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IP International Journal of Periodontology and Implantology

Journal homepage: <https://www.ijpi.in/>

Original Research Article

Role of gender & age in chronic periodontal disease

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ARTICLE INFO

Article history:

Received 05-07-2021

Accepted 16-07-2021

Available online 26-07-2021

Keywords:

Probing pocket depth (PPD)

Bleeding on Probing (BOP)

Gender

Age

Periodontal disease

ABSTRACT

Context: There is lot of literature suggesting a gender based heterogeneity in many human chronic diseases including periodontal disease.**Aims:** To analyze and compare the clinical periodontal disease parameters & serum biochemical markers of periodontal inflammation in systemically healthy age stratified adult male and female patients suffering from chronic destructive periodontal disease.**Settings and Design:** Cross sectional observational study in a hospital setting**Materials and Methods:** A total of 300 subjects, both genders were enrolled based on predefined criteria and were categorized in 6 groups of 50 subjects each. Complete medical and dental history was taken to screen before enrollment. All subjects underwent complete periodontal examination, including evaluation of Plaque index (PI), Probing pocket depth (PPD) and Clinical attachment level (CAL), Bleeding on Probing (BOP). Blood samples were taken for analysis of inflammatory biomarkers viz interleukin (IL)-1 β , osteoprotegerin (OPG), matrix metalloproteinase (MMP)- 8 & interleukin (IL)- 6.**Statistical analysis used:** IBM SPSS STATISTICS (version 22.0)**Results:** Clinical parameters of periodontal status were higher in females as compared to males except BOP. However, only PPD and CAL showed significant difference. Higher serum levels of IL-1 β , OPG and IL-6 were observed in females (2.10 + 26.82, 168.18 + 49.84 , 29.17 + 99.20 pg/ml) than males (1.90 + 7.27 , 145.00 + 39.60 , (25.83 + 189.09pg/ml) respectively, but significant difference was observed only for OPG. A statistically significant higher level of MMP-8 was observed in males (3003.33 + 772.33 pg/ml) as compared to females (1398.33 + 1218.10 pg/ml).**Conclusions:** The findings of current investigation has identified significant differences in the clinical and specific biochemical mediators(IL-1 β , IL-6, OPG, MMP-8) across groups and subgroups of the population To ascertain the impact of gender and age in the causation and pathogenesis of inflammatory periodontal disease, further well designed prospective investigations are needed .**Key Messages:** The study findings point towards the identification of specific biomarkers in individual subgroup/group based on age and gender. These shall pave path to develop predictive models, screening tools and early diagnostic strategies for chronic periodontal disease for Indian population.© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

Sexual dimorphisms are documented to exist in the occurrence of many human conditions and diseases.¹ Disorders specifically related to immunity of an individual

are greatly influenced by the effect of gender of an individual. Sex differences in immunity precede puberty, albeit less commonly. It is important to know the effect of gender in the causation and progression of periodontal disease, so as to define risk assessment and novel therapeutic strategies.² This notion draws strength from the striking differences observed in the immune functions and the

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host susceptibility profiles seen in different genders.³ There is huge body of past epidemiologic evidence that points to a higher occurrence and severity of periodontal disease in men than women.^{4,5} Majority of researchers have attributed the higher risk for periodontal breakdown in men to their different behavior patterns, habits and attitudes which form a part of environmental risk factors rather as constitutional factors.^{6–8} On the contrary, there exists evidence at par which suggests that it is inherently the sex of the individual which bears the impact on the development of periodontal disease.^{9–11} Such findings should be interpreted judiciously, keeping in view the confounders in such research studies, disease definitions, different methods used, study populations, ethnicity and sample sizes. Many scientific papers published in this regard provide inconclusive, unclear and conflicting information pertaining to the role of sex as a risk factor for chronic periodontal disease.^{12,13} Shiau J H and Reynolds MA in a metanalytic review revealed a greater risk for males than women; however, they do not appear to have a greater propensity for a more aggressive or rapid progression of periodontal tissue destruction during disease. However, consistent with finding differences in disease owing to gender, inflammatory mediators levels in the body were found to be significantly higher in males compared to females in study conducted in nonhuman primates.¹⁴ Although there is no established ground suggesting a constitutional difference between both genders in their vulnerability to inflammatory periodontal disease, the observed patterns of disease i.e higher prevalence in males reflects on general male attitudes and practice behaviors like carelessness towards maintenance of oral hygiene, smoking and tobacco habits and irregular occasional utilization of professional oral health care services.¹⁵ In the gene-based scenario, as majority of genes associated with immune cells reside on X chromosome, gives an edge to females in context of immunity, alongside the autosomal gene content is also regulated by the or sex-specific steroid hormones.^{16,17}

Age has been reported as a risk factor in natural history of periodontal disease as chronic periodontal disease is known to be a disease of middle age onset which progresses with growing age. However, aging per se does not lead to the disease but it's the cumulative effect of etiologic factors exposure, which is implied responsible for slow increase in the loss of periodontal attachment and alveolar bone. Such physiologic patterns are very mild and hardly have any clinical relevance, unless the elderly individual has a concomitant periodontal inflammation resulting from plaque accumulation and poor oral hygiene.^{18,19} Immunosenescence refers to the reduction in the immune capacity with passage of time and leading to a greater susceptibility to microbial infections in aged individuals. Aging influences the innate immunity in a significant way,

which may be projected as a dysregulated immune response rather as an immune deficiency.²⁰ The term 'inflammaging' has been aptly coined and explains the enhanced state of chronic inflammation with advancing age in humans.²¹ Higher age is generally associated with poor periodontal health and increased extent and severity of periodontitis.²²

Although previous literature has recognized gender and age, as important factors in the host susceptibility profiles, very less has been studied and understood regarding these factors. Generally, only male subjects enrolled as participants in majority of oral health and disease clinical trials. There is a compelling need of exploring gender specific biomarkers to enhance our knowledge of periodontal disease pathogenesis. There are multiple confounding factors such as lifestyle, socioeconomic strata, and environmental influences, genetic and epigenetic factors which may play important role in such multifactorial diseases e.g periodontal disease. Thus, the current study has anticipated an expansion of knowledge regarding gender and age as risk factors for chronic periodontal disease pathogenesis and mediators. So the current investigation is aimed at exploring the role of gender and age in pathogenesis of chronic destructive periodontal disease.

2. Materials and Methods

A total of 300 subjects, both males and females were enrolled from The study protocol was duly reviewed and approved by the Institutional board of Ethics..

2.1. Inclusion criteria

1. Systemically healthy, suffering from chronic destructive periodontal disease (AAP, 1999).²³
2. Age at least 25 years.
3. Minimum of 20 natural teeth, excluding third molar teeth.
4. Ability to understand, the informed consent form and willingness to participate.

Any other periodontal pregnancy/oral lesion or condition except periodontitis, Pregnancy or lactation, patients needing prophylactic antibiotics usage for dental procedures (e.g., for certain heart and orthopaedic conditions), antibiotic therapy in the previous 6months, smokers, Chronic use of nonsteroidal anti-inflammatory drugs, and rugs impacting the general immune status, any Participation in a clinical study testing a drug, biologic, device, or other intervention within the last 30 days, non –compliant individuals were excluded.

Subject population was categorized into Group A- systemically healthy male patients, with chronic periodontal disease. (n=150)
Group B- systemically healthy female patients, with chronic periodontal disease. (n=150)
Each group was further categorized in subgroups based on

the age range:(n=50)

1. Subgroup A - 25-35 years.
2. Subgroup B - 35-45 years.
3. Subgroup C - 45-55 years

2.2. Study method

Selected study subjects were explained about the purpose and method of the study and their informed consent was taken. Complete medical and dental history was taken and detailed clinical examination was carried out. All subjects underwent full mouth periodontal examination, including evaluation of Plaque index (PI) (Silness&Löe,1964)²⁴ Probing pocket depth (PPD) and Clinical attachment level(CAL,) Bleeding on Probing (BOP) (Muhlemann and Son, 1971).²⁵ PPD and CAL measurements were made at the mesio-buccal, buccal, disto-buccal, disto-lingual, lingual, and mesio-lingual positions of every tooth except third molars. PPD was measured as the distance from the gingival margin to the base of the periodontal pocket with the help of a UNC- 15 probe. Clinical attachment level (CAL) was measured to the nearest millimeter with UNC-15 probe using the cemento-enamel junction as a reference point.

Using a classical veni-puncture technique, 5ml of venous blood was obtained from the antecubital vein and the serum was separated by centrifugation after an hour. The serum samples were stored at -70°C and concentrations of interleukin (IL)-1 β , osteoprotegrin (OPG), matrix metalloproteinase (MMP) - 8 & interleukin (IL)-6 were evaluated using commercially available ELISA kits according to the manufacturer's guidelines.

For statistical analysis, recorded data of study parameters (clinical and biochemical) for the subjects in the specific groups were pooled to form group means. The intergroup comparisons for means of clinical and biochemical parameters were done using paired student t-test or Mann Whitney U-test or Wilcoxon W test. All the above mentioned analyses were conducted using IBM SPSS STATISTICS (version 22.0) and a p-value of < 0.05 was considered significant.

3. Results

The mean age of the study population was observed to be 40 and 41 years for group A and B respectively. The mean age for subgroup A,B and C in group A was 29,40 and 51 years respectively, whereas for subgroup A,B and C in group B was 29,41 and 51years respectively.(Table 1) The data analysis for clinical periodontal disease parameters revealed, mean PI score was 1.78 + 0.34 for group A and 1.83 + 0.42 for group B respectively. The mean pocket probing depth (PPD; mm/site) for group A was 2. 84 + 0.79 and 3.42 + 1.08 for group B. The mean value of clinical attachment loss (CAL; mm/site) for group A was observed

to be 3.54 + 1.23 and 4.11 + 1.45 for group B respectively. The BOP score was observed to be 1.36 +1.02 in Group A and 1.18 + 0.96 in Group B. (Table 2a) The intergroup analysis for PPD & CAL revealed a statistically significant difference (p<0.05) amongst the groups. (Table 2b) The serum levels of IL-1 β were found to be 1.90 +7.27 pg/ml for group A and 2.10 + 26.82 pg/ml for group B (p=0.48). The serum levels of OPG were observed to be 145.00 + 39.60 pg/ml for group A and 168.18 + 49.84 pg/ml for group B (p=0.005). The noted serum levels of MMP-8 in the group A were 3003.33 + 772.33 pg/ml and in the group B were 1398.33 + 1218.10 pg/ml (p=0.001). The observed serum levels of IL-6 for group A were 25.83 + 189.09 pg/ml and for group B were 29.17 + 99.20pg/ml respectively (p=0.821).(Table 3a) Statistically significant differences were seen between group A and group B for the serum levels of OPG & MMP-8. (Table 3b) Subgroup wise analysis revealed statistically significant differences between group A and group B for BOP scores in subgroup A. Statistically significant differences were seen between group A and group B for PI, PPD & serum levels of OPG & MMP-8in subgroup B. Statistically significant differences were seen between group A and group B for PPD & serum levels of OPG & MMP-8in subgroup C. (Table 4 a,b,c)

4. Discussion

The present observational study aimed at analyzing and comparing the periodontal status in systemically healthy adult male (Group A) and female (Group B) patients suffering from chronic destructive periodontal disease. The findings from study ascertained a homogenous population for data analysis that decreased the effect of confounding on the data interpretation as the mean age of both study groups, including subgroup populations did not differ significantly.(Table 1) Consistent implementation of standards in measurement of the study parameters has ensured improved reporting quality, permitted meaningful comparisons across populations, and provided better insights into the determinants of such variation. Since, inflammatory cytokines like interleukin-6 etc are documented to be sensitive to specimen type, standard EDTA plasma considered a valid point of measurement was adopted. Further, samples were kept refrigerated or cooled during processing as some inflammatory markers start degrading after 4 to 6 hours at room temperature. In general, it is recommended to keep specimens stored at or below -70 degrees Celsius, to help assure valid results and sensitivity of some inflammatory markers was reported to multiple freeze thaw cycles; hence, that was avoided.²⁶

In the present study the clinical parameters of periodontal status were higher in females as compared to males except BOP (Table 2a), where PPD and CAL showed significant difference. (Table 2b) In a consecutive dataset of Italian population, females exhibited more disease than males,

with a 3:2 prevalence ratio, and same trends in the subset of young (<35 years) patients.²⁷ There could be many underlying mechanisms, which may be accountable for the observed differences. Diverse genetic constitution, sex steroid related effects and any combination of these may impact these factors.^{28,29}

In the current investigation biochemical analysis revealed higher serum levels of IL-1 β in females (2.10 + 26.82 pg/ml) than males (1.90 + 7.27 pg/ml) ($p=0.48$). (Table 3a,b) Interleukin 1 β is considered marker of acute inflammatory phase and is one of the central mediators in the cytokine network.³⁰ The circulating levels of IL-1 β have also been documented to increase in the presence of periodontal disease. Zhu H et al(2014), reported higher levels amongst Chinese population as the severity of disease was much higher in comparison to study population.³¹ Orozco A et al reported very little serum IL-1 β levels as very stringent criteria for study subject selection accounted for the fact that hardly any perceptible levels of cytokines could be found in the serum samples of their patients.³² The reported levels by de QUEIROZ AC et al(2008), in a preliminary screening data were in line with our study.³³

In this study the serum levels of OPG observed were significantly higher in females 168.18 +49.84 pg/ml in comparison to 145.00 + 39.60 pg/ml for males ($p=0.005$). (Table 3a,b) OPG is a soluble decoy receptor produced by osteoclasts which inhibits interaction of RANK with its associated ligand RANKL. It's levels can provide reliable information on the state of periodontal disease activity.³⁴ Nauminik B et al (2013) reported high OPG levels in women as compared to men in the healthy control population of their study analyzing the levels of OPG/RANKL ratios in maintenance haemodialysis patients.³⁵ Khosla et al studied that the gender difference in OPG levels suggest that in vivo, sex steroids may influence the levels, in sync with as observed in in vitro studies. Moreover, OPG production may also rise with increase in bone turnover, probably as an internal regulatory mechanism to control bone loss.³⁶

The current investigation revealed higher levels of MMP-8 in males (3003.33 + 772.33pg/ml) as compared to females (1398.33 + 1218.10 pg/ml) ($p=0.001$). (Table 3a and b) MMPs represent superfamily of proteases involved in the regular turnover of the tissue including physiologic tissue remodeling and also in pathological loss of tissue collagen. MMP-8 is considered to be a key mediator of loss of collagen tissue in periodontitis cases.³⁷ It has been validated to be associated with the periodontal disease severity and activity, so much so that it has been basis of the commercially developed diagnostic kits also.³⁸ However, the robustness of the marker in a sex specific way has not been analyzed so far and it has been interpreted as a well discriminatory biomarkers in GCF and saliva both males and females. More often, serum or plasma MMP-8

was analysed in patients suffering from systemic diseases, which is distinctively different from our study, and is a possible reason for the varied observations and lack of comparative literature published previously. MMP -8 has been extensively studied and researched biomarker for periodontal disease status in oral biological fluids i.e GCF and saliva.

In this study, the observed serum levels of IL-6 for females (29.17 + 99.20 pg/ml) were higher as compared to males (25.83 + 189.09 pg/ml) ($p=0.821$). (Table 3a,b) IL-6 is considered a standard and useful indicator or a diagnostic marker for periodontitis as it measures long standing inflammation. IL-6 influences also B-cell differentiation and affects the immune responses. The findings are supported by de QUEIROZ AC et al(2008), who reported higher IL-6 levels in subjects with poor periodontal status.⁵² Markers of inflammation are known to strongly correlate with measures of adiposity, and this association is seem to be more strongly associated in women than in men, especially for CRP and IL-6.³⁹

In the study population of age range 25-35 (Subgroup A), the clinical parameters of periodontal status were higher in males as compared to females except for CAL. However non significant differences were observed in intergroup comparison except for BOP. (Table 4a,b). Shiao HJ et al(2010), in a systematic review emphasized that men are at greater risk for periodontal disease than women due to greater innate immune response, as well as potential differences in regulation of amplification and termination of inflammation.² In the same subset of population, the serum biochemical markers of periodontal inflammation were higher in females except for MMP-8 which was higher in males, but difference observed was non significant. (Table 4a,c) IL-1 β also regulates the production of OPG and has been associated with bone metabolism.³⁴

In the study population of age range 35-45 (Subgroup B) as well as age range 45-55 (Subgroup C), all the clinical parameters of periodontal status were higher in females except for BOP. Significant differences were observed only in PI and PPD. (Table 4a,b) In the previously published literature opposite trends have been noticed wherein males presented with poor periodontal status. This finding might be plausible because classic studies of the natural history of periodontal diseases have been conducted focusing primarily only on male gender, thus are with limited validity and questionable generalizability. The serum biochemical markers of periodontal inflammation were higher in males except for OPG which was significantly higher in females. (Table 4a,c)

The clinical parameters of periodontal status were higher for females in subgroup B and for males in subgroup A in comparison with other subgroups. In the study population of age range 45-55 (Subgroup C), the clinical parameters were observed higher in females with only PPD differences being

Table 1: Population characteristics of patients enrolled in the study by age and gender

Study characteristics		Total subject population (n=300)				
Gender		Group A(Males)			Group B(Females)	
No of subjects		150			150	
Mean age (in years)		40			41	
Age group (in years)		Subgroup A	Subgroup B	Subgroup C	Subgroup A	Subgroup B
		25-35	35-45	45-55	25-35	35-45
Mean age (in years)		29	40	51	29	41
No of subjects		50	50	50	50	50

Table 2: Descriptive data of the clinical parameters of periodontal status in Group A and Group B

S. No	Clinical Parameters		Mean	Median	Standard Deviation
1.	PI	Group A	1.78	-	0.34
		Group B	1.83	-	0.42
2.	PPD	Group A	2.84	-	0.79
		Group B	3.42	-	1.08
3.	CAL	Group A	3.54	-	1.23
		Group B	4.11	-	1.45
4.	BOP Score	Group A	1.72	1.36	1.02
		Group B	1.56	1.18	0.96
b: Comparative evaluation of clinical parameters in Group A and Group B					
S. No	Study Parameters	T (student t test)	df	p-value (2-tailed)	
1.	PI	-.646	86	0.52	
2.	PPD	-2.928	86	0.04*	
3.	CAL	-2.008	86	0.048*	
	—	U (Mann- Whitney)	W	—	
4.	BOP	807.00	1797.00	0.179	

Table 3: Descriptive data of the serum biochemical markers of periodontal inflammation in Group A and Group B

S. No	Biochemical Parameters		Mean	Median	Standard Deviation
1.	IL-1B	Group A	5.10	1.90	7.27
		Group B	10.70	2.10	26.82
2.	OPG	Group A	144.15	145.00	39.60
		Group B	172.50	168.18	49.84
3.	MMP-8	Group A	3072.58	3003.33	772.33
		Group B	1778.86	1398.33	1218.10
4.	IL-6	Group A	96.07	25.83	189.09
		Group B	48.29	29.17	99.20

Table 3b: Comparative evaluation of biochemical parameters in Group A and Group B

S.No.	Biochemical Markers	Group	Mean Rank	Sum of rank	Mann-whitney u	Wilcoxon w	p-value (2-tailed)
1.	IL-1B	A	41.14	1769.00	823.000	1769.000	0.48
		B	44.90	1886.00			
2.	OPG	A	35.80	1575.00	585.000	1575.000	0.005*
		B	50.73	2080.00			
3.	MMP-8	A	57.82	2544.00	382.000	1372.000	0.001**
		B	31.18	1372.00			
4.	IL-6	A	41.05	1765.00	772.000	1475.000	0.821
		B	39.86	1475.00			

Table 4: Subgroup wise descriptive data of study parameters in Group A and Group B

			Subgroup a			Subgroup b			Subgroup c		
S.No			Mean	Median	Standard Deviation	Mean	Median	Standard Deviation	Mean	Median	Standard Deviation
1.	PI	Group A	1.85	-	0.44	1.72	-	0.29	1.76	-	0.26
		Group B	1.73	-	0.32	1.95	-	0.30	1.80	-	0.58
2.	PPD	Group A	3.01	-	0.86	2.75	-	0.82	2.74	-	0.68
		Group B	2.98	-	0.72	3.56	-	1.17	3.76	-	1.19
3.	CAL	Group A	3.36	-	1.30	3.65	-	1.14	3.62	-	1.31
		Group B	4.18	-	1.16	3.86	-	1.49	4.32	-	1.72
4.	BOP	Group A	2.20	2.04	1.02	1.44	1.30	0.62	1.52	1.19	1.23
		Group B	1.23	1.17	0.30	1.76	1.19	1.11	1.71	1.16	1.21
5.	IL-1 β	Group A	6.30	1.50	9.44	5.78	2.04	7.25	3.12	2.01	3.99
		Group B	8.46	3.10	17.17	3.97	1.84	8.08	20.86	1.84	43.46
6.	OPG	Group A	146.42	148.48	47.27	151.21	145.15	41.80	134.16	140.76	26.95
		Group B	148.27	152.12	48.81	190.02	193.03	42.10	180.45	175.91	51.17
7.	MMP-8	Group A	2979.56	3376.67	914.86	3119.56	2976.67	898.62	3121.90	3155.00	432.29
		Group B	2811.78	2863.33	1275.35	1100.89	1056.67	637.37	1398.57	1315.00	895.29
8.	IL-6	Group A	89.33	25.00	148.81	48.93	31.67	89.19	150.42	32.50	279.44
		Group B	87.12	31.67	174.38	23.94	23.33	24.35	42.65	30.83	40.03

Table 4b : Subgroup wise comparative evaluation of clinical parameters in Group A and Group B

		Subgroup A			Subgroup B			Subgroup C		
S.No		t	Df	p-value (2-tailed)	T	df	p-value (2-tailed)	t	Df	p-value (2-tailed)
1.	PI	.838	28	0.409	2.141	28	0.041*	.234	26	0.817
2.	PPD	.110	28	0.913	-2.170	28	0.039*	-2.787	26	0.010**
3.	CAL	-1.828	28	0.078	-.423	28	0.676	-1.222	26	0.233
4.	—	U (Mann-Whitney)	W	—	U (Mann-Whitney)	W	—	U (Mann-Whitney)	W	—
5.	BOP	36.500	156.500	.002**	110.00	230.00	0.917	94.000	199.000	0.854

statistically significant. (Table 4a,b) The serum biochemical markers of periodontal inflammation were higher in males except for OPG which was higher in females. (Table 4a,c) Cross-sectional studies show that higher blood concentrations of inflammatory markers tend to be more common in frail older people. Frailty is a clinically recognizable syndrome observed in older people which is characterized by an increased susceptibility to stressors due to downgraded multiple systems, decreased physiological reserves and a decline in the ability to maintain homeostasis. Though, much published literature from cross-sectional observations label frail old women harbouring higher levels of various inflammatory or coagulation markers in blood according to Fried et al. criteria, yet it is unclear to delineate the temporality of this association owing to the design of these investigations.⁴⁰

The strength of current investigation is uniform presentation of the study population in different categories of subgroups in the investigation in a reasonably expanded sample size. Further, the selection of multipanel

biomarkers was ascribed on the basis of their respective involvement in the different aspects of periodontal disease pathogenesis viz IL-1 β (acute inflammation), IL-6 (chronic inflammation), MMP-8 (collagen destruction) and OPG (Bone resorption), which has helped providing a thorough insight and understanding to the research question posed. Still, there are few weaknesses in the analysis also such as there was limited characterisation of metabolic profile or body composition at baseline and no information on the endocrine axis. Further the apparently aberrant/contradictory patterns observed in clinical and biochemical parameters of the study seemingly in disconnect with the existing knowledge and plausibility and may possibly be attributed to the sample size of the study. It should be interpreted with caution for larger implications and recommended to be ascertained in future investigations. It is possible that the statistical analyses opted might be affected by residual confounding as we lacked detailed data on these aspects, which shall limit the validity of findings on a larger population.

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Cite this article: Jain A, Bhavsar NV. Role of gender & age in chronic periodontal disease. *IP Int J Periodontol Implantol* 2021;6(2):117-125.