|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
PubMed (National Library of Medicine ID: 101738825)
Index Copernicus Value 2018: 75.71
Original Research Article
Volume 3, Issue 11; November: 2019; Page No. 70-76

ASSESSMENT OF LEPTIN CONCENTRATION IN GINGIVAL CREVICULAR FLUID (GCF) DURING ORTHODONTIC TOOTH MOVEMENT

Dr. Samir Jain[1], Dr. Abhishek Sinha[2], Dr. Anurag Rai[3], Dr. Sapna Jain[4]
[1]MDS (Orthodontics), Professor and Head, Department of Dentistry, A.N.M.M. College and Hospital, Gaya,Bihar
[2]MDS (Orthodontics), Assistant Professor, Department of Dentistry, Patna Medical College, Patna,Bihar
[3]MDS, Professor and Head, Department of Orthodontia, Patna Dental College and Hospital, Patna,Bihar
[4]BDS, Private Practioner, Swastik Dental Clinic and Orthodontic Centre, Gaya,Bihar

Article Info: Received 15 September 2019; Accepted 05 November. 2019
DOI: https://doi.org/10.32553/ijmbs.v3i11.712
Corresponding author: Dr. Abhishek Sinha
Conflict of interest: No conflict of interest.

Abstract
The numbers of patients undergoing orthodontic treatment have increased spectacularly from past several decades. During orthodontic tooth movement the early response of periodontal tissues to mechanical stress is an acute inflammatory reaction. Mechanical stress from orthodontic appliances is believed to induce cells in the periodontal ligament (PDL) to form biologically active substances, such as enzymes and cytokines, responsible for connective tissue remodeling. Biochemical analysis of the gingival crevicular fluid (GCF) has provided a non-invasive model for investigating the cellular response of the underlying PDL during orthodontic tooth movement in vivo. In GCF, several substances such as interleukin, tumor necrosis factor, leptin, osteoprotegerin and alkaline phosphatase have been found to be significantly elevated in teeth under orthodontic forces compared with untreated control teeth. [14] Hence due to the above relevance the present study was planned for Assessment of Leptin Concentration in Gingival Crevicular Fluid (GCF) during Orthodontic Tooth Movement.

The present study was planned in Department of Private Practioner, Swastik Dental Clinic and Orthodontic Centre Gaya. Total 10 cases of orthodontic of age 13 – 15 years were evaluated in the present study. For each subject, a maxillary cuspid undergoing distal orthodontic tooth movement was used as an experimental tooth, and the contralateral cuspids served as control tooth. Orthodontic brackets were placed on the canines. Experimental canines were moved in the distal direction through an archwire by use of an elastic chain exerting an initial force of 250 g. The amount of tooth movement for each tooth was measured with digimaticcalipers. At the distal aspect of experimental and control teeth, GCF was collected for subsequent analysis and the following examinations of the periodontium were conducted: Probing depth, presence or absence of plaque, and bleeding on probing. The collection and examinations were conducted immediately before activation and at 1 hr, 1 day, and 7days after the initiation of tooth movement.

The data generated from the present study concludes that concentration of leptin in the GCF is decreased by orthodontic tooth movement. Leptin may be one of the mediators associated with orthodontic tooth movement. Orthodontic tooth movement can be carried out without any significant destructive changes in investing tissues of the teeth provided oral hygiene is properly maintained.
Keywords: Leptin Gingival crevicular fluid, GCF, orthodontic, etc.

Introduction:

Orthodontics is a specialty of dentistry that deals with the diagnosis, prevention and correction of malpositioned teeth and jaws. It can also focus on modifying facial growth, known as dentofacial orthopedics. Abnormal alignment of the teeth and jaws is common nearly 30% of the population has malocclusions severe enough to benefit from orthodontic treatment. Treatment can take several months to a few years it involves the use of dental braces and other appliances to slowly move the teeth and jaws around. If the malocclusion is very severe, jaw surgery may be used. Treatment is usually started before a person reaches adulthood since bones can more easily be moved around in children. [1]

A typical treatment for incorrectly positioned teeth (malocclusion) takes about 1 to 3 years to complete, with braces being altered slightly every 4 to 10 weeks by the orthodontist.[5] Multiple methods exist for adjusting malocclusion. In growing patients there are more options for treating skeletal discrepancies, either promoting or restricting growth using

functional appliances, orthodontic headgear or a reverse pull facemask. Most orthodontic work is started during the early permanent dentition stage before skeletal growth is completed. If skeletal growth has completed, jaw surgery can be an option. Sometime teeth are extracted to aid the aid the orthodontic treatment (teeth are extracted in about half of all of cases, most commonly the premolars). [2]

Orthodontic therapy can include the used of fixed or removable appliances. The majority of orthodontic therapy is delivered using appliances that are fixed in place, for example with braces that are bonded to the teeth with adhesives. Fixed appliances can have a greater mechanical control of the teeth and the treatment outcome is greater with the use of fixed appliances. [3]

Fixed appliances are for example used to rotate teeth that don't fit to the arch shape of the other teeth, to move multiple teeth to different places, to change the angle of teeth, or to change the position of the root of the tooth. It is not preferable if the patient has poor oral hygiene (as that can result in decalcification, tooth decay, and other problems), if the patient isn't motivated (as treatment lasts several months and commitment to oral hygiene is required), or if the malocclusions are mild.

Leptin is a hormone predominantly made by adipose cells and enterocytes in the small intestine that helps to regulate energy balance by inhibiting hunger, which in turn diminishes fat storage in adipocytes. Leptin acts on cell receptors in the arcuate nucleus of the hypothalamus. Although regulation of fat stores is deemed to be the primary function of leptin, it also plays a role in other physiological processes, as evidenced by its many sites of synthesis other than fat cells, and the many cell types beyond hypothalamic cells that have leptin receptors. Many of these additional functions are yet to be defined. In obesity, a decreased sensitivity to leptin occurs (similar to insulin resistance in type 2 diabetes), resulting in an inability to detect satiety despite high energy stores and high levels of leptin. [4]

Factors that acutely affect leptin levels are also factors that influence other markers of inflammation, e.g., testosterone, sleep, emotional stress, caloric restriction, and body fat levels. While it is well-established that leptin is involved in the regulation of the inflammatory response,[67][68][69] it has been further theorized that leptin's role as an inflammatory marker is to respond specifically to adipose-derived inflammatory cytokines. In terms of both structure and function, leptin resembles IL-6 and is a member of the cytokine superfamily. Circulating leptin seems to affect the HPA axis, suggesting a role for leptin in stress response. Elevated leptin concentrations are associated with elevated white blood cell counts in both men and women. [5]

Similar to what is observed in chronic inflammation, chronically elevated leptin levels are associated with obesity, overeating, and inflammation-related diseases, including hypertension, metabolic syndrome, and cardiovascular disease. While leptin is associated with body fat mass, however, the size of individual fat cells, and the act of overeating, it is interesting that it is not affected by exercise (for comparison, IL-6 is released in response to muscular contractions). Thus, it is speculated that leptin responds specifically to adipose-derived inflammation. Leptin is a pro-angiogenic, pro-inflammatory and mitogenic factor, the actions of which are reinforced through crosstalk with IL-1 family cytokines in cancer. [6]

Taken as such, increases in leptin levels (in response to caloric intake) function as an acute pro-inflammatory response mechanism to prevent excessive cellular stress induced by overeating. When high caloric intake overtaxes the ability of fat cells to grow larger or increase in number in step with caloric intake, the ensuing stress response leads to inflammation at the cellular level and ectopic fat storage, i.e., the unhealthy storage of body fat within internal organs, arteries, and/or muscle. The insulin increase in response to the caloric load provokes a dose-dependent rise in leptin, an effect potentiated by high cortisol levels. (This insulin-leptin relationship is notably similar to insulin's effect on the increase of IL-6 gene expression and secretion from preadipocytes in a time- and dose-dependent manner.) Furthermore, plasma leptin concentrations have been observed to gradually increase when acipimox is administered to prevent lipolysis, concurrent hypocaloric dieting and weight loss notwithstanding. Such findings appear to demonstrate high caloric loads in excess of storage rate capacities of fat cells lead to stress responses that induce an increase in leptin, which then operates as an adipose-derived inflammation stopgap signaling for the cessation of food intake so as to prevent adipose-derived inflammation from reaching elevated

levels. This response may then protect against the harmful process of ectopic fat storage, which perhaps explains the connection between chronically elevated leptin levels and ectopic fat storage in obese individuals. Leptin increases the production of leukocytes via actions on the hematopoietic niche, a pathway that is more active in sedentary mice and humans when compared to individuals which are physically active. [7]

Although leptin reduces appetite as a circulating signal, obese individuals generally exhibit a higher circulating concentration of leptin than normal weight individuals due to their higher percentage body fat. These people show resistance to leptin, similar to resistance of insulin in type 2 diabetes, with the elevated levels failing to control hunger and modulate their weight. A number of explanations have been proposed to explain this. An important contributor to leptin resistance is changes to leptin receptor signalling, particularly in the arcuate nucleus, however, deficiency of, or major changes to, the leptin receptor itself are not thought to be a major cause. Other explanations suggested include changes to the way leptin crosses the blood brain barrier (BBB) or alterations occurring during development. [8]

Studies on leptin cerebrospinal fluid (CSF) levels provide evidence for the reduction in leptin crossing the BBB and reaching obesity-relevant targets, such as the hypothalamus, in obese people. In humans it has been observed that the ratio of leptin in the CSF compared to the blood is lower in obese people than in people of a normal weight. The reason for this may be high levels of triglycerides affecting the transport of leptin across the BBB or due to the leptin transporter becoming saturated. Although deficits in the transfer of leptin from the plasma to the CSF is seen in obese people, they are still found to have 30% more leptin in their CSF than lean individuals. These higher CSF levels fail to prevent their obesity. Since the amount and quality of leptin receptors in the hypothalamus appears to be normal in the majority of obese humans (as judged from leptin-mRNA studies), it is likely that the leptin resistance in these individuals is due to a post leptin-receptor deficit, similar to the post-insulin receptor defect seen in type 2 diabetes. [9]

When leptin binds with the leptin receptor, it activates a number of pathways. Leptin resistance may be caused by defects in one or more part of this process, particularly the JAK/STAT pathway. Mice with a mutation in the leptin receptor gene that prevents the activation of STAT3 are obese and exhibit hyperphagia. The PI3K pathway may also be involved in leptin resistance, as has been demonstrated in mice by artificial blocking of PI3K signalling. The PI3K pathway also is activated by the insulin receptor and is therefore an important area where leptin and insulin act together as part of energy homeostasis. The insulin-pI3K pathway can cause POMC neurons to become insensitive to leptin through hyperpolarization. [10]

The consumption of a high fructose diet from birth has been associated with a reduction in leptin levels and reduced expression of leptin receptor mRNA in rats. Long-term consumption of fructose in rats has been shown to increase levels of triglycerides and trigger leptin and insulin resistance, however, another study found that leptin resistance only developed in the presence of both high fructose and high fat levels in the diet. A third study found that high fructose levels reversed leptin resistance in rats given a high fat diet. The contradictory results mean that it is uncertain whether leptin resistance is caused by high levels of carbohydrates or fats, or if an increase of both, is needed. [11]

Leptin is known to interact with amylin, a hormone involved in gastric emptying and creating a feeling of fullness. When both leptin and amylin were given to obese, leptin-resistant rats, sustained weight loss was seen. Due to its apparent ability to reverse leptin resistance, amylin has been suggested as possible therapy for obesity. [12]

It has been suggested that the main role of leptin is to act as a starvation signal when levels are low, to help maintain fat stores for survival during times of starvation, rather than a satiety signal to prevent overeating. Leptin levels signal when an animal has enough stored energy to spend it in pursuits besides acquiring food. This would mean that leptin resistance in obese people is a normal part of mammalian physiology and possibly, could confer a survival advantage. Leptin resistance (in combination with insulin resistance and weight gain) is seen in rats after they are given unlimited access to palatable, energy-dense foods. This effect is reversed when the animals are put back on a low-energy diet. This also may have an evolutionary advantage: allowing energy to be stored efficiently when food is plentiful would

be advantageous in populations where food frequently may be scarce. [13]

The numbers of patients undergoing orthodontic treatment have increased spectacularly from past several decades. During orthodontic tooth movement the early response of periodontal tissues to mechanical stress is an acute inflammatory reaction. Mechanical stress from orthodontic appliances is believed to induce cells in the periodontal ligament (PDL) to form biologically active substances, such as enzymes and cytokines, responsible for connective tissue remodeling. Biochemical analysis of the gingival crevicular fluid (GCF) has provided a non-invasive model for investigating the cellular response of the underlying PDL during orthodontic tooth movement in vivo. In GCF, several substances such as interleukin, tumor necrosis factor, leptin, osteoprotegerin and alkaline phosphatase have been found to be significantly elevated in teeth under orthodontic forces compared with untreated control teeth. [14] Hence due to the above relevance the present study was planned for Assessment of Leptin Concentration in Gingival Crevicular Fluid (GCF) during Orthodontic Tooth Movement.

Methodology:

The present study was planned in Department of Private Practioner, Swastik Dental Clinic and Orthodontic Centre Gaya. Total 10 cases of orthodontic of age 13 – 15 years were evaluated in the present study. For each subject, a maxillary cuspid undergoing distal orthodontic tooth movement was used as an experimental tooth, and the contralateral cuspids served as control tooth. Orthodontic brackets were placed on the canines. Experimental canines were moved in the distal direction through an archwire by use of an elastic chain exerting an initial force of 250 g. The amount of tooth movement for each tooth was measured with digimaticcalipers. At the distal aspect of experimental and control teeth, GCF was collected for subsequent analysis and the following examinations of the periodontium were conducted: Probing depth, presence or absence of plaque, and bleeding on probing. The collection and examinations were conducted immediately before activation and at 1 hr, 1 day, and 7days after the initiation of tooth movement.

The GCF sampling was performed by the method of Offenbacher et al. [15] GCF was collected from the experimental and control teeth. The tooth was gently washed with water, and the sites under study were isolated with cotton rolls (to minimize contamination from saliva) and gently dried with an air syringe. Paper strips (Periopaper, Harco, Tustin, CA, USA) were carefully inserted 1 mm into the gingival crevice and allowed to remain there for 30 seconds. After a one-minute interval, a second strip was placed at the same site. Care was taken to avoid mechanical injury. The volume of GCF in the periopaper was measured with a Periotron (Harco, Tustin, CA, USA). The paper strips from the individual sites were stored at -30°C until further processing could be carried out.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: (1) good systemic health; (2) not on antibiotic therapy within the past 6 months; (3) no use of anti-inflammatory drugs in the month preceding the study; (4) healthy periodontium, with generalized probing depth of 2 mm and no radiographic evidence of periodontal bone loss; and (5) requirements of first-premolar extraction and canine distal tooth movement as a part of orthodontic treatment.

Exclusion Criteria: Patients not willing participate in study.

Results & Discussion:

Orthodontic forces cause an initial inflammatory response followed by alterations in the vascular and neural envelope and perpetual bone and tissue remodelling accompanied by paracrine release of bioactive mediators. [16-18] During orthodontic tooth movement (OTM), host-derived enzymes are released at various stages of activation, resorption, reversal and deposition of osseous elements and degradation of the extracellular matrix. [19] Some of these enzymes have been identified in the periodontal (pdl) tissue of orthodontically moved teeth. [20] Gingival crevicular fluid (GCF) is however a better choice for assessing biomolecules or mediators as sample collection is simple, sensitive, convenient, repetitive and non-invasive. [21] Thus, the quantitative estimations of mediators in GCF reflect biochemical mechanisms associated with OTM. A systematic review (SR) by Kapoor et al [21] in 2014 studied variation in GCF level of cytokines with type

and magnitude of orthodontic forces and growth status of patients. It established a positive correlation of GCF activity index IL1RA (interleukin receptor antagonist)/ IL-1β) with intensity of pain and velocity of OTM and a negative correlation with growth status of patients. Besides cytokines, numerous other mediators also alter GCF during OTM, comprehensively reviewed in SR by Alhadlaq in 2015. [18]

Table 1: Levels of Gingival Crevicular Fluid Volume (mL)

	Control Teeth	**Cases Teeth**
Cases of	Normal Teeth	Orthodontic Treatment
Initial	0.56 – 1.23	0.55 – 1.19
1 hr	0.55 – 1.18	0.56 – 1.25
After 1 day	0.56 – 1.20	0.55 – 1.23
After 7 days	0. 58 – 1.22	0.57 – 1.17

Table 2: Levels of GCP Leptin (pg/mL)

	Control Teeth	**Cases Teeth**
Cases of	Normal Teeth	Orthodontic Treatment
Initial	1.75 – 2.99	1. 29 – 3.33
1 hr	1.31 – 3.29	1.25 – 3.31
After 1 day	1.71 – 3.11	1.39 – 3. 32
After 7 days	1.38 – 3. 35	0.98 – 2.67

Dilsiz et al., who evaluated leptin concentration in GCF before and after force application up to one week, reported a gradual decrease in GCF leptin concentration which is contradictory to our results.[20] The results in this study was also different from previous studies that measured other biomarkers during orthodontic tooth movement, where an exponential increase in concentrations of the mediators was observed after force application. The presence of leptin in gingival crevicular fluid during orthodontic tooth movement and concluded that the concentration of leptin in GCF is decreased by orthodontic tooth movement; this study also suggests that leptin may have been one of the mediators responsible for orthodontic tooth movement. [22]

Leptin's bone regulatory actions include proliferation and differentiation of osteoblasts and prolongation of the life span of human primary osteoblast by inhibiting apoptosis. [24,27] It also promotes growth of cultures of both primary osteoblasts and chondrocytes.[23, 25, 27-28] Leptin inhibits osteoclastogenesis, by down regulating RANK production from mononuclear cells. [29] Further, leptin decreases the production of osteoprotegrin which is an inhibitor of bone formation. [23]

Among the various biomarkers evaluated for orthodontic tooth movement, interleukin 1 beta was correlated to the rate of tooth movement. There was a positive correlation between concentration of interleukin 1 beta and the rate of tooth movement.[30-31] Leptin is found to control the interleukin system by stimulating secretion of interleukin 1 ß s, interleukin 1 receptor antagonist, and expression of IL 1 receptor, which could also explain the positive correlation of GCF leptin concentration to rate of tooth movement. [32]

Bremen et al. reported that orthodontic treatment duration was greater in obese individuals.[33] Such individuals were found to have greater serum leptin concentrations and increased bone mineral density. [34-35] The common age group of orthodontic patients is usually early adolescence. Due to increasing prevalence of obesity among children, [36] there is a possibility of leptin playing a major role in orthodontic tooth movement and therefore the treatment outcome.

Significantly decreased levels of leptin concentration might result from the presence of inflammation adjacent to the teeth undergoing movement. It has been shown previously that orthodontic tooth movement may therefore show local traits of a damage/ repair process with inflammation-like reactions: high vascular activity, many leukocytes and macrophages, and involvement of the immune system. [37]

Future studies are required to evaluate the levels of leptin in GCF under various force magnitudes over a long period and to clarify the protective role of leptin in periodontal disease progression. Future interventional studies involving leptin administration are expected to further clarify the pharmaco therapeutic role of leptin in orthodontic tooth movement and periodontal disease progression.

Conclusion:

The data generated from the present study concludes that concentration of leptin in the GCF is decreased by orthodontic tooth movement. Leptin may be one of the mediators associated with orthodontic tooth movement. Orthodontic tooth movement can be carried out without any significant destructive

changes in investing tissues of the teeth provided oral hygiene is properly maintained.

References:

1. Borzabadi-Farahani, Ali (2011). "An Overview of Selected Orthodontic Treatment Need Indices". In Naretto, Silvano (ed.). Principles in Contemporary Orthodontics. In Tech. pp. 215–236. doi:10.5772/19735. ISBN 978-953-307-687-4.
2. Capelli Júnior, Jonas; Fernandes, Luciana Q. P.; Dardengo, Camila de S.; Capelli Júnior, Jonas; Fernandes, Luciana Q. P.; Dardengo, Camila de S. (February 2016). "Frequency of orthodontic extraction". Dental Press Journal of Orthodontics. 21 (1): 54–59. doi:10.1590/2177-6709.21.1.054-059.oar. ISSN 2176-9451. PMC 4816586. PMID 27007762.
3. "Child Dental Health Survey 2013, England, Wales and Northern Ireland". digital.nhs.uk. Retrieved 2018-03-08.
4. Pan H, Guo J, Su Z (May 2014). "Advances in understanding the interrelations between leptin resistance and obesity". Physiology & Behavior. 130: 15769. doi:10.1016/j.physbeh.2014.04.003. PMID 247 26399.
5. Mabuchi T, Yatsuya H, Tamakoshi K, Otsuka R, Nagasawa N, Zhang H, Murata C, Wada K, Ishikawa M, Hori Y, Kondo T, Hashimoto S, Toyoshima H (2005). "Association between serum leptin concentration and white blood cell count in middle-aged Japanese men and women". Diabetes Metab. Res. Rev. 21 (5): 441–47. doi:10.1002/dmrr.540. PMID 15724240.
6. *Perrier S, Caldefie-Chézet F, Vasson MP (January 2009). "IL-1 family in breast cancer: potential interplay with leptin and other adipocytokines". FEBS Lett. 583 (2):25965.* doi:10.1016/j.febslet.2008.12.03 0. PMID 19111549.
7. Frodermann, Vanessa; Rohde, David; Courties, Gabriel; Severe, Nicolas; Schloss, Maximilian J.; Amatullah, Hajera; McAlpine, Cameron S.; Cremer, Sebastian; Hoyer, Friedrich F.; Ji, Fei; van Koeverden, Ian D. (2019-11-07). "Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells". Nature Medicine. doi:10.1038/s41591-019-0633-x. ISSN 1078-8956.
8. Myers MG, Cowley MA, Münzberg H (2008). "Mechanisms of leptin action and leptin resistance". Annu. Rev. Physiol. 70 (1): 537–56. doi:10.1146/annurev.physiol.70.113006.100707. PMI D 17937601.
9. Considine RV, Caro JF (November 1997). "Leptin and the regulation of body weight". Int. J. Biochem. Cell Biol. 29 (11): 1255–72. doi:10.1016/S1357 2725(97) 00050-2. PMID 9451823.
10. Oswal A, Yeo G (February 2010). "Leptin and the control of body weight: a review of its diverse central targets, signaling mechanisms, and role in the pathogenesis of obesity".Obesity(Silver Spring).18 (2): 221–29. doi:10.1038/oby.2009.228.PMID 19644451.
11. Harris RB, Apolzan JW (Jun 2012). "Changes in glucose tolerance and leptin responsiveness of rats offered a choice of lard, sucrose, and chow". Am J Physiol Regul Integr Comp Physiol. 302 (11): R1327–39. doi:10.1152/ajpregu.00477.2011. PMC 3378343. PMID 22496363.
12. Roth JD, Roland BL, Cole RL, Trevaskis JL, Weyer C, Koda JE, Anderson CM, Parkes DG, Baron AD (May 2008). "Leptin responsiveness restored by amylin agonism in diet-induced obesity: evidence from nonclinical and clinical studies". Proc. Natl. Acad. Sci. USA. 105 (20): 7257–62. Bibcode: 2008PNAS.105. 7257R.
13. Obici S, Rossetti L (December 2003). "Minireview: nutrient sensing and the regulation of insulin action and energy balance". Endocrinology. 144 (12): 5172–78. doi:10.1210/en.2003-0999. PMID 12970158.
14. Dilsiz A, Kilic N, Aydin T, et al. Leptin levels in gingival crevicular fluid during orthodontic tooth movement. Angle Orthod. 2010;80:504–5.
15. Offenbacher S, Odle BM, Van Dyke TE. The use of crevicular fluid Prostaglandin E2 levels as a predictor of periodontal attachment loss. J Periodontal Res 1986;21:101-12.
16. Meeran NA. Cellular response within the periodontal ligament on application of orthodontic forces. J Indian Soc Periodontol. 2013;17(1):16-20.
17. Krishnan V, Davidovitch Z. Cellular, molecular, and tissue-level reactions to orthodontic force. Am J Orthod Dentofacial Orthop. 2006 Apr;129(4):469.e1-32.
18. Alhadlaq AM. Biomarkers of orthodontic tooth movement in gingival crevicular fluid: a systematic review. J Contemp Dent Pract. 2015;16(7):578-87.
19. Apuzzo F, Cappabianca S, Ciavarella D, Monsurrò A, Silvestrini-Biavati A, Perillo L. Biomarkers of periodontal tissue remodeling during orthodontic tooth movement in mice and men: overview and clinical relevance. Sci World J. 2013 Apr 23;2013: 105873.
20. Lilja E, Lindskog S, Hammarström L. Histochemistry of enzymes associated with tissue degradation incident to orthodontic tooth movement. Am J Orthod. 1983;83(1):62-75.
21. Kapoor P, Kharbanda OP, Monga N, Miglani R, Kapila S. Effect of orthodontic forces on cytokine and receptor levels in gingival crevicular fluid: a systematic review. Prog Orthod. 2014 Dec 9;15:65.
22. Dilsiz A, Kilic N, Aydin T, et al. Leptin levels in gingival crevicular fluid during orthodontic tooth movement. Angle Orthod. 2010;80:504–5.
23. Gordeladze JO, Drevon CA, Syversen U, Reseland JE. Leptin stimulates human osteoblastic cell proliferation, de novo collagen synthesis and

mineralization: Impact on differentiation markers, apoptosis and osteoclastic signalling. J Cell Biochem. 2002;85:825–36.

24. Holloway WR, Collier FM, Aitken CJ, Myers DE, Hodge JM, Malakellis M, et al. Leptin inhibits osteoclast generation. J Bone Miner Res. 2002;17:200–9.

25. Reid IR, Comish J. Direct actions of leptin on bone remodelling. Calcif Tissue Int. 2004;74:313–6.

26. Thomas T, Gori F, Khosla S, Jensen MD, Buuguera B, Riggs B. Leptin acts on human marrow stromal cells to enhance differentiation to adipocytes. Endocrinology. 1999;140:1630–8.

27. Turner RT, Kalra SP, Wong CP, Philbrick KA, Lindenmaier LB, Boghossian S, et al. Peripheral leptin regulates bone formation. J Bone Miner Res. 2013; 28:22–34.

28. Upadhyay J, Farr OM, Mantzoros CS. The role of leptin in regulating bone metabolism. Metabolism. 2015;64:105–13.

29. Ducy P, Amling M, Takeda S Priemel M, Schilling AF, Beil FT, et al. Leptin inhibits bone formation through a hypothalamic relay: A central control of bone mass. Cell. 2000;100:197–207.

30. Iwasaki LR, Haack JE, Nickel JC, Reinhardt RA, Petro TM. Human interleukin-1β and interleukin-1 receptor antagonist secretion and velocity of tooth movement. Arch Oral Biol. 2001;46:185–9.

31. Iwasaki LR, Gibson CS, Crouch LD, Marx DB, Pandey JP, Nickel JC. Speed of tooth movement is related to stress and 1L-1 gene polymorphisms. Am J Orthod Dentofac Orthop. 2006;130:698–e1.

32. Gonzalez RR, Leary K, Petrozza JC, Leavis PC. Leptin regulation of the interleukin-1 system in human endometrial cells. Mol Hum Reprod. 2003;9:151–8.

33. Von Bremen J, Wagner J, Ruf S. Correlation between body mass index and orthodontic treatment outcome. Angle Orthod. 2012;3:371–5.

34. Leonard MB, Shults J, Wilson BA, Tershakovec AM, Zemel BS. Obesity during childhood and adolescence augments bone mass and bone dimensions. Am J Clin Nutr. 2004;80:514–23.

35. Morberg CM, Tetens I, Black E, Toubro S, Soerensen TI, Pedersen O, et al. Leptin and bone mineral density: A cross -sectional study in obese and non-obese men. J Clin Endocrinol Metab. 2003;88:5795–800.

36. World Heart Federation. Childhood Obesity Think Tank. [Last accessed on 2012 Oct 01]. Available from: http://www.world-heart-federation.org/ publications /heart-beat-e-newsletter/heart-beat-december-2006 January-2007/in-this-issue/childhood-obesity-think-tank/

37. Ducy P, Amling M, Takeda S, et al. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell. 2000;100:197–207.