Evaluation of interleukin 8, 12 & 33 serum level in patients with chronic periodontitis, aggressive periodontitis and healthy subjects

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Abstract: Periodontitis is a multifactorial inflammatory disease characterized by destruction of tooth supporting tissues. Environmental, genetic and immune factors are involved in progress of the disease. Recently numerous studies have focused on the role of different cytokines in development of periodontitis.The aim of the present study was to estimate the serum level of IL-8, IL-12 and IL-33 in patients withchronic periodontitis, generalized aggressive periodontitis (GAP) and healthy individuals.A total of 96 subjects were included in the study of which 35 patients had chronic periodontitis, 26 patients had generalized aggressive periodontitis and 35 persons was healthy group. 3ml blood obtained from each person and serum samples separated. Level of IL-8, IL-12(p70) and IL-33 were determined by enzyme linked immunosorbent assay.Data analyzed with Kruskal-Wallis, Mann-Whitney testand SPSS Ver.16 software.The level of IL-12 increased significantly in chronic and aggressive patients than in health group ($p=0.001$). On the other hand, there was no significant difference at IL8 dose level between periodontitis patients and healthy group ($p>0.05$). The amount of IL-33 was no difference between patients and healthy group ($p>0.05$).There was a significant association between the level of IL-12 with chronic periodontitis and GAP.

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Introduction:

Periodontal disease is the most common inflammatory disease in human beings which is relatively hard to control.In some cases, in spite of satisfactoryoral hygiene, severe bone deterioration and generalized periodontitis occur. Other factors other than pathogen microorganisms of the oral cavity and accumulation of dental plaque are apparently involved in pathogenesis of this disease(1,6).

Periodontitis is the inflammation of periodontium that goes beyond the gums and deteriorates the dental connective tissue. In fact, microorganisms cause periodontitis, but the clinical manifestation of this disease (its severity and extent) depends on the reaction of the host to the extent of intrusion of the bacteria. Periodontium immune cells release proinflammatorymediators in response to periodontal pathogens and their endotoxins(1). Among the many immunity and inflammatory mediators known in the gingival crevicular fluid (GCF) cytokines have attracted special attention(2,8,9). Cytokines are a group of inflammatory mediators that are produced in response to microbes and antigens and contribute to the interaction of immune cells, and proliferation and distinction of lymphocytes. Cytokines are mainly produced by activated T cells and antigen-processing cells. They affect the T cells and are, in fact, the cause of proliferation of helper T cells, which are divided into Th1 (T helper cells 1) and Th2 (T helper cells 2) cells. Th1 activates the cell immune system by releasing cytokines while Th2 mediateshumoral immunity response (HIR) by releasing cytokines. Since the cytokines are mainly produced by leukocytes and also affect other leukocytes, they are known asinterleukins(3,7,10).

Production of cytokines (including interleukins) is stimulated by microbial factors and their contents are increased in the gingival crevicularfluid and tissues of patients with periodontitis. This phenomenon is more critical in patients with aggressive periodontitis. Measuring the content of these cytokines in a patientleads to a decisive diagnosis. Moreover, these

cytokines can also be considered as the target of medications intended to prevent progression of the diseases(4,11-14). Progression of aggressive periodontitis leaves irreversible effects, including premature tooth loss in early ages with a prevalence rate of 0.1%. If the disease is diagnosed early, its progression can be stopped by controlling the disease and prescribing medicines such as levamisole and colchicine(5,16-18). Since the level of all the interleukins (except interleukins 8, 12 and 33)has beenmeasured in the previous studies; the level of interleukin-12 has been only measured in chronic and aggressive periodontitis; no decisive relationship has been found between interleukin-33 and periodontitis;and neitherinterleukin-8 nor interleukin-33 has been analyzed in aggressive periodontitis; this study is an attempt to measure the serum content of the interleukins 8, 12, and 33 in patients with chronic periodontitis and generalized aggressive periodontitis that live inSistan and Baluchestan Province.

Methodos:

This is an observational case study. The statistical population includes patients with chronic and aggressive periodontitis who have visited the periodontics department of Zahedan Dentistry Faculty. The control group consists of individuals whovisited the dentistry faculty for other reasons anddid not suffer from periodontitis. Smokers, pregnant women, patients with any systemic diseases (such as diabetes or self-immune diseases), and patients with viral, bacterial, and fungal diseases; patients with anti-inflammatory and antibiotic diseases; and patients who had consumed anti-inflammatory drugs (e.g. aspirin or ibuprofen), antibiotics, immunosuppressive drugs (e.g. cyclosporine), drugs that increase the size of the gum (such as calcium channel blockers), and antiepileptic drugs for the last 6 months are excluded from this study. By using a simple sampling method 35 samples were obtained (based on the number of visits and their availability).

The information was analyzed using the SPSS software version 16 and the statistical analysis method introduced byKruskal-Wallis and Mann-Whitney, in order to examine the mean difference between the concentrations of serum interleukins 8, 12, and 33 in patients with chronic and aggressive periodontitis and healthy individuals.

26 patients with aggressive periodontitis, 35 patients with chronic periodontitis, and 35 healthy individuals that had visited the periodontics department of Zahedan Dentistry Faculty were selected. In this study, due to the rarity of patients with aggressive periodontitis (26 individuals) the required quorum was not achieved.

Smokers, pregnant women, patients with any systemic diseases (such as diabetes or self-immune diseases), and patients with viral, bacterial, and fungal diseases; patients with anti-inflammatory and antibiotic diseases; and patients who had consumed anti-inflammatory drugs (e.g. aspirin or ibuprofen), antibiotics, immunosuppressive drugs (e.g. cyclosporine), drugs that increase the size of the gums (such as calcium channel blockers), and antiepileptic drugs for the last 6 months are excluded from the study. A written explanation of the objective of the study was provided to each patient. This document, which included the ethical principles mentioned in the Declaration of Helsinki, was signed or fingered by the patients. The criteria for labeling the individuals as patients suffering from generalized aggressive periodontitis were as follows: generalized loss of proximal connections of at least 3 permanent teeth in addition to the first molars and incisors;pocket depth and clinical attachment loss (CAL) of more than or equal to 5 millimeters in these teeth; deterioration of the bone surrounding these teeth that can be observed in pre-optical radiographstaken by parallel techniques(1,19).

The criteria for recognizing patients with chronic periodontitis were as follows: pocket depth clinical attachment loss of more than or equal to 5 millimeters and in at least one tooth in the jaw quadrate bone; and manifestation of bone deterioration in radiographs. Moreover, the pocket depth and clinical attachment loss in healthy individuals had to be also less than or equal to ($\leq$) 3 millimeters(20,21,25). 3 millimeters of venous blood was extracted from each person. The samples were kept in typical tubes without anticoagulants. After separating clot from serum, the samples were centrifuged. The obtained serum was stored at a temperature of $-20^{\circ}C$. The cytokine content of the serum samples was measured by ELISA kits (Bioscience, San Diego, CA, USA). Using these kits, the levels of interleukin-8, interleukin-12 (P70), and interleukin-33 were measured. Protocols for preparing the kits and placing the serum samples into the plates were implemented according to the instructions of the manufacturer. After plotting the related standard curve, the concentration of the aforementioned interleukins was determined in terms of pg/ml based on the optical absorption capacity of ELISA plate wells by using an ELISA reader. Furthermore, treatment of the patients continued after sampling.

For the purpose of this study, students carried out periodontal examination of the participants, extracted blood samples from their veins, centrifuged the samples and sent them to the laboratory. Moreover, the samples were examined by the biochemical laboratory staff using the ELISA test method.

Results :

96 subjects (50 male and 46 female) participated in this study. This population was divided into 4 age classes

and 60.2% of the subjects belonged to the 20-30 age grade (Table 1).

Table 1: Frequency and percentage of the target population in terms of age class

age class / frequency	20-25	26-30	31-35	≥36	Total Number
Quantity	42	20	13	21	96
Percentage	43.8	20.8	13.5	21.9	100

The mean age of healthy individuals was equal to 27.6 ± 8.73, that of patients with chronic periodontitis was equal to 37.37 ± 8.701, and that of patients with aggressive periodontitis was equal to 23.69 ± 4.443. There was a significant statistical difference between the mean ages of the subject group and control group (P=0.001)(Table 2).

Table 2: The mean distribution and standard deviation of the ages of the subjects based on their health condition

Mean age / Group	Quantity	Mean	Standard deviation	P-Value (Kruskal-Wallis)
Healthy	35	27.6	8.73	0.001
Chronic	35	37.37	8.701	
Aggressive	26	23.69	4.443	

35 healthy subjects and 35 subjects with chronic periodontitis participated in this study (18 male and 17 female). The aggressive group consisted of 26 individuals with 14 male and 12 female participants.

In the current study, the mean concentration of serum interleukin-8 was $0.045 \pm 0.19\, pg/ml$ while the maximum concentration of this interleukin was $0.9\, pg/ml$. The statistical difference between these values was not significant compared to the groups containing patients with chronic and aggressive groups (P=0.172) (Table 3).

Table 3: Comparison of the level of serum interleukin-8 in healthy individuals and patients with periodontitis

Mean value / Group	Quantity	Mean value (pg/ml)	Standard deviation	Minimum serum level (pg/ml)	Maximum serum level (pg/ml)	P-Value (Kruksal-Wallis)
Healthy	35	0.045	0.19	0	0.9	0.172
Chronic	35	0	0	0	0	
Aggressive	26	0	0	0	0	

No significant difference was observed betweenthe levels of interleukin-8 in patients with chronic periodontitisand healthy subjects (P=0.154) [Mann-Whitney]. No significant difference was also observed between the levels of this interleukin in the aggressive and healthy groups (P=0.219) [Mann-Whitney]. There is no relation between the levels of interleukin-8 in groups with chronic and aggressive periodontitis (P=1) [Mann-Whitney].

The mean and standard deviation of interleukin-12 in patients with chronic periodontitis and patients with aggressive periodontitis were $0.82 \pm 1.172\, pg/ml$ and $0.85 \pm 0.623\, pg/ml$, respectively. The aforementioned values are larger than those of the healthy group with a mean and standard deviation of $0.194 \pm 0.502\, pg/ml$. This difference was statistically significant (P=0.001). The maximum amount of serum interleukin-12, which belonged to patients with chronic periodontitis, was 5.2pg/ml (Table 4).

Table 4: Comparison of the level of serum interleukin-12 in healthy individuals and patients with chronic periodontitis patients

Mean value / Group	Quantity	Mean value (pg/ml)	Standard deviation	Minimum serum level (pg/ml)	Maximum serum level (pg/ml)	P-Value (Kruksal-Wallis)
Healthy	35	0.194	0.5017	0	2.3	0.001
Chronic	35	0.82	1.172	0	5.2	
Aggressive	26	0.85	0.632	0	3	

Comparisons showed significant relations between the levels of serum interleukin-12 in patients with chronic periodontitis and healthy individuals and the levels of serum interleukin-12 in patients with aggressive periodontitis and healthy individuals (P=0.001) [Mann-Whitney]. However, no relation existed between the levels of serum interleukin-12 in the chronic and aggressive groups (P=0.119) [Mann-Whitney].

The mean and standard deviation of serum interleukin-33 in healthy individuals was $0.269 \pm 0.961 pg/ml$ and the maximum value for this group was $2.3 pg/ml$. On the other hand, in patients with chronic and aggressive periodontitis, the mean values and standard deviations were $0.431 \pm 1.058 pg/ml$ and $0.223 \pm 0.573 pg/ml$, respectively. However, no significant statistical difference was observed between these three groups (P=0.614)(Table 5).

Table 5: Comparison of the level of serum interleukin-33 in healthy individuals and patients with periodontitis

Mean value / Group	Quantity	Mean value (pg/ml)	Standard deviation	Minimum serum level (pg/ml)	Maximum serum level (pg/ml)	P-Value (Kruksal-Wallis)
Healthy	35	0.269	0.961	0	2.3	0.614
Chronic	35	0.431	1.058	0	5	
Aggressive	26	0.223	0.573	0	2	

According to the abovetable5, the level of serum interleukin-33 in chronic and aggressive periodontitis groups does not significantly differ from that of the healthy group (P>0.05) [Mann-Whitney].

Age-based comparison of the level of serum interleukin-12 in patients with chronic and aggressive periodontitis and healthy individuals indicated that a significant statistical difference existed among the age classes 20-25, 26-30, and 31-35 (P<-0/05). Among the 46 subjects that belonged to the 20-25 age group patients with chronic periodontitis had the maximum mean and standard deviation ($1.6 \pm 1.229 pg/ml$). The statistical results of the group that included 21 subjects with more than 36 years of age did not suggest a significant relation (P=0.335) (Table 6).

Table 6: Age-based comparison of the level of serum interleukin-12 in healthy individuals and patients with periodontitis

age class (year)	Group	Number	Mean value (pg/ml)	Standard deviation	P-Value (Kruskal-Wallis)
20-25	Healthy	19	0.337	0.648	0.002
	Chronic	1	3.8	0	
	Aggressive	22	0.768	0.484	
26-30	Healthy	9	0	0	0.001
	Chronic	8	0.25	0.316	
	Aggressive	3	1.6	1.229	
31-35	Healthy	4	0	0	0.023
	Chronic	9	1.156	1.654	
More than 36	Healthy	3	0.133	0.231	0.355
	Chronic	17	0.735	0.849	
	Aggressive	1	0.4	0	

Age-based comparisonof the levels of serum interleukin-33 in patients with (chronic and aggressive) periodontitis and healthy individuals indicates that no significant relation exists between the group grades (P>0.05) (Table 7).

Table 7: Age-based comparison of the level of serum interleukin-33 in healthy individuals and patients with periodontitis

age class (year)	Group	Quantity	Mean value (pg/ml)	Standard deviation	P-Value (Kruskal-Wallis)
20-25	Healthy	19	0.179	0.404	0.166
	Chronic	1	1.2	0	
	Aggressive	22	0.264	0.616	
26-30	Healthy	9	0.033	0.1	0.218
	Chronic	8	0.562	1.144	
	Aggressive	3	0	0	
31-35	Healthy	4	1.375	2.75	0.462
	Chronic	9	0.122	0.367	
More than 36	Healthy	3	0.067	0.115	0.848
	Chronic	17	0.488	1.28	
	Aggressive	1	0	0	

The results indicated that in the healthy and chronic periodontitis groups, the mean and standard deviation for men are more than women. That is to say, the mean value of men with chronic periodontitis is equal to $1.122 \pm 1.374\, pg/ml$. However, the female group with aggressive periodontitis had a mean and standard deviation of $1.042 \pm 0.773\, pg/ml$. The Kruskal-Wallis statistical test shows that there is no relation between the levels of interleukin-12 in all male and female groups (P>0.05).

The results of the study indicated that no relation exists between the level of serum interleukin-33 and gender in the participant groups (healthy, chronic, and aggressive) (P>0.05) [Kruskal-Wallis].

Discussion

amed, the level of inflammatory factors (including interleukins) is expected to be high(23,26).

Interleukin-8 belongs to the family of supergene interleukins-8 that includes small peptides with chemotactic activity of certain types of leukocytes. This interleukin is a proinflammatory cytokine that is released by a number of cells such as monocyte, lymphocyte, and endothelial cells. Interleukin-8 absorbs polymorphonuclear (PMN) cells into the inflamed region and contributes to the release of enzyme granules by these cells(22,24). According to the obtained results, the level of serum interleukin-8 in the healthy group showed a little growth, but the level of this interleukin was not increased for the chronic and aggressive groups.

This study was aimed at determining and comparing the levels of serum interleukins 8, 12, and 33 in patients with chronic and aggressive periodontitis, and healthy individuals. The levels of serum interleukins 8 and 33 in patients did not differ significantly from those of healthy individuals. However, the level of serum interleukin-12 in patients with increasing gum inflammation was more than that of the members of the healthy group.

Periodontal diseases manifest in the form of inflammatory-immune responses of the gum and periodontal tissues against periodontopathogenic bacteria, which are regulated by inflammatory cytokines. Factors other than the presence of pathogen microorganisms in the oral cavity and accumulation of dental plaque are apparently involved in the pathogenesis of this disease. Since in the periodontal diseases the periodontium is infl

This indicates the lack of relation between the level of this serum interleukin and destruction of periodontal tissues.

Interleukin-12 is known as a proinflammatory cytokine that is released by monocyte-macrophage cells in response to antigen stimulants (such as LPS) of gram-negative bacteria. IL12 causes the production of INFg by T cells and natural killer (NT) cells. In this study, the level of serum IL12 in the chronic and aggressive periodontitis groups was more than the level of IL12 in the healthy group. This indicates that a relation exists between the level of destruction of periodontal tissues and the increase in serum IL12. The increase in the level of IL12 follows the stimulation of dendritic cells by

P.gingivalis and A.actinomycetemcomitans bacteria. This increase plays an important role in the response of Th1 and production of INFg. INFg affects the monocyte-macrophage cells and causes the production of IL12, IL1, and INFg. These proinflammatory cytokines lead to the activation of osteoclasts and deterioration of bones by indirect stimulation of osteoblast cells(26).

In the study conducted by Orozco et al. (2006) the level of IL12 (P70) in the serum obtained from patients with periodontitis was extremely low. Furthermore, the increase in the inflammation would decrease the level of IL12. In the current study, the serum level of IL12 in the chronic group had a considerable growth compared to the level of IL12 in the healthy group. The level of IL12 in the aggressive group was also more than that of the healthy group. This difference was maybe causedby the small number of the individuals who had participated in the Orozco et al. research (10 patients with periodontitis) or the difference in the kits used for these two studies(27).

In the study carried out by Sanchez et al. (2011) the serum content of IL12 (P70) in the patients with aggressive periodontitis was higher than that of the patients with chronic periodontitis or healthy subjects(26). In the current study, the level of IL12 in the aggressive group was also extremely more than that of the healthy group.

In the research that was performed by Robati et al. (2011) in Iran (Ahwaz) no relation was found between the serum content of IL12 and aggressive periodontitis(21). This finding is contradictory to the results of our study. This difference can be attributed to the effect of various genetics, ethnicity, and races on the response of the immune system and the levels of interleukins.

Interleukin-33 is a proinflammatory cytokine that increases the production of other cytokines (such as interleukins 5 and 13) by Th2 cells(28). It also leads to the activation of basophils, mast cells, NK cells, and Th2 cells. No substantial difference was observed in the serum content of interleukin-33 in the chronic group and that of the healthy and aggressive groups. No relation was also found between the level of IL33 and chronic and aggressive periodontitis.

In the study performed by Bununeli et al. (2011) the plasma content of IL33 did not vary for the healthy and chronic groups. Therefore, these researchers concluded that the level of plasma IL33 cannot be useful in distinguishing patients with chronic periodontitis and healthy individuals(29). This result matches the results obtained from our study.

In the current study, the serum content of interleukins varied for different ages. In the 20-25, 26-30, and 31-35 age grades the level of IL12 was associated with periodontitis. However, in subjects with more than 36 years of age no significant difference was seen. This can be attributed to the low number of subjects forming the healthy and aggressive groups who belong to this age group. The level of serum IL33 in the group grades under study was not relevant to the level of serum IL33 in these three groups.

There was also no considerable difference between the level of IL12 in male and female members of the healthy, chronic, and aggressive groups. Gender-based comparison of the groups did not show a relation between the levels of IL33. This shows that gender does not affect the content of blood interleukins.

Conclusion:

In the current study, the serum content of interleukins 8 and 33 in patients with chronic and aggressive periodontitis was not significantly different from that of the healthy subjects. However, the level of interleukin-12 was increased with the increase in the inflammation of periodontal tissues of the chronic and aggressive groups. Therefore, there can be a relation between the level of serum interleukin-12 (as a biomarker) and the level of destruction of periodontal tissues. Gender cannot affect the serum content of these interleukins as well.It is recommended to conduct more researches in the future on the serum contents of interleukins 8, 12, and 33 and other inflammatory factors of periodontal diseases. Furthermore, factors such as smoking, systemic diseases, and their effects on the level of interleukins present in the serum and gingival crevicular fluid should also be studied in the future studies.

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