ORIGINAL RESEARCH

Evaluation of Reactive Oxygen Metabolites, Resistin, and Red Complex Bacteria in Obese Subjects with or without Periodontitis

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Abstract

Aim: The study's aim was to assess and compare the clinical parameters, plasma reactive oxygen metabolites (ROM) levels, gingival crevicular fluid (GCF) resistin, serum resistin values, and red complex bacteria in obese or overweight subjects with and without periodontitis and also to determine the effect of non-surgical periodontal therapy (NSPT) on plasma ROM, serum, and GCF resistin values in obese or overweight subjects with chronic periodontitis.

Material and methods: A total of 160 subjects were recruited and designated into four groups with 40 subjects each as group I – obese with chronic periodontitis; group II – normal weight subjects with chronic periodontitis; group III – obese subjects with healthy periodontium; and group IV – normal weight subjects with healthy periodontium. The periodontal parameters, plasma ROM, GCF resistin and serum resistin, and red complex bacteria levels were estimated at baseline. After baseline assessment, scaling and root planing (SRP) were done in the patients of groups I and II. Two months after the completion of SRP, clinical parameters such as plaque index (PI), probing pocket depth (PPD), gingival index (GI), and clinical attachment loss (CAL), plasma ROM levels, serum resistin, and GCF resistin levels were analyzed.

Results: An increase in plasma ROM, GCF resistin, and red complex bacteria levels was observed in obese subjects with periodontal disease and the increase was noted in obese subjects with healthy periodontium. Comparing plasma ROM, GCF resistin values between groups I and II, 2 months after SRP, a decrease in these levels were observed in group II.

Conclusion: Our study results depict that obesity can be considered as a risk indicator for periodontal disease.

Clinical significance: Obesity has a negative impact on both general health and oral health. Promoting appropriate physical activity, healthy eating behavior, and oral hygiene practice are fundamental elements of the prevention of both obesity and periodontal disease.

Keywords: Adipokine, Obesity, Reactive oxygen species, Red complex bacteria, Resistin.

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Introduction

Periodontitis involves the interaction of the microorganisms and host immunoinflammatory response, causing loss of tooth-supporting structures.[1] Periodontal disease is the sixth most prevalent chronic condition globally, which is the major cause of tooth loss.[2] According to the World Health Organization (WHO), around 30–35% of the world population is affected by chronic periodontitis.[3] Around 85% of the total population in Assam, Uttar Pradesh, and West Bengal from India are affected with periodontal disease. Obesity has become the norm and almost 52% of the population is affected by this disease globally. Excessive fat accumulation leads to obesity, which is related to many chronic health conditions like cardiovascular disease, diabetes, and periodontal disease.[4]

Obesity has emerged as one of the risk indicators for periodontal disease. The association between obesity and periodontal disease was reported initially in rats and the obese hypertensive rats were more prone to periodontal tissue destruction than normal rats.[5] In humans, this association was found initially in Japanese subjects.[6,7] Many systematic reviews have reported that overweight, obesity, increased waist circumference (WC), and weight gain may be the risk factors for developing periodontal disease and worsening the periodontal measures.[8,9] The biological mechanism for the association of obesity with periodontal disease is the hyperoxidative and hyperinflammatory state created due to the increase in ROS and adipokines levels and the alteration in the subgingival microflora.

In obese subjects, there is an increase in oxidant status and ROM is a commonly used marker to assess oxidative status.[10] Periodontal tissue damage occurs due to oxidative stress including protein

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denaturation, DNA damage, and mitochondrial injury and indirect damage occurs due to activation of NF-kB and JNK pathway.[11] In obese subjects, an increase in angiotensin II levels, proinflammatory cytokines, alteration in mitochondrial uncoupling, and fatty acids oxidation by peroxisome and mitochondria lead to the excessive release of reactive oxygen species (ROS).[12] Limited studies are available relating to oxidative stress and periodontitis in obese subjects.[13,14]

Currently, adipose tissue is considered as a metabolically agile endocrine organ and it has the ability to secrete bioactive molecules termed as adipokines.[15] These adipokines may be proinflammatory or anti-inflammatory and in obese subjects, adipocytes and inflammatory cells infiltrated in the adipose tissue secrete more proinflammatory adipokines, resulting in low grade chronic inflammatory state. Resistin possesses proinflammatory properties and also induces the secretion of other proinflammatory molecules like monocyte chemoattractant protein-1.[16] Resistin is secreted not only by adipocytes but also by the macrophages infiltrated in the adipose tissue. It causes insulin resistance by interfering with insulin signaling and stimulates the expression of the suppressor of cytokine signaling-3 by which insulin regulates its own signaling cascade.[17] Due to its proinflammatory property, this adipokine resistin has an important part in induction of periodontal disease.[18]

The red complex bacteria consist of three species of pathogenic bacteria including *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*. In obese subjects, immune paralysis, an increase in proinflammatory adipokines, and metabolic modulations lead to modification in subgingival microflora.[19] Relatively, few studies are available relating to red complex bacteria and periodontitis in obese patients,[20,21] to find out the biological plausibility of obesity in periodontal disease. Hence, the present study's aim was to assess the clinical parameters such as PI, CAL, GI, and PPD and to estimate and compare the plasma ROM, GCF resistin, and serum resistin values, and red complex bacteria in obese or overweight subjects with and without chronic periodontitis. This study also attempts to determine the efficacy of NSPT on plasma ROM levels, serum, and GCF resistin values in obese or overweight subjects with chronic periodontitis.

Materials and Methods

Total of 160 subjects were recruited from the Department of Periodontics, Thaimoogambigai Dental College, Dr MGR University, Chennai, Tamil Nadu, India and this study carried out from January 2018 to December 2018. The ethical committee of Dr MGR University approved this study. Written informed consent was collected from the patients. Power of the study was calculated for each parameter from the pilot study results and forty subjects were included in each group to get the study power of 80%. The selected subjects were divided into four groups with 40 subjects each as group I – obese with chronic periodontitis; group II – normal weight subjects with chronic periodontitis; group III – obese subjects with healthy periodontium; and group IV – normal weight subjects with healthy periodontium.

The inclusion criteria for the four groups consisted of patients having a minimum number of 20 teeth, the age group between 30–45 years, groups I and III had body mass index (BMI) of above 25 and WC of above 90 cm in males and above 80 cm in females; groups II and IV had BMI of below 25 and the WC of below 90 cm in males and below 80 cm in females. The periodontally healthy group included patients having PPD of below 3 mm with no CAL. Generalized chronic periodontitis patients with PPD of more than or equal to 5 mm and CAL of more than or equal to 3 mm in more than 30% of the sites were included.[22] Patients with a history of cardiovascular disease, diabetes mellitus, hysterectomy, postmenopausal women, patients on steroid and statin medications and who underwent periodontal therapy in the past six months were excluded from the study.

The demographic variables assessed were age, socioeconomic status, height, weight, and WC. Height was measured with height scale and weight was assessed from a digital weighing machine. The BMI was calculated by dividing the person's weight in kilograms by the height in meters. Waist circumference was measured with an inch tape at the umbilical level. The periodontal parameters assessed were PPD, CAL, PI, and GI. Plaque index was assessed at four sites such as mesiobuccal, mid buccal, distobuccal and mid palatal sites around each tooth.[23] Four gingival areas of the tooth like facial, mesial, distal and lingual surfaces were assessed for GI.[24] The PPD and CAL assessments were done at six sites per tooth and measured in millimeters.

The assessments of periodontal parameters such as PI, PPD, GI, and CAL; plasma ROM levels, serum resistin and GCF resistin values, and red complex bacteria were done at baseline. Scaling and root planing was carried out in groups I and II patients. SRP was carried out in four sessions over a period of 3 weeks. Two months after completion of SRP, periodontal parameters (PI, PPD, GI, and CAL), plasma ROM levels; serum resistin and GCF resistin values were analyzed.

Sample Collection

Three milliliters of blood was obtained from the antecubital vein and 1.5 mL was poured in anti-coagulant coated tube and was centrifuged for 5 minutes to obtain plasma. The plasma ROM levels were estimated by spectrophotometry, according to Tamaki et al.[25] and it was mixed with the chromogenic substrate and acetate buffer and incubated at 37°C. The strength of the magenta color correlates with hydroperoxides levels. The ROM levels were expressed in Carratelli units (CARR U).

For serum resistin level estimation, 1.5 mL blood was collected in coagulant coated tube and was centrifuged to obtain serum and the samples were stored at −80°C till the time of assay. Collection of 2 µL of GCF was carried out using micropipette between 9 and 11 a.m. to minimize the influence of circadian rhythm and stored at −80°C until analysis. Enzyme Linked Immunosorbent Assay (RayBio ELISA Kit) was used. The strength of the color correlates with the resistin levels and it was read at 450 nm. The GCF and serum resistin levels were expressed as nanogram units (ng/L).

For red complex bacteria estimation, the plaque samples were collected subgingivally by curette and transported using phosphate buffered saline and stored at −80°C. Real-time polymerase chain reaction (RT-PCR) was used to estimate red complex bacteria. QIAamp DNA Mini kit was used to extract genomic DNA and the species-specific primers and double standard DNA-binding dye SYBR Green was used for *T. forsythia, P. gingivalis*, and *T. denticola.* Melt curve analysis was done at the thermal cycle of 59–95°C for each sample. Agarose gel was compared with melting curves for the presence of the amplicon and single PCR product. The number of red complex bacteria was depicted in cycle threshold (CT) units which is inversely proportional to bacterial numbers. The following primers were used in this study.

Description	*Sequence (5'-3')*
P. gingivalis	Forward: AGG CAG CTT GCC ATA CTG CG Reverse: ACT GTT AGC AAC TAC CGA TG
T. denticola	Forward: CCG AAT GTG CTC ATT TAC ATA AAG GT Reverse: GAT ACC CAT CGT TGC CTT GGT
T. forsythia	Forward: AGC GAT GGT AGC AAT ACC TGTC Reverse: TTC GCC GGG TTA TCC CTC

Statistical Analysis

To analyze the data statistical package for social sciences (SPSS) (IBM SPSS Statistics, version 22.0) was used. One-way analysis of variance (ANOVA) was applied to compare the demographic and clinical parameters, plasma ROM levels, GCF resistin, serum resistin levels and red complex bacteria counts among the four groups. Kruskal–Wallis test compared the mean of clinical parameters (PI, GI, and PPD) among the four groups. Pearson correlation coefficient was used to correlate plasma ROM levels, GCF resistin levels, red complex bacteria counts with demographic variables, and clinical parameters. Independent samples *t*-test compared the mean of periodontal parameter (CAL), plasma ROM levels, before and after SRP between the groups I and II. Mann–Whitney test compared the mean values of periodontal parameters before and after SRP, between the groups I and II. Paired *t*-test assessed the intragroups (I and II) comparison of GCF and serum resistin levels at baseline and after therapy.

Results

Comparison of clinical parameters among the four groups, PPD ($p = 0.001$) and CAL ($p = 0.001$) values were highest in group I compared to other groups (Tables 1 and 2). On comparison of plasma ROM, serum, and GCF resistin and red complex bacteria levels and statistically significant difference ($p = 0.001$) was found among the four groups with highest value in group I (Table 3). On the correlation of plasma ROM, GCF resistin, and red complex bacteria levels with

Table 1: Comparison of demographic variables and clinical parameter among the groups

Variable	*Group*	*N*	*Mean*	*Standard deviation (SD)*	*F-value*	*p-value*
Age	I	40	35.67	4.080	1.077	0.362
	II	40	37.17	4.764		
	III	40	35.40	5.550		
	IV	40	36.83	3.621		
BMI	I	40	31.500	2.0469	258.177	<0.001*
	II	40	22.600	0.7701		
	III	40	30.933	2.4202		
	IV	40	22.367	1.0981		
WC (cm)	I	40	100.767	3.7846	283.892	<0.001*
	II	40	78.133	3.0932		
	III	40	102.367	6.6045		
	IV	40	78.200	3.1338		
CAL (mm)	I	40	6.430	0.4129	6.653	0.012*
	II	40	6.040	0.5295		
	III	40	0.000	0.0000		
	IV	40	0.000	0.0000		

*Significant when $p < 0.05$. BMI, body mass index; WC, waist circumference; CAL, clinical attachment level

Table 2: Comparison of mean clinical parameters among the groups

Variable	*Group*	*N*	*Mean rank*	*p-value*
PI	I	40	85.20	<0.001*
	II	40	95.65	
	III	40	39.67	
	IV	40	21.48	
GI	I	40	89.25	<0.001*
	II	40	91.75	
	III	40	30.50	
	IV	40	30.50	
PPD	I	40	96.12	<0.001*
	II	40	84.88	
	III	40	32.37	
	IV	40	28.63	

*Significant when $p < 0.05$. PI, plaque index; GI, gingival index; PPD, probing pocket depth

Table 3: Comparison of plasma ROM, GCF resistin, serum resistin, and red complex bacteria levels among the groups

Variable	*Group*	*N*	*Mean*	*SD*	*p-value**
ROM (CAAR U)	I	40	462.030	23.5232	<0.001
	II	40	395.046	22.5459	
	III	40	336.428	23.0311	
	IV	40	290.550	19.1836	
GCF resistin (ng/L)	I	40	15.0557	1.6749	<0.001
	II	40	12.8337	1.34992	
	III	40	11.0670	1.39137	
	IV	40	5.3733	0.97223	
Serum resistin	I	40	25.8327	2.74465	<0.001
	II	40	19.0650	0.75984	
	III	40	15.0556	1.6643	
	IV	40	12.3233	0.9732	
Pg/CT value	I	40	16.7633	1.78976	<0.001
	II	40	22.1323	1.62568	
	III	40	26.5087	2.10047	
	IV	40	30.8157	1.42554	
Tf/CT value	I	40	17.8853	0.53915	<0.001
	II	40	19.9117	3.37848	
	III	40	23.8280	0.91508	
	IV	40	25.9957	1.12883	
Td/CT value	I	40	16.7143	0.38671	<0.001
	II	40	19.7620	0.47156	
	III	40	22.4680	0.89557	
	IV	40	25.7273	1.42788	

*Significant when $p < 0.05$. ROM, reactive oxygen metabolites; *Pg*, *Porphyromonas gingivalis*; *Tf*, *Tannerella forsythia*; *Td*, *Treponema denticola*

Table 4: Correlation of plasma ROM, GCF resistin levels, and red complex bacteria levels with demographic variables and clinical parameters

		Plasma ROM (CARR U) (units)	*GCF resistin (ng/L)*	*Serum resistin*	*Tf (CT-value)*	*Td (CT-value)*	*Pg (CT-value)*
Age	Correlation	−0.073	0.089	0.029	0.022	0.048	0.058
	p-value*	0.427	0.333	0.233	0.810	0.599	0.527
BMI	Correlation	0.537	0.426	0.415	0.306	0.457	0.445
	p-value*	0.000	0.000	0.000	0.001	0.000	0.000
WC (cm)	Correlation	0.471	0.357	0.378	0.259	0.399	0.361
	p-value*	0.000	0.000	0.000	0.004	0.000	0.000
PI	Correlation	0.764	0.850	0.861	0.784	0.839	0.810
	p-value*	0.000	0.000	0.000	0.000	0.000	0.000
GI	Correlation	0.740	0.840	0.861	0.816	0.855	0.848
	p-value*	0.000	0.000	0.000	0.000	0.000	0.000
PPD (mm)	Correlation	0.763	0.859	0.872	0.805	0.839	0.823
	p-value*	0.000	0.000	0.000	0.000	0.000	0.000
CAL (mm)	Correlation	0.762	0.859	0.862	0.816	0.860	0.848
	p-value*	0.000	0.000	0.000	0.000	0.000	0.000
	N	160	160	160	160	160	160

*Significant when $p < 0.05$. BMI, body mass index; WC, waist circumference; PI, plaque index; GI, gingival index; PPD, probing pocket depth; CAL, clinical attachment level, ROM, reactive oxygen metabolites; *Pg*, *Porphyromonas gingivalis*; *Tf*, *Tannerella forsythia*; *Td*, *Treponema denticola; CARR U, Carratelli units*

Table 5: Intergroup comparison of clinical parameters (PI, GI, and PPD); 2 months after therapy – Mann–Whitney test

	Group	*N*	*Mean rank*	*p-value*
PI, 2 months after therapy	I	40	0.74	0.796
	II	40	0.74	
GI, 2 months after therapy	I	40	0.87	0.014
	II	40	0.73	
PPD, 2 months after therapy	I	40	5.00	0.002
	II	40	4.68	
CAL, 2 months after SRP	I	40	5.11	0.013
	II	40	4.83	

*Significant when $p < 0.05$. PI, plaque index; GI, gingival index; PPD, probing pocket depth; CAL, clinical attachment level; SRP, scaling and root planing

demographic variables and clinical parameters showed a positive association except for the variable age (Table 4). On comparison of PI, GI, and PPD between the groups I and II, 2 months after SRP, showed a significant difference ($p = 0.002$) with higher reduction in group II (Table 5). Comparison of plasma ROM, GCF resistin, and serum resistin levels in groups I and II, 2 months after SRP, showed a significant difference ($p = 0.001$) with higher reduction in group II (Table 6). From results of this study, it is inferred that an increase in plasma ROM, GCF resistin, and red complex bacteria levels were observed in obese subjects with periodontal disease and the increase was also noted in obese subjects with healthy periodontium. Comparing plasma ROM, GCF resistin values between groups I and II, 2 months after periodontal therapy, a reduction in levels were observed in group II.

Discussion

Obesity is an important global health burden since the increased and atypical fat deposition in obese subjects poses a high risk to general health. Obesity creates a prooxidative stress and low-grade systemic inflammation with comorbid risks like atherogenesis and endothelial dysfunction. Chronic diseases occur in obese subjects, due to persistent systemic inflammation. The risk for periodontitis is increased in obese subjects, due to modulation of the subgingival microflora. Amar and Leeman stated that obesity disrupts the capability of the immune system to cope with infection by *P. gingivalis*.[26] Comparison of demographic variable, age, showed no significant difference among the groups. Obese subjects with chronic periodontitis had greater periodontal destruction with an increase in clinical periodontal parameters such as PPD and CAL, compared to nonobese subjects with periodontitis in the presence of similar inflammatory burden. This finding is comparable with the previous studies by Suvan et al. who reported that obese subjects had higher PPD.[27] Chaffee and Weston also observed greater CAL in obese persons with periodontitis.[8] It is accepted that the inflammatory response in obesity may activate a worsening of periodontitis.[15] In our study, both females and males were equally distributed in all groups.

Oxidative stress is connected to obesity and the rise in reactive oxygen species in obese subjects with periodontal disease could affect systemic health. Hence, measuring plasma ROM levels in obese and normal-weight subjects with periodontitis may be useful to understand the systemic influence on periodontal health.[28] In our study, we observed an increase in the plasma ROM levels in obese subjects with chronic periodontitis and healthy periodontium. This finding is comparable to the studies by Fernández–Sánchez et al.[29] and Furukawa et al.[30] who stated that increased plasma ROM may be released from accumulated fat and adipokines. A positive

Table 6: Intergroup comparison of plasma ROM, GCF resistin, and serum resistin levels; 2 months after NSPT

Variables	*Group*	*N*	*Mean*	*SD*	*t-value*	*p-value**
GC Fresistin, 2 months after SRP	I	40	12.3337	0.97549	19.115	<0.001
	II	40	6.9700	1.18759		
Serumresistin, 2 months after SRP	I	40	25.8067	2.81828	17.467	<0.001
	II	40	15.7173	1.29354		
ROM, 2 months after SRP	I	40	345.4167	33.306	5.755	<0.001
	II	40	300.6000	26.641		

*Significant when $p < 0.05$. ROM, reactive oxygen metabolites; SRP, scaling and root planing; NSPT, non-surgical periodontal therapy

correlation was also observed on correlating plasma ROM levels with periodontal and obesity parameters. Hence, it may be stated that oxidative stress has a role in obesity and periodontal disease pathogenesis and interventions to reduce oxidative stress will improve both conditions.

Adipokines are soluble proteins, induce signaling cascade by binding to receptors present in the cell, cause phenotypic changes through altered gene expression. In our study, the mean GCF resistin and serum resistin levels were higher in obese subjects as well as periodontal disease subjects. This finding is in agreement with Zimmerman et al. who showed the association of resistin levels with obesity.[31] It is stated that periodontal inflammation also upregulates the resistin levels, which may be derived from the macrophages present in the periodontal ligament. A positive correlation was also observed on correlating GCF resistin levels with periodontal and obesity parameters.

In obese individuals, persistent systemic inflammation affect the ecology of the periodontal sites, increasing the growth of subgingival periodontal pathogens. The present study also reported an increase in the red complex bacteria levels in obese subjects with periodontitis compared to other groups, a similar finding was observed by Matsushita et al. who also showed an increase in red complex bacteria counts in obese subjects.[20] *Porphyromonas gingivalis* and free fatty acid suppress the toll like receptor expression by the host, thereby inhibiting proinflammatory cytokine production and escape the host defense mechanism.[21] Combination of obesity with *P. gingivalis* lipopolysaccharide exposure enhances immune dysregulation in obese subjects with periodontal disease, leading to an alteration in subgingival bacteria colonization. Higher red complex bacteria levels were also observed in obese subjects with healthy periodontium. Silva–Boghossian et al. also reported an increased prevalence of *P. gingivalis* in periodontally healthy obese women.[32] It may be accepted that early colonization in healthy sites of obese subjects by periodontal pathogens, increase the chances for periodontal disease.

Scaling and root planing was carried out in groups I and II to determine the result of NSPT on oxidative and inflammatory markers. Intergroup comparison of periodontal parameters (GI, PPD, and CAL) in groups I and II, 2 months after SRP showed a marked decrease seen in group II than group I. Goncalves et al.[33] and Suvan et al.[34] also reported that obesity and BMI are predictors of poor clinical response following NSPT. Obese subjects have altered inflammatory response and hyperoxidative status, result in periodontitis susceptibility and poor wound healing. Comparison of plasma ROM levels in groups I and II, 2 months after SRP, observed reduction in both the groups (Table 6). However, the reduction in mean plasma ROM in group II was higher, reached almost to a normal level. SRP reduces periodontal inflammation and the inflammatory burden in the systemic circulation, by reducing the plasma ROM levels. Reduction of plasma ROM levels in group I was also seen compared to baseline; however, it did not reach normalcy, even after resolution of periodontal inflammation, as the obese subjects had mild oxidative stress with a mean ROM level of 345 CARR U. It may be stated that periodontal therapy provides benefit in terms of reducing the plasma ROM levels, thereby minimizing the risk for future systemic disease.

Marked reduction in GCF resistin was observed in group II than in group I. However, we did not find any significant difference in serum resistin levels in obese subjects with periodontitis after periodontal therapy. This finding was comparable to Goncalves et al.[33] who reported that the obesity may generate a systemic proinflammatory state in obese subjects with periodontitis with increased serum resistin level. At the systemic level, reduction in periodontal inflammation by SRP was unable to alter the serum resistin levels in obese subjects. Despite of periodontal therapy, obesity can be the modulating factor for serum resistin levels in subjects with periodontitis, advocating pro-inflammatory profile. This study has limitations of not assessing the effect of weight reduction in clinical parameters and adipokine levels and future studies are needed to determine the weight reduction efficacy on clinical parameters and adipokine levels.

Conclusion

Various mechanisms have been put forth to show the relationship between obesity and periodontal disease. Our study confirms the increase in plasma ROM, GCF resistin, and red complex bacteria in obese subjects with periodontal disease and this increase was also noted in obese subjects with healthy periodontium. Henceforth, obesity may be considered as a risk indicator for periodontal disease. Obesity has a negative impact on both general health and oral health. Promoting appropriate physical activity, healthy eating behavior and oral hygiene practice are fundamental elements of prevention in both obesity and periodontal disease.

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