The relation between Obesity and Periodontitis; Emphasis on the inflammatory state and insulin resistance

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Abstract*:* Objective*:* Several studies found a significant association between obesity and periodontal disease the adipose tissue actively secretes a variety of cytokines and hormones that are involved in inflammatory processes. On the other hand, epidemiological evidence has further suggested effects of periodontal disease on more serious systemic conditions such as cardiovascular disease. So, we conducted this study to evaluate the possible relation between obesity with its associated inflammatory state and periodontitis. Methods: The present study comprised 54 obese (21 males and 33 females) and 31 non obese healthy persons (12 males and 19 females). Clinical assessment of periodontitis was done using five periodontal indices. Anthropometric parameters, insulin resistance parameters (fasting glucose, fasting insulin and homeostasis model assessment (HOMA–IR), lipid profile, high sensitivity C-RP (hs-CRP) and resistin were measured in patients and controls. *Results*: All periodontal indices, HOMA-IR, serum resistin, hsCRP, cholesterol, and LDL-C were higher in obese subjects than none obese subjects. There was statistically significant correlation between BMI and waist circumference resistin, hsCRP, cholesterol and LDL-C with most of periodontal indices. Moderate and severe periodontitis were associated with significantly higher serum resistin, hsCRP and HOMA than mild or no periodontitis in both obese and nonobese. *Conclusion*: There is a relationship between periodontitis and obesity that could be bidirectional and mediated by the inflammatory state.
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1. Introduction:

Periodontal diseases are group of inflammatory diseases that results in progressive destruction of the periodontal ligament, formation of pockets around the teeth, and resorption of alveolar bone chiefly in a horizontal direction with loosening or loss of teeth associated with a bacterial infection [1]. Several studies found a significant association between obesity and periodontal disease [2-4, 5] which suggests that obesity could be a substantial risk factor for periodontitis. The possible causal relationship between obesity and periodontitis and potential underlying biological mechanisms remain to be established. The adipose tissue actively secretes a variety of cytokines such as interleukin-1(IL-1), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF- α) and a variety of hormones such as leptin, adiponectin and resistin that are involved in inflammatory processes, pointing toward similar pathways involved in the pathophysiology of obesity, periodontitis, and related inflammatory diseases[6]. On the other hand, epidemiological evidence has further suggested effects of periodontal disease on more serious systemic conditions such as cardiovascular disease, diabetes and complications of pregnancy[7,8]. Bullon *et al.* proposed a bidirectional relationship between metabolic syndrome and periodontitis mediated by circulating cytokines and oxidative stress[9]. So, we conducted this study to evaluate the possible relation between obesity with its associated inflammatory state and periodontitis.

2. Subjects and methods:

1. Fifty four obese (study group), 21 males and 33 females with age range 20 - 60 years were selected from the subjects attending the Obesity Clinics in Specialized Hospitals for Internal Medicine, Mansoura University. 13 to 14 patients were selected from each 10 years interval.
2. Thirty one non obese healthy persons (control group), 13 males and 18 females with age range 20- 60 years were selected from volunteers accompanying obese subjects. 7 to 8 patients were selected from each 10 years interval.

Exclusion criteria:

1. Periodontal or antibiotic therapy in the previous 3 months
2. Any systemic condition which might have influenced the course of periodontal disease or treatment (e.g. diabetes).
3. Any systemic condition which require antibiotic coverage for routine dental procedures (e.g. certain heart conditions and joint replacements).

All subjects are subjected to thorough medical history, clinical examination, anthropometric measurements including body height to the nearest 0.5 cm; body weight to the nearest 0.1 kg; body mass index (BMI) was calculated as weight/ height^2 (kg/m^2). Waist circumference was measured at the highest point of the iliac crest.

Assessment of periodontitis:

The periodontal condition was assessed by using:

A. Plaque index (PI) (10):

0 – No plaque in the gingival area,

1 – A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque was recognized only by running a probe across the tooth surface,

2 – Moderate accumulation of soft deposits within the gingival pocket and on the gingival margin and/or adjacent tooth surface that could be seen by naked eye,

3 – Abundance of soft matter within the gingival pocket and/or on the gingival margin and adjacent tooth surface.(10)

***B.* Gingival index(GI) *(11)*:**

0 – No inflammation,

1 – Mild inflammation, no bleeding elicited on probing,

2 – Moderate inflammation, bleeding on probing,

3 – Severe inflammation.

C. Bleeding on Probing (BOP) *(12)*:

The presence of the bleeding within 10 seconds indicates a positive score

D. Periodontal probing depth (PPD): by using Michigan (O) probe with William's markings, PPD was measured from the gingival margin to the base of the pocket at six points: (the distofacial, facial, mesiofacial, mesiolingual, lingual, distolingual surfaces).

E. Clinical attachment loss (CAL):

The CAL was measured as distance from the cement to enamel junction (CEJ) to the base of the pocket

The mean value of clinical attachment loss was obtained and divided into four groups: a clinical attachment of<1 mm (normal group), a clinical attachment of 1->3 mm (mild group), a clinical attachment of ≥3-5mm (moderate group) and a clinical attachment of ≥5mm (severe group)[13].

Laboratory investigations:

Serum total cholesterol (TC), Serum triglyceride (TG), and high density lipoprotein cholesterol (HDL-c) were assayed by commercially available kits supplied by Human (Germany). Low density lipoprotein cholesterol (LDL-c) was calculated according to Friedewald *et al.* [14] High sensitivity C-RP (hs-CRP) was estimated using immunoenzymometric assay supplied by Monobind Inc Lake forest. (A 92630 USA) according to Kimberly *et al.* [15]. Fasting blood glucose was determined using Coobas Integra 400 plus (Roche Diagnostic, Penzberg Germany) [16]. Serum insulin was measured using an enzyme-linked immunosorbent assay kit according to the method of Hwang *et al.* [17]. The kit was obtained from Diagnostic Systems Laboratories, Inc., Texas USA. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance proposed by Matthews *et al.* [18]: fasting glucose mg/dL × fasting insulin (μIU/mL)/ ÷ 405. The plasma concentration of resistin was measured using commercially available enzyme immunoassay kits (Phoenix Pharmaceuticals, Inc, Burlingame, California [19]. The method of measurement was performed according to the manufacturer instructions.

Statistical analysis

Data entry and analyses were performed using statistical SPSS package version 10 (SPSS, Inc., Chicago, IL, USA).Qualitative data were presented as number and percentage and quantitative data were presented as mean and standard deviation. Student t-test was used to compare means and standard deviations. Correlation between variables was done using Pearson correlation. *P* values of ≤ 0.05 and of ≤ 0.001 indicate significant and highly significant results respectively.

3. Results:

Table (1) shows the demographic, anthropometric and laboratory data for both obese and none obese groups: there were statistically significant differences between both groups with higher, BMI, waist circumference, hip circumference in the obese group(P≤0.001). The mean values of the resistin, hsCRP, cholesterol, triglycerides, HDL-C and LDL-C were higher in the obese subjects compared with none obese subjects(P≤0.001). HOMA score was significantly higher in obese than none obese (P=0.004). Periodontal status was assessed using CAL, PPD, BOP, PI and GI (Table 2). The means of scores in the obese group were (2.9±1.1mm, 3.5±0.9mm, 0.5±0.3, 1.7±0.5 and1.8±0.5) respectively. Whereas the means of scores in none obese group were (1.9±1.2 mm, 2.3±0.2 mm, 0.2±0.2, 1.2±0.3 and 1.1±0.4) respectively. Highly statistical significant differences were observed between both groups(P≤0.001). Analysis of the relation between periodontal indices (CAL, PPD, BOP, PI and GI) with clinical and laboratory parameters in obese group reveals that there was statistically significant correlation between BMI , WC and resistin with most of periodontal

indices and highly significant correlation between hsCRP, cholesterol and LDL-C with CAL (Table 3). Table (4) show the frequency of normal, mild, moderate and severe CAL in obese and none obese groups and in table (5) both obese and none obese groups are divided according to the degree of periodontitis: moderate and severe periodontitis were associated with significantly higher serum resistin, hsCRP and HOMA than mild or no periodontitis in both obese and nonobese. also, they were associated with higher WC and cholesterol in obese group.

Table 1. Demographic , anthropometric and laboratory characteristics of obese and none obese:

	Obese(study) N=54 Mean±SD	None obese(control) N=31 Mean±SD	*P* value
Male No(%) Female No(%)	(21)38.9% (33)61.1%	(13)41.9% (18) 58.1%	
Age(years)	41.7±10.8	38.7±10.2	0.122
Weight(kg)	95.6±11.3	70±8.2	>0.001
Height(cm)	165.7±7.8	171.5±7.8	>0.001
BMI(kg/m^2)	35.02±5.5	23±1.5	0.001
WC(cm)	102.3±11.3	85.4±5.8	>0.001
BP(systolic)	116.8±11.6	115.6±8.6	0.523
BP(diastolic)	73.5±6.1	72.4±4.3	0.277
hsCRP(ug/ml)	12.3±6.8	9.4±5.9	0.001
Resistin(pg/ml)	404.6±246.1	272.4±167.3	>0.001
Cholesterol(mg/dl)	281.9±96.5	190.3±60.1	>0.001
Triglycerides(mg/dl)	157.6±101.8	111.03±51.1	0.001
HDL-C(mg/dl)	40.7±8.4	52.7±12.7	>0.001
LDL-C(mg/dl)	206.5±90.4	117.6±57.3	>0.001
HOMA-IR	2.6±1.2	1.8±0.2	0.004

BMI: body mass index, WC: waist circumference, BP: blood pressure, hsCRP: High sensitivity c-reactive protein, LDL-C: Low density lipoprotein cholesterol, HDL-C high density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment of insulin resistance

Table 2.Frequancy of periodontal indices among obese and none obese groups.

	Obese N=54 Mean±SD	None obese N=31 Mean±SD	*P* value
CAL(mm)	2.9±1.1	1.9±1.2	>0.001*
PPD(mm)	3.5±0.9	2.3±0.2	>0.001*
BOP	0.52±0.3	0.24±0.2	>0.001*
PI	1.71±0.5	1.27±0.3	>0.001*
GI	1.8±0.5	1.1±0.4	>0.001*

CAL: Clinical attachment loss, ,PPD: Periodontal probing depth, BOP: Bleeding on Probing,

Table 3.Correlation between periodontal indices and resistin and some clinical and laboratory parameters among obese group.

	BMI	WC	Resistin	hsCRP	Cholesterol	TG	HDL-C	LDL-C	HOMA
CAL(r)	0.41	0.19	0.36	0.47	-0.41	0.12	-0.01	-0.46	-0.01
P	0.002*	0.16	0.001*	0.001*	0.05*	0.37	0.93	>0.001*	0.93
PPD(r)	0.31	0.10	0.31*	-0.02	0.00	-0.14	-0.04	0.03	-0.02
P	0.002*	0.43	0.02	0.88	0.98	0.29	0.75	0.77	0.88
BOP(r)	0.35	0.30	0.20	-0.00	0.01	0.17	0.06	-0.01	0.24
P	0.03*	0.02*	0.13	0.97	0.88	0.19	0.64	0.92	0.18
PI(r)	-0.09	0.05	0.17	0.19	0.08	-0.05	0.17	0.00	0.06
P	0.50	0.68	0.21	0.15	0.54	0.67	0.21	0.94	0.71
GI(r)	0.40	0.33	0.36	0.10	0.13	0.18	0.05	0.11	0.09
P	0.04*	0.01*	>0.001*	0.45	0.34	0.17	0.70	0.40	0.59
Resistin(r)	0.457	0.078	1	0.399	-0.134	0.091	-0.174	-0.079	0.217
P	0.001*	0.577		0.003*	0.334	0.512	0.207	0.57	0.115

BMI: body mass index, WC: waist circumference, hsCRP: High sensitivity c-reactive protein, TG: triglycerides, LDL-C: Low density lipoprotein cholesterol, HDL-C high density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment of insulin resistance, CAL: Clinical attachment loss, ,PPD: Periodontal probing depth, BOP: Bleeding on Probing, PI: Plaque index, GI: Gingival index

Table 4. Frequency of normal, mild, moderate and severe Clinical attachment loss (CAL) in obese and none obese groups.

		Groups		Total
		Obese	None obese	
CAL Normal (X<1)	No	7	11	18
	%	12.9.%	35.5%	21.1%
Mild (1 ≤ X<3)	No	8	7	15
	%	14.8%	22.6%	17.6%
Moderate (3≤ X <5)	No	30	13	43
	%	55.7%	41.9%	50.6%
Severe (5 ≤ X)	No	9	0	9
	%	5.5%	0%	10.5%
Total	No	54	31	85
	%	100.0%	100.0%	100.0%

Table 5. clinical and laboratory data in obese and none obese in relation to the degree of periodontitis.

	Obese with no or mild periodontitis	Obese with moderate to sever periodontitis	*P*	Non Obese with no or mild periodontitis	Non Obese with moderate to sever periodontitis	*P*
Number(%)	15(%)	39(%)		18(58.1%)	13(41.9%)	
Age	35.9±10.2	44.05±10.3	0.01	37.1±9.6	42.6±11.5	0.18
BMI(kg/m^2)	39.4±5.8	33.2±4.3	0.002	23.51.7	24.2±0.8	0.27
WC(cm)	95.5±9.1	105±11.1	0.005	85.6±6.3	84.7±5.01	0.7
hsCRP(ug/ml)	8.3±7.1	14.2±5.9	0.01	7.5±5.08	14.02±5.6	0.01
Resistin(pg/ml)	236.1±91.8	468.6±257.1	0.001	251.6±86.2	467.3±513.2	0.03
Cholesterol(mg/dl)	217.5±62.7	306.6±96.3	0.002	191.6±65.3	187.3±5	0.86
Triglycerides(mg/dl)	153.8±84.8	159.1±108.6	0.86	100.8±43.5	135.8±61.9	0.14
HDL-C(mg/dl)	41.1±8.6	39.7±7.8	0.57	51.09±11.6	56.7±14.9	0.32
LDL-C(mg/dl)	203.2±103	207.8±86.5	0.87	120.2±61.9	109.08±46.3	0.63
HOMA-IR	2.1±1.03	3.2±1.1	0.001	1.7±0.2	1.9±0.1	0.03

BMI: body mass index, WC: waist circumference, hsCRP: High sensitivity c-reactive protein, LDL-C: Low density lipoprotein cholesterol, HDL-C high density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment of insulin resistance

4. Discussion:

The mean value of all periodontal indices were significantly higher in our obese subjects compared with that of none obese subjects. These results were in agreement with previous studies, supporting the association between obesity and periodontal diseases [20-22]. The underlying biological mechanism of how obesity affects the periodontium is currently poorly understood, but what is known is that obesity has several harmful biological effects that might be related to pathogenesis of periodontitis[23]. In our study, there was a positive statistically significant correlation between periodontal indices and some of the obesity associated metabolic risk factors as WC, BMI, hs CRP, serum cholesterol and LDL. Several studies showed an association between periodontitis and central obesity[3,24], this correlation suggests that visceral adipose tissue has been shown to be metabolically more active in secreting inflammatory cytokines and hormones that are responsible for subclinical inflammation in obese patients[25].

Several studies have also reported a significant association between plasma lipids levels and the severity of periodontal disease [26-28]. Hyperlipidemia is known to cause a hyperactivity of white blood cells and increased production of oxygen radicals, which in turn causes gingival oxidative damage and the progression of periodontitis[29]. Moreover, hyperlipidemia arising from a high-fat diet, has a dysregulatory effect on immune system cells and wound healing and as a result, it increases the susceptibility to periodontitis and other infections [30] and also associated with proliferation of junctional epithelium, with increasing bone resorption in rat periodontitis[31].

In obesity, a subclinical inflammatory response is observed, with few or no symptoms, characterized by increased levels of acute-phase proteins, proinflammatory cytokines and leukocytes [32]. Resistin is a recently discovered adipocyte-secreted polypeptide that has been implicated in the development of insulin resistance [33]. Initially it was thought that resistin is mainly produced by adipocytes. However, recent studies have shown that very little resistin is produced by adipocytes, whereas large amount of resistin is produced from cells of the immunoinflammatory system like PMNs, monocytes, and macrophages [6]. In our study, the mean values of the resistin, hsCRP were significantly higher in obese subjects compared with none obese subjects. The elevated resistin in our study was significantly correlated with periodontal indices and with hs CRP, with no significant correlation with WC nor HOMA suggesting that this elevation is linked mainly to the

inflammatory state associated with obesity. Many studies have reported positive correlation between resistin levels and obesity [34-36]. Further human studies have shown no correlation of serum or plasma levels of resistin with any markers of adiposity [37, 38]. Heilbronn et al [39] reported no relationship between resistin serum levels and percentage body fat, visceral adiposity and BMI. In contrast to other adipokines, resistin was found to be only associated with body fat and is unlikely to be a major mediator of insulin resistance[40].

Epidemiological evidence has suggested that long-term effects of periodontal disease may be linked to more serious systemic conditions [7,8]. Recent work showed that individuals with periodontal pockets at baseline were more likely to develop components of metabolic syndrome, including obesity, 4 years later [41] and statistically significant increase in the prevalence of coronary heart disease in patients with periodontitis after adjusting for risk factors such as smoking, diabetes, alcohol intake, obesity and blood pressure[42]. In our study, we subdivided obese and control subjects according to the degree of periodontitis, we found that moderate and severe periodontitis were associated with significantly higher serum resistin, hsCRP and HOMA than mild or no periodontitis in both obese and nonobese . They were also associated with higher WC and cholesterol in obese group. So, we can suggest that the presence of periodontitis is associated with an inflammatory state and insulin resistance in both obese and non obese. It has been found that periodontal disease can lead to persistent low level bacteremia, an elevated white cell count and systemic endotoxemia, which together could affect endothelial integrity, the metabolism of plasma lipoproteins, blood coagulation and platelet function [43,44].so, we can suggest that the presence of periodontitis, especially if severe degree, could be an indicator of more metabolic risk in obese subjects. From the previous results, we can conclude that there is a relationship between periodontitis and obesity with its associated inflammatory state, this relationship provides an example for systemic disease predisposing to oral infection, and once the oral infection is established, it exacerbates the systemic disease.

Conflict of interest

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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