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Cover Page Footnote

To The Editor, We intend to publish an article entitled" Low Bone Mineral Density And Clinical Attachment Loss In Postmenopausal Women" in your esteemed journal. on behalf of all the contributors, i will correspond with the journal from this point onward. we have no confict of interest among ourselves. we have none funding. We hereby transfer, assign, or otherwise convey all copyright ownership exclsively to the journal. positive response is anticipated. thanking you Corresponding author Dr Aastha Baldodia; MDS senior resident department of periodontics PGIDS ROHTAK INDIA email: aasthabaldodia626@gmail.com Other contributors: Dr Rajinder Kumar Sharma; MDS Senior professor and Head of department periodontics PGIDS ROHTAK INDIA Dr Shikha Tewari; MDS Senior Professor periodontics PGIDS ROHTAK INDIA

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ORIGINAL ARTICLE

Association among hsCRP Levels, Bone Mineral Density, and Periodontal Parameters in Postmenopausal Women

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ABSTRACT

Association of Osteoporosis and periodontitis is well documented. Osteopenia being the initial state of bone loss prior to osteoporosis; finding its correlation with clinical attachment loss holds significance in the process of establishing early reduction in BMD as a risk factor for periodontitis. **Objectives:** The present cross sectional study aimed to explore the association of osteopenia with serum high sensitivity C-reactive protein (hsCRP) levels, and periodontal parameters in narrow age range postmenopausal (PM) women. **Methods**: 112 participants in this single centred cross sectional study were bifurcated into test group: osteopenic PM women [n=62], and control group: normal bone mineral density [BMD] PM women [n=50]. BMD, serum levels of hsCRP, and periodontal parameters were recorded. **Results:** Clinical attachment loss [CAL] and hsCRP were found to be significantly higher in the osteopenic PM group. **Conclusion**: An association of osteopenia with increased CAL in PM women was found, implicating postmenopausal osteopenia associated with increased risk of periodontitis. The present study hints towards the comprehensive management of Periodontitis and osteopenia in postmenopausal women by maintaining a good coordination between the physicians and dentists.

Key words: bone diseases, bone density, C-reactive protein, chronic periodontitis, menopause

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INTRODUCTION

Periodontitis being a multifactorial chronic disease; involves inflammation of the supporting tissues of the teeth resulting in destruction of periodontal ligament, and eventually bone loss.[1]Systemic risk factors have an important role in the development of periodontitis by modifying complex and dynamic interactions occurring between the infectious agents and host response.[2] Osteoporosis and periodontitis has a well-established association.[3] In postmenopausal (PM) women, clinical attachment loss (CAL) had been independently and inversely associated with hip bone density.[4] A significant association between worsening T score and alveolar crestal bone loss is reported.[5]

Osteoporosis is a systemic disease with systemic inflammatory burden while periodontitis involves local inflammation of the supporting structure of teeth; sharing bone loss as a common feature.[6] Biological plausibility of PM systemic bone loss influencing at least part of periodontal destruction mainly rest on the possibility of rapid resorption of alveolar bone in lowered local BMD owing to systemic bone loss. Inflammatory factors mediating the PM systemic bone loss may also partly modify the local inflammatory response in periodontium leading to rapid loss of alveolar bone in periodontitis. Furthermore PM systemic bone loss, and alveolar bone loss in periodontitis may share common risk factors including genetic predisposing factors and lifestyle modifications.[7]

C-reactive protein [CRP] is a serological marker of inflammation in the body. Higher serum levels of CRP were found to be associated with lower bone density in a large population based study.[8] Increased CRP levels are also showed in patients with severe clinical attachment loss [CAL] than minimal or no attachment loss.[9] Advancing age has been reported to be common risk factor shared by both periodontitis and osteoporosis.[10,11] World Health Organization(WHO)

reported osteoporosis in one in six women at 50 years of age. There was a 50% increase in prevalence of osteoporosis in women on turning 80 years old.[12] The proportion of PM women exhibiting normal BMD decreases sharply with increasing age. Borell and Papapaou reported higher severity and prevalence of periodontal disease with advancing age.[13] However, most of the cross-sectional studies conducted to evaluate the association of osteoporosis with periodontitis included PM women within a wide age range.[4,6,14] Hence, it is hypothesized that the participants within a narrow age range may provide authenticity to the association of periodontitis with BMD.

An imbalance between bone resorption and formation leading to reduction in bone mass is known as osteopenia, which on further demineralization results in osteoporosis. Osteopenia being the initial state of bone loss prior to osteoporosis; finding its correlation with periodontitis holds significance in the process of establishing early reduction in BMD as a risk factor for periodontitis. The present study evaluated the association of osteopenia with serum high sensitivity CRP levels and periodontal parameters in narrow age range PM women.

METHODS

Subjects recruitment

This single center cross sectional study was approved by the ethical committee of Postgraduate Institute of Dental Sciences, Rohtak, India [PGIDS/IEC/2014/114]. Prior informed consent from every participant was taken before inclusion in the study. 243 individuals were screened for the study. 112 participants who met the study criteria were accepted for the study. The test group comprised of 62 osteopenic PM women with CP. 50 PM women with normal BMD, and CP constituted the control group.

Inclusion criteria

Participants included in the study: aged 52 -59 years; Osteopenic, or normal BMD PM women reported natural menopause, and postmenopausal years equal or more than five years; and exhibiting CP along with presence of 20 or more natural teeth (excluding third molars). As per the WHO criteria[15:] BMD standardized T-score, osteopenia (between -1.0 and -2.5), Normal BMD (-1.0 or above).

CP criteria

Patient should have minimum 20 teeth excluding third molars, out of which: at least 4 teeth should exhibit one or more sites with a probing depth (PD) ≥ 4mm, CAL ≥ 3mm along with presence of bleeding on probing (BOP) at the same site.[16]

Exclusion criteria

- Any systemic disease affecting BMD and/or altering CRP levels including Rheumatoid
- Arthritis, Systemic Lupus Erythematosis, Ankylosing Spondylitis, Chronic Obstructive
- Pulmonary Disease, cardiovascular disease etc;
- Any systemic disease affecting periodontium like diabetes mellitus or immunological disorder;
- Patients with reported drug history in the past 3 months: steroids, immune suppressants, antibiotics, non-steroidal anti-inflammatory drugs, anti-convulsants, thiazide diuretic agents, statins, or any other host modulatory drug;
- Patients reporting any acute or chronic infection, gastro-intestinal disorders, thyroid and parathyroid disease;
- History of early onset of menopause, or/and hysterectomy;
- History of less than 5 years since menopause;
- Patient reporting use of any medication or treatment for osteoporosis/osteopenia such as calcium and vitamin D supplementation, bisphosphonates and hormone replacement therapy;
- Patients taking tobacco in any form;
- Patients who underwent non-surgical or surgical periodontal treatment in previous one year.

A detailed medical history was taken to rule out the diseases mentioned in exclusion criteria.

BMD measurement

In postmenopausal women, BMD was evaluated in lumbar spine region (L1-L4) using Dual Energy Xray Absorptimetry (DXA, Hologic QDR explorer version 12.6:3; Hologic) for 90 seconds with an exposure of .07mGy.

hsCRP estimation

Blood samples taken from anticubital vein were collected in plain additive less vacutainer tube, and serum hsCRP levels were determined with the help of an estimation kit (C - reactive protein (Latex) High-Sensitive Assay, Roche Diagnostics).

Periodontal examination

After meeting the selection criteria, full-mouth periodontal examination was done in all the participants. The following parameters were recorded: Plaque index (PI), Gingival index (GI), BOP, Pocket depth [PD], and CAL. PD and CAL were recorded with a UNC 15 Probe (Hu Freidy).[17,18,19]

Intra-examiner reproducibility

Inter-examiner variability was excluded as periodontal examination was undertaken by one trained and calibrated examiner; masked to the group division of the participants. Intra examiner variability was precluded by following a calibration protocol in which examiner reproducibility was evaluated twice on 10% of representative samples at the same visit. Intra examiner exact reproducibility was calibrated at 85% of sites for GI, and within 1 mm at >90% and >85% of sites for PD and CAL respectively.

Data Analysis

Assuming fixed effect size to be 0.6 with two sided $\alpha = 0.05$ and power 0.80 with allocation ratio of 1:1, sample calculated came out to be 47 in each group (G*Power v.3.0.10, Heinrich-Heine University Düsseldorf), The Shapiro–Wilk test was used to examine normality of data distribution. CAL was found to be normally distributed among all the parameters. Descriptive data was expressed as mean±SD. The intergroup comparison was assessed by Mann–Whitney *U* test or Student *t* test (independent). Partial correlation was used in the pooled data to find the relationship between T-score and other study parameters. The variables having significant correlations were then put into multiple linear regression stepwise analysis; for acquiring model of predictor variables with CAL as the dependent variable

A model was formed for facilitating Binary logistic regression analysis to appraise the association between CAL and BMD (T-score) (osteopenia as 0 and normal BMD as 1). In this model, the outcome variable was set as AL ≥ 4.28mm [reference value was set as equal as or higher than median CAL value] to compute the odds ratio (OR) and 95% confidence interval (CI). This model was fitted to relate presence/absence of CAL≥4.28mm at baseline as the outcome variable, and study groups comprised of test and control group, as the categorical predictor variable. It was verified by the Hosmer–Lemeshow goodness-of-fit test. Having a significance level at 0.05, all statistical analyses were two-tailed. [SPSS, version 25.0 for Windows, IBM].

RESULTS

The data pertaining to 112 participants comprising of 62 and 50 participants in test and control group respectively, was taken into consideration for statistical considerations. Table 1 shows comparative evaluation of all the study parameters including periodontal parameters and serum hsCRP levels between the groups. PI and age showed no significant difference between the groups, whereas GI, BOP, PD, CAL and hsCRP were significantly increased in the test group ($p < 0.05$).

A partial correlation among all the study parameters revealed a significant correlation of CAL with T-score, GI, BOP, PD and hsCRP in the pooled data (Table 2).

On applying multiple linear regression analysis, CAL was significantly associated with T-score and PD ($p > 0.05$) (Table-3).

The logistic regression analysis revealed that osteopenia was found to be associated with higher odds of CAL ≥ 4.29 ($OR_{adjusted}$ = 2.78, 95% CI = 1.28 to 6.02) (Table 4). A scatter plot was made to elicit the relationship between T-score and CAL (Figure-1).

DISCUSSION

An inverse association was found between BMD and CAL in postmenopausal women in the present study, and these findings are in compliance with other studies.[4,20,21,22]

Our study included newly diagnosed osteopenic and normal BMD participants as per the WHO criteria. The PM women included in the study had their natural menopause after the age of 45 years, as early onset of menopause is an established factor for osteoporosis.[23] An increased rate of bone loss in the first 5 years after menopause has been shown; hence PM women with history of natural menopause with more than five postmenopausal years were included in the study.[24]

Higher prevalence of periodontal disease and osteoporosis has been found with increasing age.[11-13]In the present study, osteopenic and normal BMD PM women within a narrow age range [52-59 years] were included so as to provide authenticity to the association results by ruling out the confounding effects of age in this association. Studies have emphasized that smoking may lead to reduced BMD, and smokers are more likely to develop periodontitis.[10-11] A significant association between smoking and CAL in PM females has been reported in literature.[25] Therefore, smokers were not included in the study.

During menopause, estrogen deficiency causes serum levels of IL-6, and TNF-α via T cell activation leading to upregulation of octeoclastogenesis and downregulation of osteoblast formation. These inflammatory cytokines have also been implicated in the destruction in periodontitis. IL-6 acts on hepatocytes, and produces CRP in the liver in response to inflammation. It is called as an acute phase reactant because its serum level increases with increased inflammation in the body.[26]

The present study has showed higher serum hsCRP levels in osteopenic PM women. Similar finding of higher serum hsCRP levels in the test group is also shown in a study by Koh et al.[27] It supports the hypothesis that increased serum levels of inflammation may contribute towards osteoclastic activation through RANK-RANKL-OPG imbalance leading to reduction in bone mineral density. These changes may also act on the periodontal tissues causing more CAL and alveolar bone reduction.[23,28] Further findings of higher GI, BOP and CAL in the test group can be verified with higher hsCRP levels in this group. This could explain the destructive effects of heightened systemic inflammation on the deteriorated periodontal parameters in the osteopenic PM women.

Table 1. Intergroup comparison of parameters

PARAMETERS	TEST GROUP	CONTROL GROUP	p-value
Bone Mineral density[T score] ‡	-1.603±0.412	0.129±0.812	0.000*
High sensitivity C-reactive Protein [mg/l]‡	2.560±1.348	2.061±1.059	0.045*
Plaque Index‡	2.122±0.292	2.081±0.284	0.453
Gingival Index‡	2.123±0.222	1.969±0.386	0.009*
Bleeding on probing[%]‡	88.510±9.380	84.973±9.290	0.048*
PocketDepth [mm]‡	3.850±0.525	3.630±0.508	0.032*
Clinical attachment Loss [mm]†	4.516±0.525	3.780±0.583	0.000*

Table 2. Correlation of different variables on applying partial correlations analysis after controlling the confounders [PI, Age] in the pooled data

			Correlations					
Control Variables	Parameters	Partial correlation significance level	hsCRP	BMD	GI	BOP	PD	CAL
Age & PI	HsCRP	Correlation	X.	-.217	.039	.095	.215	.212
		Significance [2-tailed]	X.	.023*	.609	.323	.024*	.026
	BMD	Correlation	-.217	X.	.097	-.185	-.122	-.417
		Significance [2-tailed]	.023*	X.	.313	.053	.205	.000*
	GI	Correlation	-.039	.097	X.	.186	.256	.233
		Significance [2-tailed]	.689	.313	X.	.052*	.007	.014
	BOP	Correlation	.131	-.185	.186	X.	-.105	-.249
		Significance [2-tailed]	.095	.053	.052*	X.	.274	.009
	PD	Correlation	.215	-.122	.256	-.105	X.	.560
		Significance [2-tailed]	.024*	.205	.007	.274	X.	.000*
	CAL	Correlation	.212	-.417	.233	-.249	.560	X.
		Significance [2-tailed]	.026	.000*	.014	.009	.000	X.

On partial correlation analysis hsCRP[p≤0.05] was significantly and positively correlated with BOP and CAL [p≤0.05]. Whereas CAL was significantly and positively correlated with hsCRP levels, GI, BOP and PD. Significant and negative correlation was found between BMD [lumbar region] with CAL, and hsCRP in the present study. Similar result was concluded by de Pablo et al. who conducted a large population based study, in which association of higher serum levels of CRP and lower BMD was found.[8]

A significantly negative association was found between CAL [dependent variable] and BMD. The regression coefficient revealed BMD as a significant predictor of CAL. It was earlier found that reduced BMD plays as a risk factor for the progression of periodontal disease in the elderly.[29]Though osteoporosis is not the primary cause of periodontitis but plays a role as a risk indicator that may help in the progression of periodontal disease. Some studies have obtained significant results while correlating osteoporosis with periodontal disease.[7,20,21,30] The logistic regression analysis in the present study revealed that osteopenic PM women were two times more likely to exhibit higher CAL than normal PM women. This finding may be attributed to the increased systemic inflammatory burden as shown by increased serum hsCRP levels in the test group. It can be speculated that systemic factors that affect remodeling of bone can also tend to modify local tissue responses in periodontal tissues. Moreover

Table 3. Multiple linear regression model for CAL in PM women

Dependent Variable	Model Predictors	ß unstandardized	Standard Error	ß standardized	p-value
CAL	CONSTANT		0.397		0.000
	BMD	-0.206	0.045	-0.332	0.000*
	PD	0.650	0.095	0.518	0.000*

* p ≤0.05 indicates significance

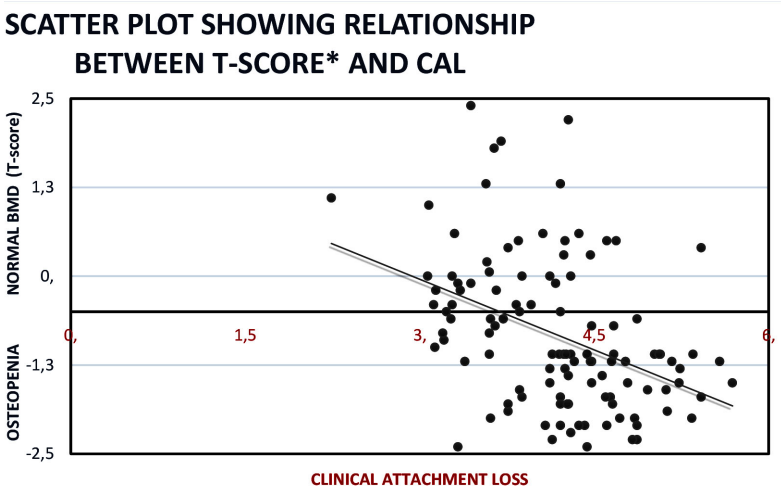

Figure 1. Relationship between T-score and CAL in a scatter plot

Table 4. Logistic regression analysis of the association between CAL≥4.28mm [median value] as the outcome with the study groups

Model study group 1	Unadjusted	Adjusted†
Odds ratio	2.78	2.76
Confidence interval [95%CI]	1.28-6.02	1.28-5.97
p-value*	0.010	0.009

* *p* ≤0.05 indicates signifihcance. †Adjusted for Age

lifestyle factors and genetic susceptibility responsible for reduced BMD may also contribute to increased bone loss in periodontitis.

Passos et al revealed that women exhibiting osteopenia\ osteoporosis were twice as likely to show periodontitis as those with normal BMD.[12] It is pertinent to note that osteopenic and osteoporotic patients were included together in one group in the above mentioned study. In our study, specifically osteopenic PM women were associated with increased CAL, implicating postmenopausal osteopenia associated with increased risk of periodontitis.

Apart from providing essential oral health services in PM women, findings of increased CAL may also necessitate further attention to their systemic bone health.

Stringent inclusion and exclusion criteria were followed as there was recruitment of only newly diagnosed osteopenic, and normal BMD women of narrow age range with exclusion of patients with early menopause and early PM women. Some of the limitations of the study are non-inclusion of systemic inflammatory cytokines estimation, rate of bone resorption and serum vitamin D level estimation.

CONCLUSION

The results of the present study presents knowledge that may aid in the development of the basis for better coordination between physicians and dentists, conferring collective action for recommending lifestyle changes of patients for better management of

periodontitis, and osteopenia in PM women, leading to better oral health and a longer lifespan.

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CONFLICT OF INTEREST
None.

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