cavity. It consists mainly of water (99.5%), organic (0.3%) and non-organic components (0.2%)[1]. It could be an important source of diagnostic biomarkers as an alternative to blood[2-6]. Assays are available to analyze various salivary parameters. Problems of cellular debris and turbidity may interfere with many analytical techniques. Such problems can be solved by centrifugation or collecting and storing saliva samples at temperatures that stop metabolism[2]. Measurement of leptin in this biomaterial is quite simple. It is a non-invasive method and could be alternative to blood sampling for detecting oral diseases and results of orthodontic treatment.[2,7]
Leptin is a 16-KDa, nonglycosylated polipeptide hormone-like produced mainly by adipocytes and also by the placenta, stomach, skeletal muscles, brain, salivary glands and osteoblasts. It is also known to exhibit various actions on body weight hemostasis, lipid metabolism, thermogenesis, bone formation, angiogenesis, wound healing and hematopoiesis[2,8-16]. Researchers see strong correlation between saliva leptin level and body mass index BMI. Plasma levels increase in obese subjects and decrease after weight loss [8,17].
Leptin plays a role of cytokine and hormone. As a hormone, it modulates food intake, feeling of hunger, fat storage. As a cytokine, it takes part in bone remodeling-resorption and formation, by two pathways: direct osteoblastic stimulation or indirect suppressive effect through the hypothalasmus[8,18]. Leptin has similar structure and function with cytokines such as: IL-1, IL-6, IL-10, IL-12, granulocyte stimulating factor. It might modulate the host response to infectious agents and play a role in mounting inflammatory responses in the body through induction of synthesis of other proinflammatory cytokines and stimulation of phagocytosis by macrophages[8,19-21].

The multifunctionality of leptin, wide distribution, noninvasive analysis allows us to do more researchers about its processes[8,12,13].
The purpose of this study was to systematically review leptin levels and role in the saliva of various individuals with dental problems.

## Materials and methods

A literature review was conducted based on the following databases: PubMed and Dentistry & Oral Sciences Source, with the use of the key words: saliva, leptin, healing, orthodontic tooth movement, periodontitis. For analysis, newest papers published in the years 2000-2018 in the English language were selected. Inclusion criteria were: 1) empirically-based 2) published in a peer-reviewed journal 3) comprised saliva samples 4) measured leptin levels. Studies were excluded if not enough data were available for this review.

## Results and discussion

Researchers noticed that leptin concentration decreased after putting orthodontic force on teeth. In their study Jayachandran et al. discovered grater leptin concentration in overweight subjects than normal weight individuals. They also noticed lesser tooth movement in the first ones [8,22].
Umeki et al. reported Ob-R (leptin receptor) expression in the epithelial tissue and vascular endothelial cells in the oral connective tissue and their positive influence on RT7 cells (oral mucosa cells). They accelerated the migration of these cells in the presence of leptin[13]. Khorsad et al. noticed significant leptin decrease in patients with periodontal diseases[12].
The majority of chosen studies had measure of leptin levels during orthodontic treatment, periodontitis and wound healing. All leptin measurements were based on self-report studies.

## Orthodontic treatment

Recent studies assessed leptin levels in gingival cervicular fluid (GCF) during orthodontic tooth movement[23]. It is also expressed in saliva, which is noninvasive method biomaterial collection and its concentration is high in comparison with plasma samples.
An inflammatory response localized around the tooth is frequently observed. A remodeling process takes place in periodontal tissues after the application of orthodontic forces [1,8,19-21,24,25].
Dilisiz et al. have demonstrated that after force application, several proinflammatory cytokines tend to increase in the first 24 hours. After that, the system reaches a new hemostasis until the next force activation. A significant increase of salivary leptin concentration was seen after 1 hour and decrease after 1 month [8,23].
This decrease is not surprising because periodontal changes always take place during orthodontics. Changes in the stress strain distribution in the

periodontium after the application of orthodontic forces start apposition and resorption processes. These forces compress the PDL fibers(periodontal ligament) and reduce the space in the pressure area. On the other site, fibers are stretched, and the result is widening of the periodontal space. However, another study reported that both bone resorption and apposition can be present in the tension site, as well as in the site of compression[23,26].
The results of many other studies also showed a significant decrease in saliva leptin levels of the test teeth, while the control teeth did not demonstrate any such decrease. This can be correlated to leptin's bone stimulatory effects, which could be stronger than its inhibitory effects. Leptin's bone inhibitory effects are indirect through the hypothalasmus. It might increase bone mass, which could delay orthodontic tooth movement [8,22,27].
Furthermore, several studies reported the correlation between salivary leptin levels and overweight or normal weight individuals. The patients with obesity had grater mean leptin concentrations and a significantly lesser rate of tooth movement, the normal weight patients had lower concentrations of leptin but higher rate of movement[8,22,27,28].
The other findings showed that height was the strongest predictor for leptin levels in overweight-obese patients. This may be explained by the fact that bone is crucial source of leptin [29].

**Leptin influence on wound healing in the oral mucosa**

The oral mucosa is very sensitive to many incentives. The most important are mechanical stresses, such as abrasions during chewing and biting, chemical or biological. They often fail to heal, turning into chronic ulceration. Umeki et al. investigated the physiological role of leptin in wound healing in the oral mucosa. Healing of the ulcer was completed faster in the leptin-treated group and more blood vessels were formed in the tissues where leptin was used in comparison with the control group[13]. It stimulates angiogenesis by supplying nutrients, oxygen and many bioactive substances[13,16]. Findings show that vascular and epithelial cells are target cells for leptin. In this study, they confirmed the possibility that wounds on oral mucosa and skin are healing after leptin expression. It also prevents the oral cavity of abnormalities such as lichen planus or stomatitis, which is often result of radiotherapy or chemotherapy for head and neck cancers[13].
Frank et al. reported leptin influence on various cells proliferation: skin keratinocytes- expression of epidermal growth factor (EGF) and keratinocyte growth factor (KGF), lungs epithelial cells, pancreatic beta cells, monocytes, endothelial cells and hemopoietic cells [14,30].
Umeki et al. explored promoting of wound healing in the oral mucosa by enhancing angiogenesis and epithelial cell migration. This knowledge could be useful as a treatment for many patients[13].

## Healthy people and patients with advanced periodontitis

Petersen et al. say that advanced periodontitis affects 10-15% of adults worldwide. Clinical attachment loss CAL-5mm(clinical attachment loss) or more[31]. Active cytokines are responsible for the bone loss and connective tissue damage[12]. Johnson and Serio in 2001 showed that leptin is present in healthy gingival tissues or marginal inflammation, it increased in the pocket depth and decreased with the progression of inflammation[32]. Gingiva is a source of leptin synthesis. Unfortunately, it is not clear which cells produce leptin in gingiva. Karthikeyan and Pradeep found a significant decrease in leptin concentration in the GCF during destruction of periodontal tissues[33]. Purwar et al. concluded that level of salivary leptin level in chronic periodontitis was significantly lower than in healthy patients. They also found that non-surgical therapy could induce leptin production[34]. Sattari et al, did not reported inflammatory role in periodontitis[35]. Selvarajan et al. suggested a potential protective role for leptin to periodontal health[36]. Khorsand et al. noticed salivary leptin levels are higher in healthy people and indicate its protective role in gingival tissues. It promotes osteogenesis through direct effect on osteoblasts. However, the mechanism has not been explored[12]. Summarizing, they reported that expression of leptin gene have a significant role in the modulation of periodontal inflammation.

Bozkurt et al. reported lower leptin levels in GCF in smokers. It showed that smoking damages the mechanism regulating leptin levels[32]. Aydin et al. haven't found crucial differences in salivary leptin concentration between males and females[37]. Gangadhar et al. examined that leptin levels in patients with periodontitis was attributed to its release into the blood serum [38].

However, further studies are needed to assess changes in salivary leptin levels in periodontal diseases.

## Conclusion

1.Leptin may be one of the mediators associated with orthodontic tooth movement. There is a strong correlation between the tooth movement and salivary leptin concentration.

2.It is greater salivary leptin level in overweight individuals compared with healthy individuals.

3.Subjects with higher Body Mass Index had lesser rate of tooth movement compared with normal weight patients.

4.Leptin promotes wound healing in the oral mucosa.

5.Salivary leptin levels decrease significantly, in patients with advanced periodontitis.

Competing interests
None of the authors declare competing financial interests.

## References


1. Buczko P, Knaś M, Grycz M, Szarmach I, Zalewska A. Orthodontic treatment modifies the oxidant-antioxidant balance in saliva of clinically healthy subjects. Adv in Med Sci 2017;62;129-135.
2. Thanakun S, Watanabe H, Thaweboon S, Izumi, Y. An effective techique for the processing of saliva for the analysis of leptin and adiponectin. Peptides 2013;47;60-65.
3. Mamali I, Roupas N, Armeni A, Theodoropoulou A, Markou K, Georgopoulos N. Measurment of salivary resistin, visfatin and adiponectin levels. Peptides 2012;33;120-124.
4. Toda M, Tsukinoki R, Morimoto K. Measurment of salivary adiponectin levels. Acta Diabetol 2007;44;20-22.
5. Loo J, Yan W, Ramachan P, Wong D. Comparative human salivary and plasma proteomes. J Dent Res 2010;89;1016-1023.
6. Pfaffe T, Cooper-White J, Beyerlein P, Kostner K, Punyadeera C. Diagnostic potential of saliva: current state and future applications. Clin Chem 2011;57;675-687.
7. Jiang J, Park N, Hu S, Wong D. A universal pre-analytic solution for concurrent stabilization of salivary proteins, RNA and DNA at ambient temperaturę. Arch Oral Biol 2009;54;268-273.
8. Jayachandran T, Srinivasan B, Padmanabhan S. Salivary leptin levels in normal weight and overweight individuals and their correlation with orthodontic tooth movement. Angle Orthod. 2017; 87(5);739-744.
9. Reseland J, Syversen U, Bakke I, et al. Leptin is expressed in and secreted from primary cultures of human osteoblasts and promotes bone mineralization. J Bone Miner Res. 2001;16;1426-1433.
10. Groschl M, Rauh M, Wagner R et al. Identification of leptin in human saliva. J Clin Endocrinol Metab. 2001;86;5234-5239.
11. Randeva H, Karteris E, Lewandowski K, Sailesh S, O'Hare P, Hillhouse E. Circadian rhythmicity of salivary leptin in healthy subjects. Mol Genet Metab. 2003;78;229-235.
12. Khorsand A, Bayani M, Yaghobee S, Torabi S et al. Evaluation of salivary leptin levels in healthy subjects and patients with advanced periodontitis. J of Dent. 2016;13(1);1-9.
13. Umeki H, Tokuyama S, Ide S, Okubo M, Tadokoro S, Tezuka M, Tatehara S, Satomura K. Leptin promotes wound healing in the oral mucosa. PLoS ONE 2014;9(7);1-9.
14. Frank S, Stallmeyer B, Kampfer H, Kolb N, Pfeilscifter J. Leptin enhances wound re-epithelialization and constitutes a direct function of leptin in skin repair. J Clin Invest. 2000;106;501-509.

15. Murad A, Nath A, Cha S, Demir E, Flores-Riveros J, et al. Leptin is an autocrine/paracrine regulator fo wound healing. FASEB J. 2003;17;1895-1897.
16. Stallmeyer B, Kampfer H, Podda M, Kaufmann R, Pfeilschifter J, et al. A novel keratinocyte mitogen: regulation of leptin and its functional receptor in skin repair. J Invest Dermatol. 2001; 117;98-105.
17. Paul R, Hassan M, Nazar H, Gillani S, Afzal N, Qayyum I. Effect of body mass index on serum leptin levels. J Ayub Med. Coll Abbottabad. 2011;23(3);40-43.
18. Lago R, Gomez R, Lago F, Gomez-Reino J, Gualillo O. Leptin beyond body weight regulation: current concepts concerning its role in immune function and inflammation. Cell Immunol. 2008;252(1-2);139-145.
19. Fantuzzi G, Faggioni R. Leptin in the regulation of immunity, inflammation and hematopoiesis. J Leukoc Biol. 2000;68;437-446.
20. Agrawal S, Gollapudi S, Gupta S. Leptin activates human B cells to secrete TNFα, IL-6 and IL-10 via JAK2/STAT3 and p38MAPK/ERK1/2 signaling pathway. J Clin Immunol. 2011;31;472-478.
21. Meyers J, McTiernan A, Ulrich C. Leptin and immune function: integrating the evidence. Nutr Res. 2005;25;791-803.
22. Von Bremen J, Wagner J, Ruf S. Correlation between body mass index and orthodontic treatment outcome. Angle Orthod. 2013;83;371-375.
23. Dilisiz A, Kilic N, Aydin T, Ates N, Zihini M, Bulut C. Leptin levels in gingival cervicular fluid during orthodontic tooth movement. Angle Orthod. 2010;80(3);504-509.
24. Alhashimi N, Frithiof L, Brudvik P, Bakhiet M. Orthodontic tooth movement and de novo synthesis of proinflammatory cytokines. Am J Orthod Dentofacial Orthop. 2001;119;307-312.
25. Lee K, Park Y, Yu H, Choi S, Yoo Y. Effects of continous and interrupted orthodontic force on interleukin-1β and prostaglandin E2 production in gingival cervicular fluid. Am J Orthod Dentofacial Orthop. 2004;125;167-168.
26. Thilander B, Rygh P, Reitan K. Tissue reactions in orthodontics. In: Graber TM, ed. Orthodontics: Current Principles and Techniques. St Louis, MO: CV Mosby 2000;117–156.
27. Javed F, Yu W, Thornton J, Colt E. Effect of fat on measurement of bone mineral density. Int J Body Compos Res. 2009;7;37.
28. Myers M, Leibel R, Seeley R, Schwartz M. Obesity and leptin resistance:distinguishing cause from effect. Trends Endocrinol Metab. 2010;21;643-651.
29. Abdalla Ibrahim M, Choo S. Salivary leptin level in young adult males and its association with anthropometric measurements, fat distribution and muscle mass. Europ Endocrinol. 2018;14(2);94-98.

30. Groschl M, Topf H, Kratzsch J, Dotsch J, Rascher W, et al. Salivary leptin induces increased expression of growth factors in oral keratinocytes. J Mol Endocrinol. 2005;34;353-366.
31. Petersen P, Ogava H. Strengthening the prevention of periodontal disease: the WHO approach. J Periodontol 2005;76(12);187-193.
32. Bozkurt F, Yetkin Ay Z, Sutcu R, Delibas N, Demirel R. Gingival cervicular fluid leptin levels in periodontitis patients with long-term and heavy smoking. J Periodontol. 2006;77(4);634-640.
33. Karthikeyan B, Pradeep A. Leptin levels in gingival cervivular fluid in periodontal health and disease. J Periodontal Res 2007;42(4);300-304.
34. Purwar P, Khan M, Mahdi A, Pandey S, Singh B, Dixit J, et al. Salivary and serum leptin concentrations in patients with chronic periodontitis. J Periodontol. 2015;86(4);588-594.
35. Sattari M, Joze Khaje Nouri B, Mouzeh M, Mehr Mofakhkham S, Haji Molla Hosseini M, Yeganeh F. The association between leptin and chronić periodontitis. J Dent Sch Shahid Beheshti Univ Med Sci. 2011;29(4);285-288.
36. Salvarajan S, Perumalsamy R, Emmadi P, Thiagarajan R, Namasivayam A. Association between gingival cervicular fluid leptin levels and periodontal status-A biochemical study on Indian patients. J Clin Diagn Res. 2015;9(5);48-53.
37. Aydin S, Halifeoglu I, Ozercan I, Erman F, Kilic N, Aydin S, et al. A comparison of leptin and gherlin levels in plasma and saliva of young healthy subjects. Peptides 2005;26(4);647-652.
38. Gangadhar V, Ramesh A, Thomas B. Correlation between leptin and the health of the gingiva: A predictor of medical risk. Indian J Dent Res. 2011;22(4);537-541.