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EFFECT OF NON SURGICAL PERIODONTAL THERAPY ON LEVELS OF INFLAMMATORY BIOMARKERS IN STAGE III/IV GENERALIZED PERIODONTITIS PATIENTS VERSUS PERIODONTALLY HEALTHY INDIVIDUALS

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ABSTRACT

Aim of the present study : To assess the levels of Interleukin-17 and Interleukin-18 in the gingival crevicular fluid (GCF) of stage III/ IV generalized periodontitis patients compared to their levels in periodontally healthy individuals.

Subjects and methods: Fifty subjects were included; twenty five of them are diagnosed with stage III/ IV generalized periodontitis and the other twenty five are periodontally healthy subjects. Probing depth (PD), clinical attachment level (CAL), plaque index (PI) and gingival index (GI) were recorded for all the enrolled subjects. GCF levels of Il-17 and IL-18 were analyzed by enzyme-linked immunosorbent assay (ELISA).

Results: Clinical parameters and GCF levels of Interleukin -17 and Interleukin -18 were higher in stage III/ IV generalized periodontitis than periodontally healthy subjects and both Il-17 and Il-18 are positively correlated.

Conclusion: Higher levels of Interleukin -17 and Interleukin -18 in stage III/ IV generalized periodontitis and their decrease after non surgical treatment show that they may have a role in pathogenesis of aggressive periodontitis.

KEYWORDS: Stage III/IV generalized periodontitis, interleukin-17, interleukin-18, GCF

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INTRODUCTION

Periodontitis is one of the inflammatory diseases related to many factors as bacterial agents present in the dental plaque biofilm, host susceptibility, and various environmental factors**.** The clinical characteristics of periodontitis involve gingival inflammation, clinical attachment loss (CAL), alveolar bone resorption, periodontal pocket formation (PD), and gingival recession. ***(Flemmig, 1999, Kinane, 1999, Tonetti and Mombelli, 1999).***

In 2009 ,the incidence and intensity of periodontal tissue destruction were described to be around 47% among the United States mature population as documented by ***Eke***'s research at ***2012***.The result of periodontal diseases is periodontal inflammation ***(Seymour et al., 2007)*** which finally leads to bone resorption, mobile teeth, and quick teeth loss ***(Poorsattar et al., 2014)***.

Therefore, phase 1 periodontal therapy comprising scaling and root planing with manual or powered instruments is considered as the main and typical treatment resulting in removal of calculus and disruption of any remaining biofilms ***(Axelsson and Lindhe 1981).*** Due to the increased incidence of periodontal disease, it is needed to identify new approaches for diagnosis of such diseases. Many biologic markers in body fluids such as gingival crevicular fluid (GCF) can be used as markers for observing first alterations in periodontal tissues and can also govern the usefulness of the periodontal therapy ***(Luke et al., 2015).***

IL-17 can be synthesized by many cells as macrophages, natural killer cells and mast cells ***(Yao et al., 1995)***. Powerful intracellular biologic effects can occur when IL-17 combine with other cytokines ***(Korn et al., 2009).***

The RANKL gene appearance was found to be increased by IL-17 which also decreases the osteoprotegerin gene expression in osteoblasts, together with increasing the bone resorption ***(Lubberts et al., 2003)***.

Similar to other inflammatory cytokines, IL-17 helps in bone remodeling and shows an intrabony defensive role against periodontal disease organisms such as ***porphyromonas gingivalis (PG) (Yu et al., 2007)***. Accordingly, the role of IL-17 remains uncertain ***(Takahashi et al., 2005, Kramer and Gaffen 2007, Kadkhodazadeh et al., 2013).***

IL-1 cytokine family include many cytokines as Interleukin 18 (IL-18) that can be synthesized by keratinocytes, macrophages, epithelium cells of intestine, bone forming cells, and adrenal gland cortex cells ***(Dinarello 1999).***

Together with IL1b , IL-18 has a proinflammatory role and increases immune responses by stimulating production of additional cytokines as, IL-8, TNF-a, and IL-1b and also increases the reaction of T helper 1 (Th1) and T helper 2 (Th2) cells ***(Dinarello 2000, Gracie et al., 2003)***.It is also able to increase neutrophil chemotaxis and bone resorption; so it can be considered as a significant factor for cleaning of viruses and intracellular pathogens ***(Netea et al., 2002, Arend et al., 2008).***The increased levels of IL-18 in host body fluid samples from diseased patients confirmed its role in pathogenesis of periodontal disease ***(Orozco et et al., 2006 and 2007, Figueredo et al., 2008).***

Due to the importance of early diagnosis of periodontal disease and the deficiency of data regarding the relationship between IL-17 and IL-18 and these diseases, the present study was performed.

SUBJECTS AND METHODS

Ethics approval

Research ethical committee in Faculty of Oral and Dental medicine, Future University in Egypt has accepted this clinical study with number (FUE. REC(2)/2-2023) and was also listed at https://clinicaltrials.gov/ under the number (NCT05295576).

Oral consent was taken from patients as many of them can't read or write

1-Populations:

A total of 50 individuals were enrolled and categorized as;

Group A that included 25 stage III/IV generalized periodontitis patients and

Group B which included 25 periodontally healthy controls.

2- Inclusion criteria: Medically free subjects from both genders with age range between 30 to 60 years old were included **(Kerr and Millard 1965).**

3-Exclusion criteria: Patients with periodontal surgeries in the last 6 months, Subjects with prior usage of antibiotics in the last 6 months ,Smokers, Pregnant and lactating females were excluded

4-Clinical parameters:

- ***Plaque Index (PI) :as discussed by Silness and Loe, 1964.***

- Gingival Index (GI):

The degree of gingival inflammation was recorded by means of gingival index of **(Löe and Silness, 1963),** which divided tissues surrounding each tooth into four gingival scoring units: Disto -facial papilla, facial margin, mesio-facial papilla, and the entire lingual gingival margin.

- ***Probing depth (PD) and Clinical Attachment level (CAL):***

Both were recorded in 6 points (3 buccal and 3 lingual/palatal) using William's graduated periodontal probe. Pocket depth was measured from the gingival margin to the base of the pocket while clinical attachment level was measured from the cemento-enamel junction (CEJ) to the base of the periodontal pocket **(Glavind and Löe 1967)**.

5. GCF sampling:

In **group A** ,the site with deepest probing depth was selected for GCF sampling while in **group B** , any site was sampled using PerioPaper strips* according to guidelines provided by ***Bıyıkoğlu et al., 2013*** and ***Kinney et al., 2014.***

6. Phase I periodontal therapy

After baseline GCF sample collection and clinical measurements, group A patients received phase I periodontal therapy.

7. Analysis of Il-17 and Il-18 levels in GCF:

GCF samples were examined by enzyme-linked immunosorbent assay (ELISA).Procedures were achieved according to the manufacture directions in the kits.

Statistical Analysis

Numerical data were explored for normality by checking the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). IL-17 and IL-18 levels data showed normal (parametric) distribution while PI, GI, PD, CAL and amounts of change in all parameters showed non-normal (non-parametric) distribution. Numerical data were presented as mean and standard deviation (SD) values. For parametric data; Student's t-test was used to compare between mean age values in the two groups. Repeated measures ANOVA test was used to compare between the groups and study the changes within group regarding IL-17 and IL-18 levels. Qualitative data were presented as frequencies and percentages. Chi-square test was used to compare between gender data in the two groups. The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

* PerioPaper, ProFlow, Amityville, NY, USA

RESULTS

Base line demographics

There was no significant statistical difference between mean age values in the two groups. There was also no statistically significant difference between gender distributions in the two groups.

Plaque Index (PI)

At base line; stage III/IV generalized periodontitis group showed higher statistical significant mean PI than control group (*P*-value <0.001, Effect size = 1.598). After three months; there was no statistical significant difference between the two groups (*P*-value = 0.209, Effect size = 0.003). There was a statistical significant decrease in mean PI in stage III/IV generalized periodontitis group after three months (*P*-value <0.001, Effect size = 0.834).

Gingival Index (GI)

At base line; stage III/IV generalized periodontitis group showed higher statistical significant mean GI than control group (*P*-value <0.001, Effect size = 2.243). After three months; there was no statistical significant difference between the two groups (*P*-value = 0.386, Effect size = 0.215). There was a statistical significant decrease in mean GI in stage III/IV generalized periodontitis group after three months (*P*-value <0.001, Effect size = 0.822).

Probing Pocket Depth (PD)

At base line as well as after three months; stage III/IV generalized periodontitis group showed statistically significantly higher mean PD than control group (*P*-value <0.001, Effect size = 3.313) and (*P*-value <0.001, Effect size = 2.3), respectively. There was a statistically significant decrease in mean PD in stage III/IV generalized periodontitis group after three months (*P*-value <0.001, Effect size = 0.891).

Clinical Attachment Level (CAL)

There was a statistical significant decrease in mean CAL in stage III/IV generalized periodontitis group after three months (*P*-value <0.001, Effect size = 0.854).

Interleukin-17 (IL-17) level

At base line as well as after three months; stage III/IV generalized periodontitis group showed higher statistical significant mean IL-17 level than control group (*P*-value <0.001, Effect size = 0.843) and (*P*-value = 0.001, Effect size = 0.21), respectively. There was a statistical significant decrease in mean IL-17 after three months in stage III/IV generalized periodontitis group (*P*-value <0.001, Effect size = 0.689).

Interleukin-18 (IL-18) level

At base line as well as after three months; stage III/IV generalized periodontitis group showed statistically significantly higher mean IL-18 level than control group (*P*-value <0.001, Effect size = 0.685) and (*P*-value <0.001, Effect size = 0.428), respectively. There was a statistically significant decrease in mean IL-18 after three months in stage III/IV generalized periodontitis group (*P*-value <0.001, Effect size = 0.657).

Correlation between IL-17 and IL-18 levels in stage III/IV generalized periodontitis group

There was a statistically significant direct correlation between IL-17 and IL-18 levels at base line as well as after three months (r = 0.295, *P*-value = 0.038) and (r = 0.417, *P*-value = 0.003), respectively.

TABLE (1) Descriptive statistics and results of Student's t-test and Chi-square test for comparison between base line characteristics in the two groups

	Stage III/IV periodontitis (n = 25)	Control (n = 25)	*P*-value
Age			
Mean (SD)	35.2 (6.2)	36.2 (3.7)	0.492
Gender [n (%)]			
Male	8 (32%)	8 (32%)	1
Female	17 (68%)	17 (68%)	

: Significant at P ≤ 0.05

TABLE (2) The mean, standard deviation (SD) values, results of Mann-Whitney U test and Wilcoxon signed-rank test for comparison between clinical parameters in the two groups and the changes within each group

Clinical parameter	Time	Stage III/IV periodontitis (n = 25)		Control (n = 25)		*P*-value	Effect size (*d*)
		Mean	SD	Mean	SD		
	Base line	2.28	0.74	1	0.59	<0.001*	1.598
PI	3 months	0.8	0.58	1	0.59	0.209	0.003
	Change	1.48	0.82	-		-	-
P-value (Effect size)				<0.001*		(*d* = 0.834)	
	Base line	1.96	0.68	0.56	0.51	<0.001*	2.243
GI	3 months	0.72	0.61	0.56	0.51	0.386	0.215
	Change	1.24	0.78	-		-	-
P-value (Effect size)				<0.001*		(*d* = 0.822)	
	Base line	5.4	0.91	1.36	0.57	<0.001*	3.313
PD (mm)	3 months	2.96	0.73	1.36	0.57	<0.001*	2.3
	Change	2.44	1.04	-		-	-
P-value (Effect size)				<0.001*		(*d* = 0.891)	
	Base line	6.28	1.28	-		-	-
CAL (mm)	3 months	4.44	0.92	-		-	-
	Change	1.84	1.07	-		-	-
P-value (Effect size)				<0.001*		(*d* = 0.854)	

: Significant at P ≤ 0.05

TABLE (3) The mean, standard deviation (SD) values, results of repeated measures ANOVA for comparison between Interleukin 17 and 18 levels in the two groups and the changes within each group

Interleukins	Time	Stage III/IV periodontitis (n = 25)		Control (n = 25)		*P*-value	Effect size (*Partial* η^2)
		Mean	SD	Mean	SD		
	Base line	42.4	4.28	21.52	4.91	<0.001*	0.843
IL-17	3 months	26.44	4.82	21.52	4.91	0.001*	0.21
	Change	15.96	5.77	-		-	-
P-value (Effect size)				<0.001*		(*Partial* η^2 = 0.689)	
	Base line	280.4	95.6	13.43	4.66	<0.001*	0.685
IL-18	3 months	117.22	68.48	13.43	4.66	<0.001*	0.428
	Change	163.18	102.7	-		-	-
P-value (Effect size)				<0.001*		(*Partial* η^2 = 0.657)	

: Significant at P ≤ 0.05

TABLE (4) Results of Pearson's correlation coefficient for the correlation between IL-17 and IL-18 levels

Time	Correlation coefficient (*r*)	*P*-value
Base line	0.427	0.033*
3 months	0.470	0.018*

: Significant at P ≤ 0.05

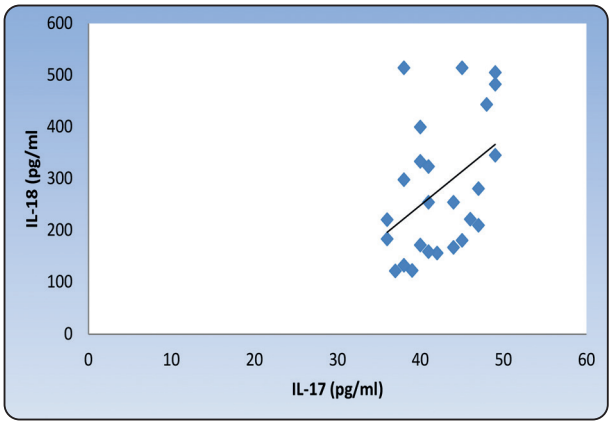

Fig. (1) Scatter diagram representing direct correlation between IL-17 and IL-18 levels at base line

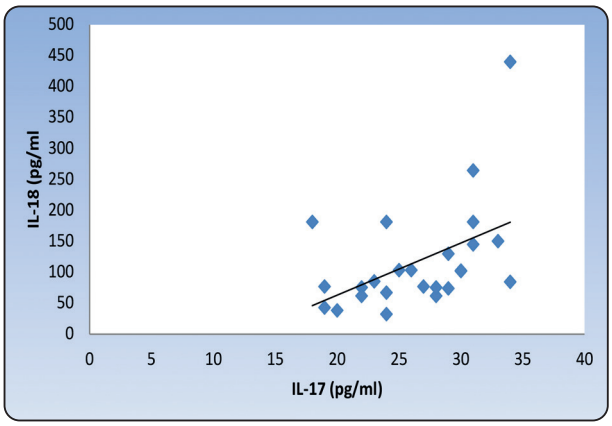

Fig. (2) Scatter diagram representing direct correlation between IL-17 and IL-18 levels after three months

DISCUSSION

The current study showed that all periodontal clinical parameters (e.g., PI, GI, PPD, CAL) were higher in the periodontitis group more than the healthy group. Also, IL-18 and IL-17 GCF concentrations were reported to be higher in patients with periodontitis more than the healthy controls. This was in agreement with studies of ***Ozçaka et al., 2011 and Banu et al., 2015***.

The current study was performed on stage III/IV generalized periodontitis patients (previously known as chronic periodontitis ***(Armitage 1999)***). Staging in the new periodontal disease classification refers to degree of periodontal disease severity or amount of periodontal tissue destruction. Stage III/IV periodontitis patients suffer from interdental clinical attachment loss ≥ 5mm with teeth loss ranging from 4 teeth (Stage III) to 5 teeth or more (Stage IV).Extent in the new classification refers to distribution of the periodontal disease. Generalized pattern means that more than 30% of the existing dentition is affected ***(Caton et al., 2018)***.

Current study outcomes revealed greater levels of IL-17 in GCF of stage III/IV generalized periodontitis patients more than the periodontally healthy subjects. This was in accordance with ***Awang et al., 2014*** who reported increased salivary and gingival serum concentrations of IL-17 in the group of chronic generalized periodontitis patients more than the healthy controls and they also confirmed that IL-17 concentration is directly correlated to clinical criteria as CAL and PPD. Also, ***Chitrapriya et al., 2015***; ***Yang et al., 2016*** documented lower levels of IL-17 in the healthy group compared to chronic generalized periodontitis group. However, some studies reported decreased levels of IL-17 in chronic generalized periodontitis versus periodontally healthy subjects which may be due to inconsistent case selection (***Yetkin et al., 2009; Ozçaka et al., 2011***).

Due to IL-17 inflammatory and bone resorption effects in many inflammatory bone diseases, it is proposed that this biomarker has a major role in periodontal disease pathogenesis ***(Kramer and Gaffen, 2007)***.

Moreover, The results of the present study showed higher levels of IL-18 in GCF of periodontitis patients, which were in accordance with the studies of ***Orozco et al.,2006, Figueredo et al.,2008, Pradeep et al.,2009 and Nair et al.,2016*** ;so IL-18 is recognized as an important biomarker of periodontal tissues destruction. In contrast to the current study results about IL-18, ***Chitrapriya et al., 2015*** reported variable concentrations of IL-18 and they attributed this to sampling regions with less inflammatory changes in the periodontitis group .

CONCLUSION

The current study confirms positive role of IL-17 and IL-18 in pathogenesis of periodontal disease due to the reported higher concentrations of both markers in stage III/IV generalized periodontitis patients compared to the periodontally healthy subjects and the decrease after non surgical periodontal treatment for the periodontitis group. The current study also confirms that IL-17 and IL-18 are directly correlated; when one of them increases, the other marker increases.

REFERENCES

- Arend WP, Palmer G, Gabay C. IL-1, IL-18, and IL-33 families of cytokines. Immunol Rev 2008;223:20-38.
- Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontology. 1999;4:1–6.
- Awang RA, Lappin DF, MacPherson A, Riggio M, Robertson D, Hodge P, et al. Clinical associations between IL-17 family cytokines and periodontitis and potential differential roles for IL-17A and IL-17E in periodontal immunity. Inflamm Res 2014;63:1001-12.
- Axelsson P, Lindhe J. The significance of maintenance care in the treatment of periodontal disease. J Clin Periodontol 1981;8:281-94.
- Banu S, Jabir NR, Mohan R, Manjunath NC, Kamal MA, Kumar KR, et al. Correlation of Toll-like receptor 4, interleukin-18, transaminases, and uric acid in patients with chronic periodontitis and healthy adults. J Periodontol 2015;86:431-9.
- Bıyıkoğlu B, Buduneli N, Aksu K, et al. Periodontal therapy in chronic periodontitis lowers gingival crevicular fluid interleukin-1beta and DAS28 in rheumatoid arthritis patients. Rheumatol Int. 2013;33(10):2607-2616.
- Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S. et al. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. J Clin Periodontol. 2018; 89:S1–s8.
- Chitrapriya MN, Rao SR, Lavu V. Interleukin-17 and interleukin-18 levels in different stages of inflammatory periodontal disease. J Indian Soc Periodontol 2015;19:14-7.
- Dinarello CA. Interleukin-18, a proinflammatory cytokine. Eur Cytokine Netw 2000;11:483-6.
- Dinarello CA. Interleukin-18. Methods 1999;19:121-32.
- Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ; CDC Periodontal Disease Surveillance workgroup: James Beck (University of North Carolina, Chapel Hill, USA),Gordon Douglass (Past President, American Academy of Periodontology), Roy Page (University of Washin. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res 2012;91:914-20.
- Figueredo CM, Rescala B, Teles RP, Teles FP, Fischer RG, Haffajee AD, et al. Increased interleukin-18 in gingival crevicular fluid from periodontitis patients. Oral Microbiol Immunol 2008;23:173-6.
- Flemmig, T. F. 1999. Periodontitis. Ann Periodontol, 4, 32-8.
- Glavind L, Löe H. Errors in the clinical assessment of periodontal destruction. J Periodontal Res. 1967;2(3):180-184.
- Gracie JA, Robertson SE, McInnes IB. Interleukin-18. J Leukoc Biol 2003;73:213-24.
- Kadkhodazadeh M, Baghani Z, Ebadian AR, Youssefi N, Mehdizadeh AR, Azimi N. IL-17 gene polymorphism is associated with chronic periodontitis and peri-implantitis in Iranian patients: A cross-sectional study. Immunol Invest 2013;42:156-63.
- Kerr D A., Millard H D.: Oral Diagnosis, 1965; 2nd edition.

- Kinane, D. F. 1999. Periodontitis modified by systemic factors. Annals of Periodontology, 4, 54-63.
- Kinney JS, Morelli T, Oh M, et al. Crevicular fluid biomarkers and periodontal disease progression. J Clin Periodontol. 2014;41(2):113-120.
- Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. Annu Rev Immunol 2009;27:485-517.
- Kramer JM, Gaffen SL. Interleukin-17: A new paradigm in inflammation, autoimmunity, and therapy. J Periodontol 2007;78:1083-93.
- Loe H, Silness J. Periodontal disease in pregnancy. I. prevalence and severity. acta odontol scand. 1963;21:533-551.
- Lubberts E, van den Bersselaar L, Oppers-Walgreen B, Schwarzenberger P, Coenen-de Roo CJ, Kolls JK, et al. IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF-kappa B ligand/osteoprotegerin balance. J Immunol 2003;170:2655-62.
- Luke R, Khan SN, Iqbal PS, Soman RR, Chakkarayan J, Krishnan V. Estimation of specific salivary enzymatic biomarkers in individuals with gingivitis and chronic periodontitis: A clinical and biochemical study. J Int Oral Health 2015;7:54-7.
- Nair V, Bandyopadhyay P, Kundu D, Das S. Estimation of interleukin-18 in the gingival crevicular fluid and serum of Bengali population with periodontal health and disease. J Indian Soc Periodontol 2016;20:260-4
- Netea MG, Stuyt RJ, Kim SH, Van der Meer JW, Kullberg BJ, Dinarello CA. The role of endogenous interleukin (IL)-18, IL-12, IL-1beta, and tumor necrosis factor-alpha in the production of interferon-gamma induced by Candida albicans in human whole-blood cultures. J Infect Dis 2002;185:963-70.
- Orozco A, Gemmell E, Bickel M, Seymour GJ. Interleukin 18 and periodontal disease. J Dent Res 2007;86:586-93.
- Orozco A, Gemmell E, Bickel M, Seymour GJ. Interleukin-1beta,interleukin-12 and interleukin-18 levels in gingival fluid and serum of patients with gingivitis and periodontitis. Oral Microbiol Immunol 2006;21:256-60.
- Ozçaka O, Nalbantsoy A, Buduneli N. Interleukin-17 and interleukin-18 levels in saliva and plasma of patients with chronic periodontitis. J Periodontal Res 2011;46:592-8.
- Poorsattar Bejeh-Mir A, Parsian H, Akbari Khoram M, Ghasemi N, Bijani A, Khosravi-Samani M. Diagnostic role of salivary and GCF nitrite, nitrate and nitric oxide to distinguish healthy periodontium from gingivitis and periodontitis. Int J Mol Cell Med 2014;3:138-45.
- Pradeep AR, Daisy H, Hadge P, Garg G, Thorat M. Correlation of gingival crevicular fluid interleukin-18 and monocyte chemoattractant protein-1 levels in periodontal health and disease. J Periodontol 2009;80:1454-61.
- Seymour GJ, Ford PJ, Cullinan MP, Leishman S, Yamazaki K. Relationship between periodontal infections and systemic disease. Clin Microbiol Infect 2007;13 Suppl 4:3-10.
- Silness J, Loe H. periodontal disease in pregnancy. ii. correlation between oral hygiene and periodontal condtion. acta odontol scand. 1964;22:121-135.
- Takahashi K, Azuma T, Motohira H, Kinane DF, Kitetsu S. The potential role of interleukin-17 in the immunopathology of periodontal disease. J Clin Periodontol 2005;32:369-74.
- Tonetti, M. S. & Mombelli, A. 1999. Early-onset periodontitis. Annals of Periodontology, 4, 39-52.
- Yang X, Li C, Pan Y. The influences of periodontal status and periodontal pathogen quantity on salivary 8-hydroxydeoxyguanosine and interleukin-17 levels. J Periodontol 2016;87:591-600.
- Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, et al. Human IL-17: A novel cytokine derived from T cells. J Immunol 1995;155:5483-6.
- Yetkin Ay Z, Sütçü R, Uskun E, Bozkurt FY, Berker E. The impact of the IL-11: IL-17 ratio on the chronic periodontitis pathogenesis: A preliminary report. Oral Dis 2009;15:93-9.
- Yu JJ, Ruddy MJ, Wong GC, Sfintescu C, Baker PJ, Smith JB, et al. An essential role for IL-17 in preventing pathogen-initiated bone destruction: Recruitment of neutrophils to inflamed bone requires IL-17 receptor-dependent signals. Blood 2007;109:3794-802.