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EVALUATION OF SERUM INTERLEUKIN-1β AND INTERLEUKIN-6 LEVELS IN PATIENTS WITH CHRONIC PERIODONTITIS IN RELATION TO ATHEROSCLEROTIC HEART DISEASE

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Abstract:

Background: Periodontitis and Atherosclerotic diseases are highly widespread diseases characterized by chronic inflammatory process. Through the last years, there has been an increase attention on the effect of oral health on atherosclerosis and other cardiovascular disease. Interleukin-1β and Interleukin-6 are considered as examples of important mediators in inflammation that share inflammatory process in both periodontitis and atherosclerosis.

Aims of the study: To assess the periodontal health status in study and control group, also to estimate the serum levels of interleukin-1β and interleukin-6 in all groups, and test the relationship between the serum levels of these biomediators with clinical periodontal parameters in all groups.

Materials and Methods: 80 male subjects, were included in this study with age limit between (40-60) years old; they were separated into{chronic periodontitis with Atherosclerotic heart disease group(n=30) and chronic periodontitis group(n=30)} and control group(n=20) which are healthy systemically and without periodontal diseases. The condition of Periodontal health was estimated by evaluation of the periodontal parameters clinically {Gingival index, Plaque index, Bleeding on probing, Clinical attachment level, Probing pocket depth}. 5ml venous blood was collected from study and control groups. After centrifusion, serum samples were kept frozen at (-20)°C. The serum interleukin-1β and interleukin-6 levels were quantified by mean of enzyme–linked immune–sorbent assay (ELISA).

Results: The results illustrated that the mean levels of all periodontal parameters and serum levels of interleukin-1β and interleukin-6 were higher in the (Chronic periodontitis & Atherosclerotic) group than in the (Chronic periodontitis) group and control group with highly significant differences. Regarding the correlation between each of serum interleukin-1β and interleukin-6 levels with clinical periodontal parameters in each study group, the correlation was positive and significant with most of these parameters.

Conclusion: The current results may provide support for the relationship between chronic periodontitis and Atherosclerosis, and suggest that the periodontitis may act vital role in activation and triggering immune response systemically. Chronic periodontitis may participate to the inflammation-associated with atherosclerotic process.

Keywords: Atherosclerosis Heart disease, chronic periodontitis, Interleukin-1β and Interleukin-6.

INTRODUCTION

For many years, the coronary heart diseases (CHD) are a critical reason of mortality and morbidity than any other disease [(1)]. CHD is often accompanied by different changes and modification of oral periodontal tissues. Chronic periodontitis (CP) is periodontal disease (PD) marked by chronic inflammation of this tissue that in turn lead to damage of periodontium and resorption of alveolar bone [(2)].

Atherosclerosis is coronary heart disease arises as outcome of hardening and lumen reduction of the arteries that supply the heart due to build of

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atherosclerotic plaque [3]. It is characterized by local and systemic host responses, in which cells such as B and T lymphocytes and macrophages had an important role in the pathogenesis of this disease by discharge of cytokines and other inflammatory biomediators [4].

In recent decades, the most active discussed in the literature, is the relationship between CHD and chronic periodontitis, these diseases share many risk factors, metabolic syndrome, role of immune cells, increase in WBC counts, inflammatory mediators and the role of bacterial lipopolysaccharides [5].

A large number of studies have indicated the presence of a certain positive correlation of clinical signs and inflammatory changes in chronic periodontitis with atherosclerosis and CHD [6]. Chronic periodontitis may amplify systemic inflammatory mediators levels as a consequence of ingoing bacteria and inflammatory / anti-inflammatory cytokines into the blood, which accordingly, may affect other organs and systems, in the first place - the vascular endothelium, thus potentially contribute to the inflammation-associated atherosclerotic disease [7].

In serologic studies, the high titers of antibodies are marked to periodontal bacteria in atherosclerosis and CHD disease, and some of these viable bacteria isolated straightly from an atherosclerotic plaque [8]

Interleukin-1β and Interleukin-6 are considered as important mediators of inflammation that share inflammatory process in both periodontitis and atherosclerosis.

IL-1β is a key mediator and plays an important function in immunity and inflammation [9].

In periodontal tissues IL-1β is known to enhance fibroblast synthesis of collagenase and prostaglandin E2 (PGE2) and upregulates matrix metalloproteinase (MMP), so it is a potent stimulator of bone resorption [10]. The activity of this cytokine, serve to signal neutrophil and monocyte migration from the vasculature into the periodontal tissue [11].

The proatherogenic effect of IL-β is due to its capability to modulate a number of key actions drawn in the complex inflammatory process of atherogenesis that affect vessel wall and atherosclerotic plaque [12].

Interleukin-6 (IL-6) may also be considered among factors that contributing to the relationship between chronic infections such as periodontitis and CHD, displaying pro-inflammatory and pro-coagulant properties. IL-6 has a significant function in the pathogenesis of PD, it may have an action on monocyte differentiation into osteoclasts that have mean role in bone destruction [13] [9].

Levels of IL-6 may throw in to the exacerbation of atherosclerosis; it have been shown to contribute to both, atherosclerotic plaque development and plaque destabilization via a variety of mechanisms. These involve mainly the release of other proinflammatory cytokines, stimulation of acute phase protein secretion, and the activation of matrix metalloproteinases [14].

However, the presence of these relationships must be taken in consideration by the dentist and internist, For example, the «American Journal of Cardiology» and «Journal of Periodontology» publicized the consensus on periodontitis and atherosclerotic heart disease that advised to notify patients with moderate to severe periodontitis of a possible higher hazard of cardiovascular disease and necessitate to undertake cardiac evaluation [15].

Therefore this study was carried out in order to clarify the relationship between these two diseases from particular aspects, thus from this study and other studies at present and in the future, one may reach to clear results make the prevention of these diseases possible and diminish the hazard of new cardiovascular events and maintain good oral hygiene of subjects.

MATERIALS AND METHODS

Eighty (80) subjects, males aged (40-60) years old were recruited in this study. They were from patients seeking treatment in the cardiology clinic in Baghdad Teaching Hospital and patients were seeking periodontal treatment in Teaching Hospital at periodontic department of Baghdad College of Dentistry. All the individuals were informed about the purpose of these investigations and consented to its protocol.

The subjects were divided into study and control groups. Study groups include:

- CP + ATH group: Thirty patients examined to possess chronic periodontitis and Atherosclerosis according to catheterization and they were on (plavix drug 75 mg), admitted to the cardiology clinic in Baghdad Teaching Hospital.
- CP group consists of thirty patients examined to have chronic periodontitis and didn't have any systemic diseases. Chronic periodontitis in patients was defined as the presence of equal or less than 30% from sites with pocket depths ≥4mm with clinical attachment loss of (1-2) mm or greater, this is made in accord with the worldwide classification system for PD [16].
- Control group consists of twenty patients with clinically healthy periodontium this was defined by GI scores<0.5 [17] with no pockets or clinical attachment loss and no history of any systemic diseases. This group represents as a base line data for the level of serum Interleukin-1β (IL-1β) & Interleukin-6 (IL-6).

Clinical periodontal parameters examination was performed by using Michigan O periodontal probe on four surfaces (mesial, buccal/ labial, distal and lingual/ palatal) of all teeth except third molar, all subjects must have at least 20 teeth. The collected data include:-

1. Assessment of Soft Deposits by the Plaque

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Index System (PL.I) according to Silness and Loe [17].
2. Assessment of Gingival Inflammation by the Gingival Index System (GI) according to Löe [18].
3. Assessment of Gingival Bleeding on Probing (BOP): Periodontal probe inserted to the bottom of the gingival crevice or pocket and is moved gently along the root surface. If bleeding occur within 30 seconds after probing, the site was given as score (1), and a score (0) for the non-bleeding site [19].
4. Assessment of Probing Pocket Depth (PPD): It's defined as the distance from gingival margin to the most apical penetration of the periodontal probe inserted into the gingival crevice or periodontal pocket [20].
5. Assessment of Clinical Attachment Level (CAL): It is the distance from the cementoenamel junction to the location of the inserted probe tip (bottom of gingival crevice or periodontal pocket [20].

After the clinical periodontal parameters examination, 5ml venous blood was collected from study and control groups. After centrifusion, serum samples were kept frozen at (-20) °C. Serum levels of (IL-1β) & (IL-6) were determined by mean of Enzyme Linked Immuno- Sorbent Assay (ELISA).

ELISA Kit for quantitative determination of serum (IL-1β) & (IL-6) of (Bioassay Technology Laboratory).

Statistical analysis was assessed using t-test, ANOVA test, LSD, Games-Howell, Shapiro –Wilk test and Pearson's coefficient of correlation.

RESULTS

The current results revealed that mean values of (PL.I, GI, PPD and CAL) were higher in CP+ATH group than the CP group and control group, with highly significant differences between the two study groups. The percentage of score-1 of BOP sites was higher in CP+ATH group than the CP group with highly significant difference. The statistical analyses of clinical periodontal parameters for CP and CP+ ATH groups are summarized in table (1), while the result of control group to compare with other study groups.

Table (2) showed that the serum mean levels of IL-1β and IL-6 were higher in CP+ATH group followed by CP group then the control group, the mean values with Std. Dev. for IL-1β were (1967.12 ±185.7, 1364.71 ±139.1, 605.28 ±27.8 respectively) and for IL-6 were (respectively) with highly significant differences ($p<0.001$) among all the groups. Regarding both immunological parameters intergroup comparisons of serum mean values of IL-1β as well as IL-6 between all pairs of the study and control groups demonstrated highly significant differences, as shown in table (3). In CP group there was weak positive correlation between BOP with serum IL-1β levels, While there were significant, moderate positive correlations with each of (PL.I,GI) at $p<0.05$, and highly significant, strong positive correlations with (PPD and CAL) at $p< 0.01$. For CP+ATH group, there were weak positive correlations between serum IL-1β levels with PL.I and PPD, while significant, strong positive correlations were observed with each of (GI, BOP and CAL) at $p<0.05$. It was demonstrated that in CP group moderate positive correlation between serum IL-6 levels and (PL.I, BOP and PPD) at $p<0.05$ as well as strong positive correlations with GI and CAL, at $p>0.01$. In CP+ATH group highly significant strong positive correlations were revealed between serum IL-6 levels with (GI, and PPD) at $p<0.01$, while the correlation was weak positive with (PL.I and BOP) and moderate with CAL at $p<0.05$, as shown in table (4).

Table 1-a : Statistical analysis of mean values of clinical periodontal parameters (PL.I, GI, and BOP) for the study and control groups with comparison of significance between study groups

Groups	PL.I		GI		BOP			
					Score 1		Score 0	
	Mean	S.D.	Mean	S.D.	No	%	No	%
Control	0.50	± 0.112	0.57	0.119				
CP	1.69	±0.125	1.74	±0.121	1656	58.09%	1196	41.91
CP+ATH	1.78	±0.136	1.83	±0.131	1588	61.26%	1004	38.47
T-test between study groups	-2.65		-2.935		-2.912			
Sig	S		HS		HS			

S : Significant at P<0 .05. HS : Highly Significant at P<0.001

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Table 1-b : Statistical analysis of mean values of clinical periodontal parameters (PPD and CAL) for the study groups with comparison of significance

Groups	PPD		CAL	
	Mean	S.D.	Mean	S.D.
CP	4.15	±0.295	3.89	±0.256
CP+ATH	4.72	±0.410	4.55	±0.397
T-test between study groups	6.276		-7.662	
Sig	HS		HS	

HS : Highly Significant at P<0.001

Table2: Statistical analysis of mean values of serum (IL-1β and IL-6) for all groups with comparison of significance

Groups	IL-1β (pg/l.)		IL-6 (ng/l.)	
	Mean	S.D.	Mean	S.D.
CP+ATH group	1967.12	±18	248.65	±22.90
CP group	1364.71	±13	196.26	±16.25
Control group	605.28	±27	98.34	±7.30
F-test	544.898		438.528	
Sig.	HS		HS	

HS : Highly Significant at P<0.001

Table 3: Inter groups comparisons of the mean values of serum (IL-1β pg/l. and IL-6 ng/l.) between all pairs of each study groups and Control group

Groups	IL-1β			IL-6		
	Mean difference	S.E.	P-value	Mean difference	S.E.	P-value
CP --CP+ATH	-602.413	42.374	0.000	-52.38400	5.12898	0.000
CP--Control	759.429	26.152	0.000	97.92450	3.38823	0.000
CP+ATH--Control	1361.842	34.481	0.000	150.30850	4.49028	0.000

Table 4: Pearson's Correlation Coefficients among serum levels of (IL-1β and IL-6) and clinical periodontal parameters in CP+ATH and CP group

Immunological Parameters	Groups	Statistical analysis	PL.I	GI	BOP	PPD	CAL
Interleukin-1β	CP Group	Pearson`s Coefficient *(r)*	0.445	0.409	0.298	0.638	0.701
		P-value	0.0137	0.024	0.0109	0.000	0.000
		Sig.	S	S	NS	HS	HS
	CP +ATH Group	Pearson`s Coefficient *(r)*	0.361	0.493	0.433	0.378	0.457

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		P-value	**0.05**	**0.005**	**0.016**	**0.039**	**0.011**
		Sig.	**NS**	**HS**	**S**	**S**	**S**
Interleukin-6	**CP group**	**Pearson` s Coefficient *(r)***	**0.411**	**0.635**	**0.429**	**0.454**	**0.619**
		P-value	**0.024**	**0.000**	**0.0180**	**0.011**	**0.000**
		Sig.	**S**	**HS**	**S**	**S**	**HS**
	CP +ATH Group	**Pearson` s Coefficient *(r)***	**0.345**	**0.627**	**0.365**	**0.645**	**0.453**
		P-value	**0.061**	**0.000**	**0.047**	**0.000**	**0.016**
		Sig.	**NS**	**HS**	**S**	**HS**	**S**

DISCUSSION

Chronic periodontitis is a chronic multifactorial inflammatory disease caused by bacterial microorganisms and characterize by progressive damage of the tooth supporting tissue leading to tooth loss, also it leads to entry of bacteria in the blood stream; The bacteria stimulate the host inflammatory reaction by several mechanisms. The host immune response favors atheroma formation, maturation and exacerbation [21].

The mean values of (PL.I , GI, BOP score 1, PPD and CAL) were higher in CP+ATH group than CP group which could be explained in that plaque is the major etiological factor in periodontitis and it is expected to be accumulate more in chronic periodontitis because the presence of dental plaque is the main clinical finding for chronic periodontitis and it is coincide with the severity and the time being of the disease, another possible explanation of such results as the hospitalized Atherosclerotic heart disease patients neglect the oral hygiene measures and didn't brush their teeth regularly, so that more gingival inflammation could be seen in CP+ ATH group. Plaque biofilm bacteria liberate a variety of by-products (toxins, enzymes and H2S), that provoke an inflammatory response which is defending mechanism but also is accountable for periodontal loss, pocket formation, bone resorption, mobility and teeth loss [22]. These results obtained from the present study were similar to that reported by other investigators [22] [23] [24].

The serum levels of IL-1β and IL-6 in this study were higher in the study group with chronic periodontitis and atherosclerotic heart disease than other groups with highly significant differences between the groups at (P≤0.01). The results of this study were in consistent with (Wu T et al., 2010; Zhu et al., 2015) [25] [26] for serum levels of IL-1β, and in agreement with (Shuang et al., 2013; Ruhollah et al., 2015) [27] [28] for serum levels of IL-6 in study and control groups.

Several studies reported that IL-1β cytokine acts a essential factor in the pathogenesis of PD[29]. The IL-1β involvement during atherogenesis could be demonstrated by its ability to cause instability of atheromatous plaque due to upregulation of MMP at the site of plaque formation, also it mediates vascular smooth muscle cells proliferation and migration during inflammation which plays key roles in the development of atherosclerosis [30] [36].

Serum IL-6 may be raised due to systemic exposure to oral bacteria and LPS that enter the circulation from periodontal pocket, which in turn act on the liver to excite release of acute phase proteins including C-reactive protein (CRP) [31]. In atherosclerosis, IL-6 has proinflammatory properties and a pro-coagulant effect, also the raising in its levels may throw into the aggravation of atherosclerosis. Also the retention of LDL in the intima of a vessel may undergo oxidative changes and consequently may increase the output of chemokines and proinflammatory cytokines, mainly IL-6 [32] .

Regarding the positive correlation of serum IL-1β levels with clinical perio dontal parameters, in both study groups, make the IL-1β level as a sensitive and reliable marker of chronic inflammation activity and its elevation may demonstrate tissue destruction [33]. Periodontally IL-1β is known to cause multiplication of keratinocytes, fibroblasts, and endothelial cells and to augment fibroblast synthesis of collagenase,

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hyaluronate, fibronectin and (PGE2). IL-1β upregulates (MMP) and downregulates tissue inhibitor of (MMP) production and it is also a influential stimulator of bone resorption, lead to increase PPD and loss of attathment [(34)] .

The positive correlation between IL-6 levels and different periodontal parameters can be assigned to the plaque bacteria and bacterial by products locally produced pro-inflammatory cytokines guide to the rising of systemic IL-6 levels [(35)]. Also IL-6 is secreted by osteoblasts which may have an effect on differentiation of monocyte into osteoclasts that have key role in alveolar bone resorption which is hallmark of periodontitis progression [(9)] . This positive correlation results appeared in agreement with (Al-Ghurabei et al., 2012; Zhu et al., 2015) [(33)] [(26)] for serum IL-1β, also in consistent with (Wu T et al., 2010; Etemadifar et al., 2015) [(25)] [(28)] for serum IL-6.

It has also been revealed that in clinically healthy gingiva, inflammatory biomediators such as IL-1β and IL-6 are existed in low quantities, this indicates that cytokines are prominent factors of normal tissue homeostasis [(35)] .

In a conclusion, the patients with chronic periodontitis have levels of serum IL-1β and IL-6 were higher than normal range, which may be predict that patients with chronic periodontitis at a hazard of atherosclerotic heart diseases, also The significant positive correlations between serum levels of (IL-1β & IL-6) and different clinical periodontal parameters can be used as a marker for activity of diseases

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