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Correlation of Salivary Retinol Binding Protein 4 (RBP4) Levels and Periodontal Severity in Patients with Chronic Periodontitis

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Abstract: Pro-inflammatory cytokines play a vital role in periodontitis, obesity and chronic diseases. Retinol binding protein 4 (RBP4), a novel adipokine has been implicated as a pro-inflammatory marker in obesity and other systemic diseases. In periodontal disease, RBP4 correlated with markers of low-grade inflammation. RBP4 can directly induce the production of pro-inflammatory mediators involved in leukocyte recruitment and adherence, including vascular cell adhesion molecule-1, intercellular adhesion molecule-1 etc. The present study explores the correlation of salivary RBP4 levels with periodontal parameters, BMI, and WHR in chronic periodontitis patients. A total of 91 subjects were included. Full mouth probing depth, clinical attachment levels, and bleeding on probing, BMI & WHR were recorded. Unstimulated salivary samples were collected and analyzed for RBP4 levels. Pearson's correlation coefficient test was done to correlate RBP4 with BMI, WHR and Periodontal parameters. Correlation between RBP 4 and BMI, WHR was negative, weak and not significant ($r = -0.016$, $p = 0.880$; $r = -0.165$, $p = 0.120$). Correlation between RBP4 and PPD, CAL was negative, and not statistically significant ($r = -0.076$, $p = 0.475$; $r = -0.106$, $p = 0.318$). In underweight Group, RBP4 values did not correlate with any of the periodontal parameters. In the normal weight group, the RBP4 values correlated with only CAL ($p = 0.47$). In overweight and morbidly obese group, no correlation was found between RBP4 and periodontal parameters. There is no association between RBP4, Periodontal parameters, WHR and BMI in Chronic periodontitis patients

Keywords: Retinol Binding Protein 4, RBP 4, Chronic periodontitis, Obesity and Body mass index.

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1. INTRODUCTION

Periodontal diseases are caused by bacterially derived factors and antigens that stimulate a local inflammatory reaction and activate innate immune response leading to the loss of the connective tissue attachment and alveolar bone. Chronic periodontitis generates an inflammatory burden that interact with body environments and hence has an association with systemic diseases like diabetes, cardiovascular diseases, obesity[1]. Obesity is the strongest risk factor next to smoking for periodontitis.[2] There is an increased risk for periodontitis for every increase in body mass index scores.[3] Obesity increases the host's susceptibility by modulating the immune and inflammatory systems that predisposes to inflammatory tissue destruction and leaves an individual at greater risk of periodontitis.[4] Fat tissue produces a vast amount of cytokines and hormones, collectively called adipokines, which may modulate periodontitis[5]. Retinol Binding Protein 4 (RBP4) is a novel adipokine which is recently added to the list of adipokines. Retinol Binding Protein 4 protein belongs to the lipocalin family and is the specific carrier for retinol in the blood. It delivers retinol from the liver to the peripheral tissues.[6] Adipokines are cytokine-like hormones produced by adipose tissue. Adipokines regulate not only energy metabolism and appetite, but also other bodily functions. Numerous studies have demonstrated that adipokines play a crucial role in cartilage and bone homeostasis, metabolism, and inflammation and that these molecules may be a causal link between obesity and OA. Retinol binding protein 4 (RBP4) was discovered to be a adipocyte-derived factor involved in the pathogenesis of type 2 diabetes. RBP4 is most abundant in the liver, followed by adipose tissue. In a recent study, higher waist circumference and waist-to-hip ratio were associated with higher RBP4 levels and markers of systemic inflammation[7]. RBP4 elevation contributes to endothelial inflammation and plays a causative role in the development or progression of vascular inflammation during cardiovascular disease and diabetic microvascular complications.[8] Role of RBP4 was also reported in non-alcoholic fatty liver disease. Hepatocytes are principal source of circulating RBP4. RBP4 directly stimulates lipogenesis in hepatocytes and induces non-alcoholic fatty liver disease[9]. Recently, RBP4 has been reported in crevicular fluid in chronic periodontitis patients.[10] In periodontal disease, RBP4 appears to be correlated with some markers of low-grade inflammation. RBP4 can directly induce production of proinflammatory mediators involved in leukocyte recruitment and adherence, including vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, monocyte chemoattractant protein-1 and interleukin-6 in both macrovascular and microvascular human endothelial cells. Furthermore, serum RBP4 levels are positively correlated with circulating inflammatory factors, such as IL-6 and high sensitivity C-reactive protein. Adipokines such as leptin, resistin, adiponectin, visfatin are considered as a markers of inflammation in chronic periodontitis. There are several studies correlating various adipokine levels with periodontal status. Literature search reveals studies correlating RBP4 and obesity whereas there are no studies correlating RBP4 levels and periodontitis. In lieu with the above, this study explores the correlation of salivary RBP4 levels with periodontal parameters, BMI and WHR in chronic periodontitis patients.

2. MATERIALS AND METHODS

2.1 Study Basics

The study was approved by the institutional ethical committee (IGIDSIEC2016NDP15KPGSBPAI). Subjects for this study were recruited from the out patients reporting to the OPD of Department of Periodontology, Indira Gandhi Institute of Dental Sciences, Pondicherry. The study protocol was explained to the patients and duly signed written informed consent was obtained. It was done in accordance with declaration of Helsinki.

2.2 Inclusion and Exclusion Criteria

Chronic Periodontitis patients with >30 years of age (Male/Female) with at least 15 natural teeth remaining were selected. Generalized Chronic periodontitis cases were defined according to AAP 1999 workshop as PPD ≥ 4mm or CAL ≥ 2 mm in at least 30% of the recorded sites. Subjects with systemic diseases like Type 2 Diabetes, Cardiovascular Diseases, Hypertension, Smokers and alcoholic, Pregnant and lactating mothers, patients who underwent any periodontal therapy in the past 6 months and patients who were under antibiotic treatment in the past 3 months were excluded.

2.3 Sample Collection and Protocol

A total of 91 subjects were included in the study. Participant's medical and dental histories were obtained. Data collected included full mouth probing depth (PD) and clinical attachment levels (CAL) measured at six sites around the teeth, and presence or absence of bleeding on probing (BOP) by modified sulcus bleeding index.[12] All clinical recordings were done by a single calibrated examiner. BMI and Waist to hip ratio was also measured for all participants. BMI was calculated for each subject by taking weight in kilograms divided by the square of the height in meters (kg/m2). The subjects were classified according to the BMI into 5 categories: underweight (< 18.5), normal (18.5 – 22.9), overweight (23 – 24.9), obese (25 – 29.9) and morbidly obese (> 30). Waist to hip ratio (WHR) is the ratio of the circumference of the waist to that of the hips. The waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference was measured around the widest portion of the hip using an inch tape.

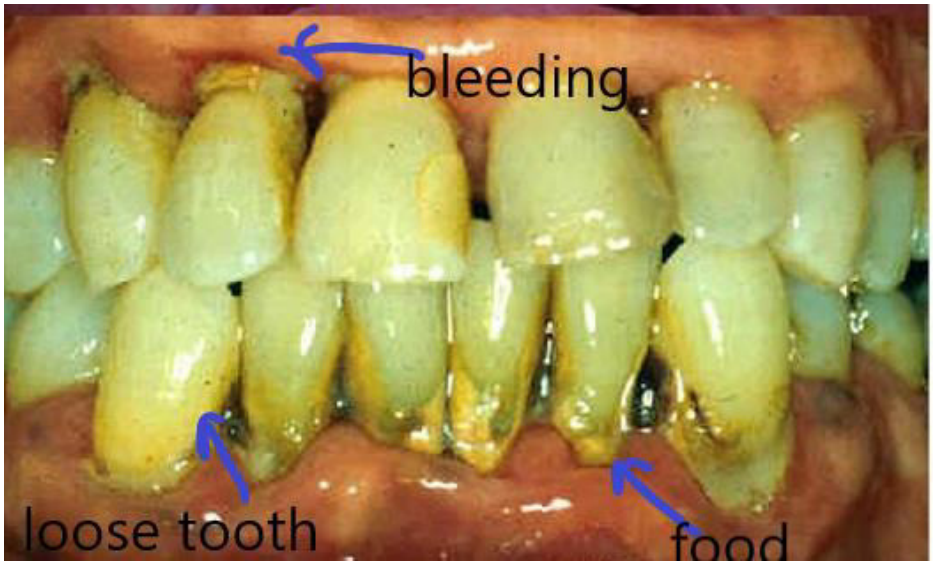


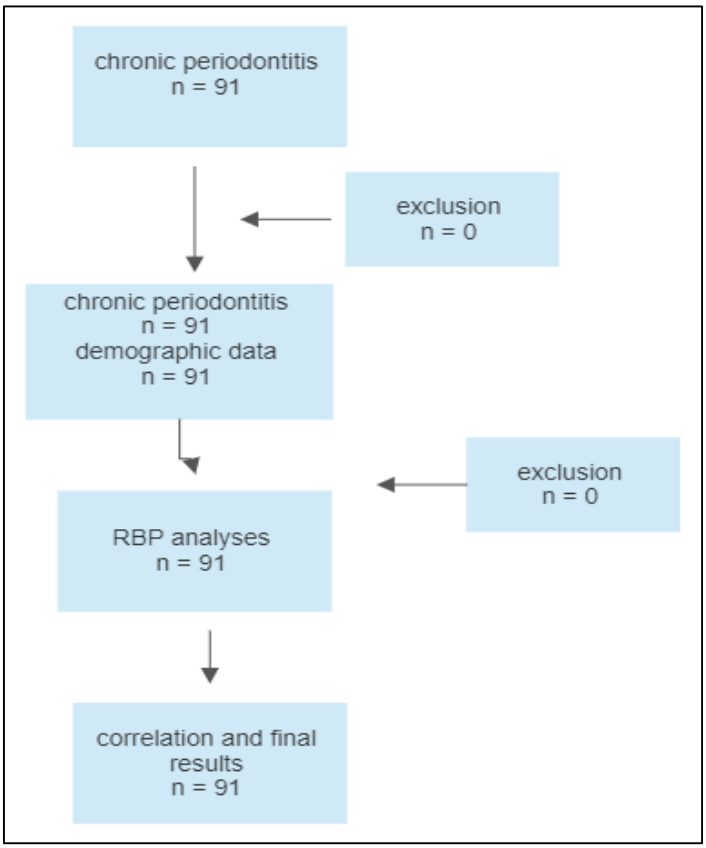
Fig 1 showing a few features of chronic periodontitis

2.4 Salivary Sampling

Unstimulated salivary samples were collected and stored at-20°C. The samples were centrifuged at 3000 RPM for 15 minutes. Salivary RBP4 levels were assessed with Human RBP4 ELISA kit*. This Elisa Kit works on the biotin double antibody sandwich technology to assay the Human RBP4. The assay range for detection of RBP4 kit was 0.5mg/L -180mg/L and the sensitivity is 0.26mg/L.

3. STATISTICS ANALYSIS

The student t tests were used for mean and standard deviation while pearson corelationwas used for corelative analyses. According to standards concentrations and the corresponding Optical Density (OD) values, the linear regression equation of the standard curve was calculated. Then according to the OD value of samples, the concentration of corresponding sample was calculated.



4. RESULTS

The mean age of the subjects in the study was 42.29 ± 8.01 of which male were 60.4% and female were 39.6% respectively. The mean BMI and WHR were 25.10 ± 3.69 and 0.90 ± 0.09 respectively. The Mean PPD study was 3.43 ± 0.37 and CAL was 3.48 ± 0.33. The mean BOP of the subjects was 0.79 ± 0.33 (Table 1). In this study, the range of Salivary RBP4 in chronic periodontitis patients was 3.0 to 46 mg/L. The mean RBP4 was 23.02 ± 7.73.mg/L.

Table 1

		95% Confidence Interval	
Variable	**Mean ± Standard Deviation**	**Upper limit**	**Lower limit**
Age	42.49 ± 8.01	40.81	44.17
BMI	25.10 ± 3.69	24.33	25.88
WHR	0.90 ± 0.09	0.88	0.92
RBP4	23.02 ± 7.73	21.40	24.64
BOP	0.79 ± 0.33	0.72	0.87
PPD	3.43 ± 0.37	3.35	3.50
CAL	3.48 ± 0.33	3.41	3.55

Pearson's correlation coefficient test was done to correlate RBP4 with BMI and WHR of the entire study sample. The correlation between RBP 4 and BMI was negative, very weak and not significant (r = - 0.016, p = 0.880). Likewise, the correlation between retinol binding protein4 and WHR was also negative, very weak and not significant (r = - 0.165, p = 0.120). (Table 2)

Table 2: Correlation of RBP4 levels with BMI and WHR

Variable 1	Variable 2	Pearson correlation	Significant 2 tailed (p-value)
RBP4	BMI	- 0 .016	0.880 (NS)
	WHR	-0.165	0.120(NS)

(Level of significance is set at p < 0.05
S - Significant correlation; NS – Not significant)

Pearson's correlation coefficient test was done to correlate RBP4 and Periodontal parameters. The correlation between RBP4 and BOP was not significant (r = 0.091, p = 0.393). The correlation between RBP4 and PPD was negative, and not statistically significant (r = - 0.076, p = 0.475). The correlation between RBP4 and CAL was negative, and not statistically significant (r = - 0.106, p = 0.318). (Table 3)

Table 3: Correlation of RBP4 levels with periodontal parameters

Variable 1	Variable 2	Pearson correlation	Significant 2 tailed (p-value)
RBP4	BOP	0.091	0.393 (NS)
	PPD	- 0.076	0.475 (NS)
	CAL	- 0.106	0.318 (NS)

Level of significance is set at p < 0.005 S - Significant correlation; NS – Not significant

Considering the Underweight Group (BMI < 18.5), the RBP4 values did not correlate with any of the periodontal parameters, BMI and WHR. In the normal weight group (BMI < 18.5 - 22.9), the RBP4 values correlated with only CAL (p = 0.47) among the periodontal parameters and no correlation was found between RBP4 levels and BMI and WHR. (Table 4). In the overweight Group (BMI < 23-24.5), no correlation was found between RBP4 and other periodontal parameters. But WHR correlated with BOP (p = 0.44). In the morbidly obese Group (BMI < 25-29), similar observations were made. The RBP4 values had no correlation with periodontal parameters. (Table 4)

Table 4: Non parametric correlation between parameters

			Underweight group = <18.5						Normal weight group = 18.5 - 22.9						Overweight group = 23-24.5						Obese group = 25-29.9						Morbidly obese group = >29.9					
			BOP	PPD	CAL	RBP4	WHR			BOP	PPD	CAL	RBP4_value	WHR			BOP	PPD	CAL	RBP4_value	WHR			BOP	PPD	CAL	RBP4_value	WHR			BOP	PPD	CAL	RBP4_value	WHR
Spearman's rho	BOP	Correlation Coefficient	1.000	-.543	-.086	-.300	.314	BOP	Correlation Coefficient	1.000	.304	.310	-.342	.314	BOP	Correlation Coefficient	1.000	.367	.370	.227	.479*	BOP	Correlation Coefficient	1.000	.363*	.332*	.209	.236	BOP	Correlation Coefficient	1.000	.313	.313	.156	.922**
		Sig. (2-tailed)	.	.266	.872	.624	.544	BOP	Sig. (2-tailed)	.	.221	.210	.165	.205		Sig. (2-tailed)	.	.135	.130	.364	.044		Sig. (2-tailed)	.	.023	.039	.201	.149		Sig. (2-tailed)	.	.450	.450	.713	.001
									N	18	18	18	18	18		N	18	18	18	18	18		N	39	39	39	39	39		N	8	8	8	8	8
	PPD	Correlation Coefficient	-.543	1.000	.657	.200	-.657	PPD	Correlation Coefficient	.304	1.000	.838**	-.263	.341	PPD	Correlation Coefficient	.367	1.000	.999**	.103	.432	PPD	Correlation Coefficient	.363*	1.000	.929**	.148	-.090	PPD	Correlation Coefficient	.313	1.000	1.000**	.156	.229
		Sig. (2-tailed)	.266	.	.156	.747	.156	PPD	Sig. (2-tailed)	.221	.	.000	.291	.166		Sig. (2-tailed)	.135	.	.000	.683	.073		Sig. (2-tailed)	.023	.	.000	.368	.587		Sig. (2-tailed)	.450	.	.	.713	.586
									N	18	18	18	18	18		N	18	18	18	18	18		N	39	39	39	39	39		N	8	8	8	8	8
	CAL	Correlation Coefficient	-.086	.657	1.000	.400	-.086	CAL	Correlation Coefficient	.310	.838**	1.000	-.474*	.374	CAL	Correlation Coefficient	.370	.999**	1.000	.108	.432	CAL	Correlation Coefficient	.332*	.929**	1.000	.097	-.056	CAL	Correlation Coefficient	.313	1.000**	1.000	.156	.229
		Sig. (2-tailed)	.872	.156	.	.505	.872	CAL	Sig. (2-tailed)	.210	.000	.	.047	.127		Sig. (2-tailed)	.130	.000	.	.668	.074		Sig. (2-tailed)	.039	.000	.	.559	.734		Sig. (2-tailed)	.450	.	.	.713	.586
									N	18	18	18	18	18		N	18	18	18	18	18		N	39	39	39	39	39		N	8	8	8	8	8

	RBP4	Correlation Coefficient	-.300	.200	.400	1.000	.500	RBP4_value	Correlation Coefficient	-.342	-.263	-.474*	1.000	-.418	RBP4_value	Correlation Coefficient	.227	.103	.108	1.000	.057	RBP4_value	Correlation Coefficient	.209	.148	.097	1.000	-.008	RBP4_value	Correlation Coefficient	.156	.156	.156	1.000	.024
		Sig. (2-tailed)	.624	.747	.505	.	.391	RBP4_value	Sig. (2-tailed)	.165	.291	.047	.	.084		Sig. (2-tailed)	.364	.683	.668	.	.822		Sig. (2-tailed)	.201	.368	.559	.	.959		Sig. (2-tailed)	.713	.713	.713	.	.955
									N	18	18	18	18	18		N	18	18	18	18	18		N	39	39	39	39	39		N	8	8	8	8	8
	WHR	Correlation Coefficient	.314	-.657	-.086	.500	1.000	WHR	Correlation Coefficient	.314	.341	.374	-.418	1.000	WHR	Correlation Coefficient	.479*	.432	.432	.057	1.000	WHR	Correlation Coefficient	.236	-.090	-.056	-.008	1.000	WHR	Correlation Coefficient	.922**	.229	.229	.024	1.000
		Sig. (2-tailed)	.544	.156	.872	.391	.	WHR	Sig. (2-tailed)	.205	.166	.127	.084	.		Sig. (2-tailed)	.044	.073	.074	.822	.		Sig. (2-tailed)	.149	.587	.734	.959	.		Sig. (2-tailed)	.001	.586	.586	.955	.
									N	18	18	18	18	18		N	18	18	18	18	18		N	39	39	39	39	39		N	8	8	8	8	8

. Correlation is significant at the 0.05 level (2-tailed).
****. Correlation is significant at the 0.01 level (2-tailed).***

5. DISCUSSION

The aim of the present study was to explore the correlation of salivary RBP4 levels with periodontal parameters, BMI and WHR in chronic periodontitis patients. A bidirectional link between obesity and periodontitis has been studied in the past few years. The association between obesity and periodontitis is due to release of pro-inflammatory cytokines into the systemic circulation from adipose tissue in obese individuals which provides a systemic inflammatory overload which will directly induce agglutination of blood in the microvasculature, decreasing blood flow to the gingiva in obese people and facilitating the progression of periodontitis.[1] Fat tissue produces a vast amount of cytokines and hormones, collectively called adipokines. Adipokines are also produced by periodontal cells and then regulated by periodontal pathogens.[9] The inflammatory mediators from adipose tissue like leptin, visfatin, adiponectin and resistin has been extensively studied in periodontitis cases.[10-12] Recently RBP4 has been recently identified as an adipokine associated with obesity. In the present study, on analyzing the correlation between Retinol Binding Protein 4 and BMI in chronic periodontitis patients, it was negative, weak and not significant (p-value=0.880). On analyzing the different groups, RBP4 did not correlate with BMI on any of the groups. This was in accordance with few other studies.[13,14] Graham et al. observed that in obese patients with and without diabetes, serum RBP4 levels, positively correlated with BMI.[15] Chielle OE et al. also reported that the serum concentration of RBP4 levels increased proportionately with overweight and obese individuals.[7] In another study, serum RBP4 and regional fat distribution was investigated with and without diabetes in a Chinese population where no association was found between serum RBP4 and BMI. On contrary, in another study, elevated serum RBP4 was associated with components of the metabolic syndrome, including increased body-mass index, waist-to-hip ratio, serum triglyceride levels, and systolic blood pressure and decreased high-density lipoprotein cholesterol levels.[15] Similarly, plasma RBP4 concentrations are increased with elevated BMI in obese human subjects with impaired glucose tolerance and type-2 diabetes[16]. In the present study, the correlation between retinol binding protein 4 and WHR was negative, very weak and not significant (p-value=0.120). Group analysis also did not find any correlation of RBP4 with WHR. This was in accordance with few other studies. In a study, RBP4 was significantly associated with Hepatic Fat Content, but independent of BMI, weight and waist circumference in Non-Alcoholic Fatty Liver Disease. On contrary, in another study, the change in RBP4 level was significantly correlated with WHR[17]. In the present study, on analyzing the correlation between RBP4 and periodontal parameters no significant correlation was detected. Looking into the group analysis, in the normal weight group (BMI < 18.5 - 22.9), the RBP4 values correlated with CAL (p = 0.47). On contrary to this study, The

GCF and serum values of the RBP4 correlated with the periodontal parameters.[18] Kanoriya D et al in his study found that there was increase in RBP4 levels in both GCF and serum of obese patients with chronic periodontitis than periodontally healthy obese patients[19]. Herrera et al in an interventional study showed that patients with chronic periodontitis (CP) had higher RBP4 levels than those without CP in both lean and obese populations. Number of teeth with PD ≥4 mm was independently associated with RBP4. He also demonstrated that following periodontal therapy the levels of RBP4 decreased which correlated with improvement in periodontal status[20]. Increased pro inflammatory cytokines are well documented to be associated with both obesity and periodontal [21] and given that RBP4 levels rise in obesity, diabetes and metabolic syndrome[15,22,23], it has been hypothesized that RBP4 may mediate the inflammatory response that links obesity and periodontitis. Indeed, it has been shown that RBP4 can contribute to the development of an inflammatory state in white adipose tissue through induction of JNK and TLR-4 in infiltrated macrophages due to an increase in the release of TNFα .[24] But our study found a decline of RBP4 levels with periodontal disease progression and the mechanism is unknown. However, the following limitations have to be consideration. RBP4 was evaluated only over a single time and in a small sample of population. Therefore, further longitudinal prospective studies that evaluate RBP4 levels in serum and gingival crevicular fluid over longer periods of time in a larger population is necessary to validate the results of this study.

6. CONCLUSION

Within the limitations of this study, it was observed that in the entire sample there is no association between RBP4, Periodontal parameters, WHR and BMI in Chronic periodontitis patients. However in the normal weight group, the RBP4 values correlated with CAL among the periodontal parameters. In the overweight Group, WHR correlated with BOP.

7. AUTHOR CONTRIBUTION STATEMENT

Jananni Muthu, ,Priyadharshini – data collection, Shahinaz Begum, Pratebha. B- manuscript preparation and supervision, Vineela. K, Saravanakumar. R, , - concept and design

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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