Serum Level of TNF-α and IL-17 in Patient Have Chronic Periodontitis Associated Rheumatoid Arthritis

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ABSTRACT

Background: chronic periodontitis and rheumatoid arthritis are widely prevalent diseases and are characterized by tissue destruction due to chronic inflammation. Recently, there is growing evidence that the two diseases share many pathological features the aims of the study To determine the periodontal health status in patient have chronic periodontitis with rheumatoid arthritis and compare it with those having chronic periodontitis without Rheumatoid arthritis and determine the serum levels of interleukin -17(IL-17), tumor necrosis factor- alpha (TNF-a) in both groups and compare with the control group (subject samples neither have periodontitis nor arthritis) and correlate these immunological markers with the periodontal parameters Plaque index , gingival index , bleeding on probing, probing depth, clinical attachment level and number of missing teeth.

Materials and methods: Eighty (80) males and females subjects with age range (30-45) years were recruited in this study they were divided into three main groups The chronic periodontitis with rheumatoid arthritis group consist of thirty (30) subjects and second group consist of thirty (30) subjects have chronic periodontitis and third group consist of twenty (20) subject case control group. All subjects had normal weight and height range according to BMI (body mass index) that it value is (18.5-25), Clinical periodontal parameters used in this study were Plaque index, gingival index, bleeding on probing, clinical attachment level index, probing pocket depth and number of missing teeth was measured in all groups at four surfaces of all presented teeth Blood samples were collected from all individuals and examined to determined serum level of interleukin -17 and tumor necrosis factor-a by mean of enzyme-linked immune–sorbent assay.

Results: The present study showed patients with chronic periodontitis and rheumatoid arthritis had higher prevalence of sites presenting dental plaque, a higher rate of gingival inflammation and bleeding on probing greater probing depth, greater attachment loss and high number of missing teeth compared to those had chronic periodontitis only and control subjects . Also highly significant differences between studied group regarding serum level of IL-17 and TNF-a atp < 0.001, as well as, it revealed that mean serum levels of IL-17 were statistically higher in chronic periodontitis with rheumatoid arthritis group (607.9 ± 79.9) than Chronic Periodontitis group (421.4 ± 5.9) and Control groups (15.9 ± 2.7) similarly serum level of TNF-a (402.2 ± 41.2 319.4 ± 526 85.3 ± 4.9) respectively at p < 0.001. Regarding correlation, the current study observed strong positive correlation between serum levels of IL-17 andTNF-a with PL.I, GI, BOP, PPD CAL and the number of missing teeth in the PRA at p<0.001. Also this study reveal significant correlation between the two immunological markers (TNF-a and IL-17) in chronic periodontitis with rheumatoid arthritis group and in Chronic Periodontitis group.

Conclusion: It was concluded that there was higher potentiality to chronic periodontitis involvement among rheumatoid arthritis patients, that correlated positively with increase the level of serum levels of IL-17 and TNF-a accordingly with high score of clinical parameters that had recorded. That mean TNF –a and IL-17 may play an important role in increase the severity of periodontitis as well as rheumatoid arthritis.

Keywords: chronic periodontitis, rheumatoid arthritis, Serum level ,TNF-a , IL-17.**(J Bagh Coll Dentistry 2017; 29(1):104-110)**

INTRODUCTION

The periodontal diseases range from the relatively simple form of gingivitis to more destructive form of periodontitis, periodontal disease are not only effect the dentition, but may also be a threat to general health[(1)] .

Periodontitis, the most common oral disease, is destructive inflammatory disease of the supporting tissues of the teeth and is caused by alveolar bone destruction due to a chronic inflammation [(1)].

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group of specific microorganisms [(2)].So it was characterized by both connective tissue and

Rheumatoid arthritis (RA) was another form of a chronic destructive inflammatory disease which is characterized by the accumulation and persistence of an inflammatory infiltrate in the synovial membrane that leads to synovitis and the destruction of the joint architecture resulting in impaired function.it were also associated with inflammatory destruction of joint connective tissue and bone destruction [(3)].

In particular, RA as a chronic inflammatory joint disease carries many characteristics and pathogenetic processes that have similarities to periodontitis. The relationship between rheumatoid arthritis and periodontitis were controversial [(4)].

Periodontitis and RA represent an imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines, which considered the cause for tissue damage.[5]

Cytokines were the mean of communication between immune and non-immune cells. Hence these cytokines are essential to the pathogenesis of several diseases, including periodontal disease and Rheumatoid arthritis. [6]

Periodontitis had obviously cytokine profiles as that of RA, disease progression is due to continuous and persistence accumulation of pro-inflammatory cytokines as IL-1β and TNF-α together with low levels of IL-10 and transforming growth factor β (TGF-β). All might give a good picture for the active stages of both RA and PD [6].

The role of pro-inflammatory cytokine, TNF-α, is of special interest for the understanding of immune responses in both RA and PD [7].because of the treatment with anti-TNF-α medication was commonly used to control the inflammatory process in RA; such therapy may also be relevant for the management of PD [8].

The production of IL-17 by Th17 subset of CD4 T-cell identified in 2003 .it has been associated with the pathogenesis of numerous autoimmune and inflammatory diseases, including rheumatoid arthritis, inflammatory bowel diseases, psoriasis and periodontitis [9].

The present study was carry out to study the serum cytokine profile (IL-17 and TNF-α) in chronic periodontitis subjects with RA compared to those without RA disease and the influence of the serum levels of these cytokines on clinical periodontal parameters in studied groups.

MATERIALS AND METHODS

The sample in this study consisted of Eighty (80) males and females subjects with age range (35-45) years. The sample was divided into three groups

(Chronic periodontitis/rheumatoid arthritis) Group(PRA)

Thirty patients (30) diagnosed to have chronic periodontitis disease, and have rheumatoid arthritis. They were from attendants seeking treatment in the rheumatology clinic in Baghdad Teaching Hospital. The rheumatoid arthritis state was diagnosed according to the Revised Criteria for the classification of Rheumatoid Arthritis of the American College of Rheumatology [10] and also according to the laboratory investigation(ESR,Latex test).

(Chronic periodontitis / non- rheumatoid arthritis) Group (CP)

thirty patients (30) were recruited from the attendants to the clinic of the Department of Periodontics /College of Dentistry /Baghdad University.Chronic periodontitis in patients was defined as the presence of at least four sites with probing pocket depth ≥4mm with clinical attachment level ≥1-2mm, this made according to the international classification system for periodontal disease [11].

(Control / systemically healthy) Group (C)

Twenty patients (20) with clinically healthy periodontium and healthy systemic status. This group represents controls.

Clinical examination:

Clinical periodontal parameters include {Plaque Index (PLI) Silness&Loe[12], GingivalIndex (GI) Loe&Silness[13], Bleeding on Probing (BOP), Probing Pocket depth (PPD), Clinical Attachment Level (CAL) and number of missing teeth}. Also all subjects had normal range of BMI (body mass index) that it value is (18.5-25)[26].

Blood collection and biochemical analysis

The blood was collected between (9 am-12 pm), the blood samples were taking from their arms from cubital Fossa (cubital vein), and put it in a evacuated [Ethylene Diamine Tetra Acetic acid (EDTA)] tubes as anticoagulant tubes, after centrifuging plasma samples preserved immediately into other plain tubes and preserved in freeze (-15Cº) until they have been assayed for IL-17 and TNF-αby ELISA according to manufacturer's protocol of instruction at the RayBio IL-17 ELISA (Enzyme-Linked Immunosorbent Assay) kit and TNF-α (Human) ELISA Kit Protocol.

RESULTS

Clinical Analysis

High significant differences were found between the mean (PLI, PPD and CAL) of PRA group and CP group by using T-test at $P < 0.001$ and highly significant (GI) differences found between the same groups Table (1).

Inter group comparison by median of the sites with positive BOP presented in Table (2) with each group there was high significant difference between sites with positive BOP compare to non-bleeding sites. The number of missing teeth between PRA group and CP group, using Mann–Whitney U test at-alpha $p < 0.05$ reveal highly significant difference as shown in table (2).

Table 1: Statistical Differences of the periodontal parameters (PLI. GI, PPD and CAL) among all studied groups.

Parameters	Chronic Periodontitis Rheumatoid arthritis (n=30)	Chronic Periodontitis (n=30)	Control (n=20)	p-value
Gingival index Mean ± SD	1.9 ± 0.3	1.8 ± 0.4	0.5 ± 0.2	<0.001*,[a]
Plaque index Mean ± SD	2.1 ± 0.2	1.9 ± 0.3	0.6 ± 0.2	<0.001*,[a]
Probing pocket index Mean ± SD	5.2 ± 0.3	4.3 ± 0.5	-	<0.001*,[T]
Clinical attachment level Mean ± SD	6.2 ± 0.7	4.1 ± 0.5	-	<0.001*,[T]
[a] ANOVA test, [T] Independent t-test, * significant at alpha level <0.05				

Table 2: Median and significant differences of bleeding on probing and missing teeth for the studied groups.

Parameters	PRA group (n=30)	CP group (n=30)	Cgruop (n=20)	p-value
Bleeding on probing Median (range)	63 (38-73)	53 (11-71)	8 (6-11)	<0.001*,[W]
Number of missing teeth Median (range)	5 (0 - 10)	1 (0 - 4)	-	<0.001*,[W]
Kruskal-Wallis nonparametric test, [W] Mann-whitney U test * significant at alpha level <0.05				

Immunological findings

The higher values of IL-17 were in PRA Group (607.9 ± 79.9 pg/ml) compare to CP group (421.4 ± 5.9 pg/ml) and C group (15.9 ± 2.7 Pg/ml).

The current study pointed out that TNF-α reported higher increase in concentration in PRA group (402.2 ± 41.2 pg/ml) as compared with CP group (319.4 ± 52.6 pg/ml) and C group (85.3 ± 4.9 pg/ml).

Using ANOVA test to show significant of statistical difference. It appear that there was a high significant difference for both (IL-17 and TNF-α) among studied groups table (3).

LSD test values between each two groups reveal a high significant difference in the level of IL-17 and TNF-α $p< 0.01$ as shown in table (4).

Table 3: Mean and significant differences of the levels of interleukin-17and Tumor Necrosis Factor-alpha among included patients according to their group, n=80.

Parameters	PRA (n=30) Mean ± SD	CP (n=30) Mean ± SD	C (n=20) Mean ± SD	p-value
level of interleukin17 (pg/ml)	607.9 ± 79.9	421.4 ± 5.9	15.9 ± 2.7	<0.001*
Tumor Necrosis Factor-alpha (pg/ml)	402.2 ± 41.2	319.4 ± 52.6	85.3 ± 4.9	<0.001*
ANOVA test, * significant at alpha level <0.05				

Table 4: Last significant differences of the levels of interleukin-17and Tumor Necrosis Factor-alpha between the included groups accordingly.

Groups	level of interleukin17 (pg/ml) Mean ± SD	Tumor Necrosis Factor-alpha (pg/ml) Mean ± SD
PRA	607.9 ± 79.9	402.2 ± 41.2
CP	421.4 ± 5.9	319.4 ± 52.6
p-value	<0.001*	<0.001*
PRA	607.9 ± 79.9	402.2 ± 41.2
C	15.9 ± 2.7	85.3 ± 4.9
p-value	<0.001*	<0.001*
CP	421.4 ± 5.9	319.4 ± 52.6
C	15.9 ± 2.7	85.3 ± 4.9
p-value	<0.001*	<0.001*
LSD TEST, *significant at alpha level <0.01		

Correlations between the immunological parameters and clinical periodontal parameters to each group.

The periodontal clinical parameters (PLI, GI.PPD, CAL) of PRA group shown in table (5) have a high positive correlation with immunological parameters (IL-17 and TNF-α) using Pearson's correlation test significant at p <0.01

While the periodontal clinical parameters (BOP and the number of missing teeth of PRA

Interleukin -17 have high positive correlation to TNF-α within each of the studied group as shown in the table (6)

group have a high positive correlation with immunological parameters (IL-17 and TNF-α) using Spearman correlation test significant at p <0.01.

Accordingly the correlation that shown in CP group exhibit the same correlation between periodontal parameters and immunological parameters as in the PRA group.

For C group, (GI and PLI) get a high positive correlation with serum level of IL-17 and TNF-α .

Table 5: Correlation of the levels of interleukin-17and TNF-α with periodontal health parameters according to each group.

Chronic periodontitis Rheumatoid arthritis (PRA)(n=30)		**(GI) P**	**(PLI) P**	**(PPD) P**	**(CAL) P**	**(BOP) S**	**(Missing teeth) S**
IL-17 (pg/ml)	R	0.880**	0.853**	0.837**	0.922**	0.926**	0.876**
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
TNF-α (pg/ml)	R	0.768**	0.711**	0.672**	0.801**	0.847**	0.797**
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Chronic periodontitis (CP) (n=30)		**(GI) P**	**(PLI) P**	**(PPD) P**	**(CAL) P**	**(BOP) S**	**(Missing teeth) S**
IL-17 (pg/ml)	R	0.973**	0.958**	0.918**	0.868**	0.895**	0.942**
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
TNF-α (pg/ml)	R	0.879**	0.906**	0.928**	0.885**	0.847**	0.906**
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Controls (C) (n=20)		**(GI) P**	**(PLI) P**	**(PPD) P**	**(CAL) P**	**(BOP) S**	**(Missing teeth) S**
IL-17 (pg/ml)	R	0.889**	0.875**	-	-	0.845**	-
	p-value	<0.001	<0.001	-	-	<0.001	-
TNF-α (pg/ml)	R	0.922**	0.939**	-	-	0.897**	-
	p-value	<0.001	<0.001	-	-	<0.001	-
P Pearson's correlation, S Spearman's rho correlation, ** Correlation is significant at the 0.01 level (2-tailed).							

Table 6: Correlation of between the levels of interleukin-17 and TNF-α within each of the study groups accordingly.

Groups		IL-17 (pg/ml)	
PRA (n=30)	TNF-α (pg/ml)	r	0.844**
		p-value	<0.001
CP (n=30)	TNF-α (pg/ml)	r	0.900**
		p-value	<0.001
C (n=20)	TNF-α (pg/ml)	r	0.775**
		p-value	<0.001
Pearson's correlation, ** Correlation is significant at the 0.01 level (2-tailed).			

DISCUSSION

Chronic periodontal disease can be considered a potential focus of infection, which worsens the metabolic control of patients with RA. [14].The pathobiology of periodontal disease) and rheumatoid arthritis is similar, both are inflammatory chronic diseases, with activation of complement, production of cytokines and release of other inflammatory cell products [15, 16].The relationship between periodontal disease and rheumatoid arthritis still controversial [17, 18]. current study revealed highly significant differences among the studied groups regarding PL.I; P.P.D; CAL and B.O.P, significant level of GI and PLI that is probably because patients with RA might be more likely to obtain temporomandibular joint involvement, severe hand dysfunction (caused by arthritis) which hinder the patient's oral hygiene practices due to restriction of movements, at the same time, decreased saliva from secondary Sjögren's syndrome all enhances plaque accumulation as well as, RA patients may be emotionally depressed about their illness causing the deterioration of the attention to the personal hygiene [19,20].

The elevated level of GI and PLI reflects a higher inflammation in the PRA Group than the CP group and could be related to the increase in the plaque as the plaque is the causative factor of gingival inflammation. This result is agreed with (Kässer) [20]. The percentage of sites with BOP was significantly higher in PRA group than CP group. The potential altered abilities of RA patients to perform effective oral hygiene could result in an increased BOP that exacerbates the risk for enhanced tissue destruction in periodontitis. Moreover, interesting observations regarding the complexity of the oral and systemic challenge provide unique mechanisms by which dysregulation of host responses could occur [21]. The mean value of PPD and CAL in PRA group was significantly higher compared to CP alone. This could be related to local and systemic factors. The local factor is the plaque which was significantly higher in the PRA group and this has influenced PPD in this group. The systemic factor in the PRA patients is the defect in the immune system which could result in inflammatory-mediated destruction predisposing to periodontitis due to an unbalanced cytokine expression profile [22] Clinical attachment level refers to the distance from the cementoenamel junction (CEJ) to the location of the inserted probe tip. Thus, loss of fibers attachment expressed at the clinical level was due to the cumulative effect of destructive pathological processes in periodontal together with the protective and destructive effect of the immunological processes.

The present study reported highly significant differences in mean IL-17 values among the studied groups at p <0.001 also IL-17 in PRA group is highly elevated than clinically healthygroup.

Interleukin-17 plays a role in osteoclastogenesis via activation of RANKL, causing bone destruction in inflamed joints

The severity of RA increase by increase the serum level of IL-17 in CP patient and significant increase of serum level of IL-17 than healthy group and that showed in [23]. IL-17 induces cytokine and chemokine expression and may play a role in skeletal tissue destruction and inflammatory processes.

Patients with PRA have markedly elevated in Tumor necrosis factor-α levels compared with subjects of CP alone and healthy group at p <0.001. These findings suggest that anti-TNF-α may influence the destruction processes (as

reflected by the greater PPD and CAL) These observations suggest that periodontal inflammation may be related to high levels of systemic and local TNF-α in patient with RA[24].

TNF-α plays a central role in the host inflammatory reaction, which is related to the breakdown of alveolar bone as well as loss of connective tissue attachment that related to highly significant association between serum level of TNF-α and number of teeth lost in PRA group and CP group [24]. Consequently, in chronic periodontal infection, bacteria and/or their components disseminate from the inflamed areas into the circulation to challenge the immune system, the circulating and resident immune cells of the body indicate that peripheral blood monocytes challenged by bacterial LPS produce inflammatory mediators like IL-1β and TNF- α [25].

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الخلاصة

الخلفية :امراض اللثة والروماتيزم الرثوي امراض شائعة في المجتمع وهي تتميز بتحطيم الانسجه بسبب الالتهاب المزمن ,الدراسات الحديثة تشير الى وجود صفات مرضيه مشتركه بين المرضين.

اهداف الدراسة :لتحديد حالة اللثة الصحية لدى مرضى التهاب اللثة المزمن والمصابين بالروماتيزم الرثوي ومقارنتهم بالمرضى المصابين بالتهاب اللثة المزمن وليس لديهم روماتيزم رثوي وايضا تحديد مستوى السيرم لكل من (انتر لوكين 17 و تي ان اف الفا) في كلا المجموعيتن ومقارنتهم مع المجموعه الغير المصابه بأي من الامراض وربط علاقه بين الدلائل المناعيه مع دلائل التهاب اللثه السريري (مؤشر الصفيحة الجرثومية ,مؤشر التهاب اللثة,مؤشر عمق جيوب اللثة,مؤشرفقدان الانسجة الرابطة وعدد الاسنان المفقودة)

المواد والطرق:تم اخذ عينات ثمانين شخص من اثنى وذكر يتراوح اعمارهم بين (30-45) المعنين في هذه الدراسه ولقد تم تقسيمهم الي ثلاث مجاميع .مجموعة التهاب اللثة المزمن والمصابين بالروماتيزم الرثوي تتألف من 30 شخص. المجموعه الثانيه تتألف من 30 شخص مصابين بألتهاب اللثة المزمن المجموعه الثالثه تتألف من عشرين شخص والتي تعتبر المجموعه الغير مصابه بأي مرض . كل الاشخاص يمتلكون معدل وزن وطول طبيعيان استنادا الى احكام القياس في(بي ام اي) الذي قيمته (18.5-25) ايضا لقد تم قياس مؤشر(الصفيحة الجرثومية,مؤشر التهاب اللثة,مؤشرعمق جيوب اللثة,مؤشرفقدان الانسجة الرابطة وعدد الاسنان المفقوده) لكل المجاميع على الاسطح الاربعه لكل الاسنان الموجودة , عينات الدم التي جمعت من كل الافراد تم فحصها لمعرفة مستوى السيرم لكل من (انتر لوكين- 17 وتي ان اف الفا) بواسطه الانزيم الرابط بالمناعه.

النتائج: هذه الدراسة اظهرت المرضى المصابون بالتهاب اللثة المزمن والمصابين بالروماتيزم الرثوي لديهم ميل اكبر لوجود الصفيحة الجرثومية في الاسنان ومعدل اعلى لالتهاب اللثة,زيادة كبيره في عمق جيوب اللثة وزيادة كبيره في فقدان الانسجة الرابطة.وعدد عالي من الاسنان المفقودة مقارنتاً مع المصابين بالتهاب اللثة المزمن فقط والمجموعه الغير مصابه.

ايضا هناك زيادة واضحه وفرق في التركيز لكل المجاميع في مستوى السيرم(انترلوكين -17 وتي ان اف الفا) كذلك تكشف ان معدلات مستوى السيرم لل (انترلوكين -17) احصائيا عاليه في مجموعه المرضى المصابون بالتهاب اللثة المزمن مع المصابين بالروماتيزم الرثوي (607.9 ± 79.9) من مجموعه المصابين بالتهاب اللثه المزمن (421.4 ± 5.9) والمجموعه الغير المصابه (15.9 ± 2.7). وهذا يشابه مستوى السيرم لل (تي ان اف الفا) في بقية المجاميع (402.2 ± 41.2 319.4 ± 526 85.3 ± 4.9) . وبخصوص الترابط, الدراسه الحاليه تظهر ترابط قوي ايجابي بين مستويات السيرم لل (انترلوكين -17) و (تي ان اف الفا)مع (مؤشر الصفيحة الجرثومية ,مؤشر التهاب اللثة,مؤشر عمق جيوب اللثة,مؤشرفقدان الانسجة الرابطة وعدد الاسنان المفقودة) في مجموعه المصابون بالتهاب اللثة المزمن مع المصابين بالروماتيزم الرثوي .

كذلك هذه الدراسه تكشف ترابط واضح بين الدلائل المناعيه الاثنين (انترلوكين -17 و تي ان اف الفا) في مجموعة المرضى المصابون بالتهاب اللثة المزمن مع المصابين بالروماتيزم الرثوي وفي مجموعة التهاب اللثة المزمن.

الخلاصة: ان النتائج تشير الى ارتفاع معدل امراض اللثة لدى المرضى المصابين بالروماتيزم الرثوي والتي ترتبط ايجابيا مع زياده في مستوى السيرم لل (انترلوكين-17 و تي ان اف الفا) بالتتابع مع ارتفاع عالي في النتائج اللثويه السريره التي قد سجلت والذي يعني ان (تي ان اف الفا والانترلوكين -17) تلعب دور مهم في زيادة شدة امراض اللثة و كذلك في زيادة امراض الرماتيزم الرثوي .