

The relationship between adipokines and periodontitis

KEYWORDS

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Adiponectin;

Leptin;

Resistin;

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Summary

Obesity is associated with an increased risk for developing characteristic features of metabolic syndrome, including hypertension, type 2 diabetes, and dyslipidemia. Interestingly, chronic exposure to periodontal pathogens' endotoxin and increased cytokine production have been proposed to enhance the risk for causing type 2 diabetes and cardiovascular complications. Obesity has also recently been reported to be associated with periodontitis. Obesity induces macrophage accumulation in adipose tissue, promotes chronic low-grade inflammation, and increases adipokines derived from adipocytes. In this review, we summarize recent advances in understanding the roles of adipokines in chronic inflammatory states such as periodontitis and focus primarily on adiponectin, leptin, and resistin. Understanding the role of adipokines may help elucidate relationships among periodontitis, obesity, type 2 diabetes, and cardiovascular diseases.

1. Introduction

Periodontitis is a chronic inflammatory state caused by periodontopathic bacteria that evade immune defenses. In cases of severe periodontitis, serum levels of interleukin-1 beta (IL-1 β), IL-6, and tumor necrosis factor-alpha (TNF- α) were shown

to be elevated [1]. Periodontal inflammation can activate monocytes in periodontal tissues, resulting in the production of proinflammatory cytokines such as TNF- α and IL-6 and the initiation of periodontal tissue destruction. Increasing evidence suggests that chronic low-grade inflammation, as occurs with periodontitis, plays an important role in the pathogenesis of systemic diseases [2].

Metabolic syndrome is defined by an amalgam of obesity-associated disorders, including dyslipidemia, hypertension, hyperglycemia. Of these, visceral adiposity appears to be essential for the diagnosis of metabolic syndrome; indeed, visceral adiposity was shown to be more important in metabolic syndrome than overall adiposity [3].

Periodontitis is closely associated with diabetes and obesity [4, 5], and individuals who were obese or had metabolic syndrome were shown to be at risk for developing periodontitis [6, 7]. Specifically, the relationship between obesity and deep periodontal pockets was independent of glucose tolerance status, suggesting a direct association between obesity and periodontitis [8]. Body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) was positively correlated with periodontal attachment loss [9]. Nevertheless, the biological mechanisms that relate obesity with periodontitis are unclear.

Adipose tissue participates in the regulation of energy homeostasis and is an active endocrine organ that secretes more than 50 biologically active substances, collectively termed adipokines. Adipokines such as the hormone-like proteins: leptin and adiponectin, the classical pro-inflammatory cytokines: TNF- α and IL-6, and plasminogen activator inhibitor 1 (PAI-1) play a number of different biological roles (Fig. 1) [10], acting in both paracrine and endocrine fashions. Some of these cytokines appear to be key regulators of the inflammatory response and are crucial for the progression of periodontitis. T cells that secrete such cytokines have an important function in periodontal inflammation. For example, T helper (Th) cells were shown to be associated with bone resorption by periodontopathic bacteria. Th cells are divided into two functional subsets on the basis of cytokine secretion; Th1 secretes IL-2, IL-12, and interferon- γ , and Th2 secretes IL-4, IL-5, and IL-13. Diseased periodontal tissues initially show predominance of Th1-type cytokines, followed by a rise in Th2-type cytokines in later stages of periodontitis [11]. Recent studies have also defined novel roles for Th17 cells, which secrete IL-17, TNF- α , and granulocyte colony stimulating factor (G-CSF) [12]. In this review, we discuss the possible relationship of adipokines and cytokines with periodontal inflammation. There are many signs that regarding the associations between periodontitis and each adipokines [12-18] (Table 1).

2. Relationship of adipokines with inflammation

Adipose tissues contain preadipocytes, endothelial cells, leukocytes, and macrophages. The numbers of macrophages in or near adipose tissues are small in lean subjects. In obese mice and humans, however, macrophages are increased in abundance and accumulate near adipocytes [19, 20]. Macrophages in adipose tissues may increase the production of inflammatory cytokines such as TNF- α and IL-6 that contribute to obesity-related systemic disease (Fig. 2) [21]. The close relationship between adipocyte size and macrophage abundance in adipose tissues suggests that obesity promotes inflammation [22]. Similarly, proinflammatory cytokines such as IL-6 are induced to a greater extent in co-culture systems after stimulation with lipopolysaccharide (LPS) from *Escherichia coli*, which is thought to promote the development of type 2 diabetes and vascular complications [23].

Macrophages in adipose tissues can secrete different panels of cytokines. Analogous to the Th1/Th2 concept, these macrophages are classified into M1 and M2 macrophages based on their cytokine generation. M1 macrophages are suspected to be the major source of IL-1, IL-6, and TNF- α [24]. It is thought that increased circulating TNF- α plays an important role in insulin resistance, and increased circulating IL-6 has been associated with an increased risk for cardiovascular disease. M2 macrophages have been

reported to be induced primarily by IL-4 and IL-13 and are capable of producing anti-inflammatory compounds. Obesity causes an M2 to M1 shift in adipose tissue macrophages.

3. Adiponectin

Adiponectin is a 30-kDa polypeptide that is specifically and highly expressed in human adipose tissues [25]. This protein has been shown to enhance insulin sensitivity and reduce circulating fatty acids and triglycerides in muscle and liver [26]. Adiponectin was first cloned from mice [27] and was subsequently cloned from humans [25]; human adiponectin shares 83% amino acid identity with mouse adiponectin [28]. The circulating level of adiponectin is relatively high (5–10 µg/ml). Serum adiponectin levels are decreased in obese humans and in patients with type 2 diabetes [29]; hence, the adiponectin level tends to reflect insulin sensitivity. Adiponectin circulates in the blood in trimeric (low molecular weight, LMW), hexameric (medium molecular weight, MMW), and multimeric (high molecular weight, HMW) forms [30]. Among these forms, HMW adiponectin was shown to be decreased in obesity and diabetes [31] and is associated with an increased risk for the development of diabetes, independent of total adiponectin [32]. Recent studies suggested that the ratio of HMW to total adiponectin or

to LMW (and not the absolute amount of adiponectin) in peripheral blood reflects insulin sensitivity [33]. The adiponectin isoforms have different effects on human monocytes [34]. HMW adiponectin induced IL-6 in human monocytes but did not suppress IL-6 secretion induced by LPS. Moreover, the globular form of adiponectin (gAd), which is generated from full-length adiponectin with proteolytic cleavage by elastase secreted from activated macrophages and/or neutrophils, is a powerful inducer of TNF- α and IL-6 secretion in primary human peripheral macrophages. However, pre-exposure of macrophages to gAd induced NF- κ B activation and tolerance to further gAd and LPS exposure, resulting in the repression of TNF- α and IL-6 secretion [35].

We reported that periodontal conditions did not relate to decreased adiponectin levels [13, 14], and an antimicrobial periodontal treatment did not increase adiponectin levels [18]. HMW adiponectin but not LMW is induced a dose-dependent increase in production of IL-8 and MCP-1 in human peripheral blood mononuclear cell, in vitro [36]. This suggested that HMW adiponectin is proinflammatory. The relationships of HMW adiponectin with periodontal inflammation should be examined, since the ratio of the high molecular weight of adiponectin to that of total may be a better predictor of periodontal inflammation.

Adipose TNF- α mRNA expression was elevated in obese mice and humans [37], and

the administration of adiponectin suppressed TNF- α mRNA expression in local tissues and decreased circulating levels of TNF- α . The anti-inflammatory properties of adiponectin appear to antagonize the effects of TNF- α [38]. This may be related to the structural resemblance between the cytokines, despite the lack of similarity between their primary sequences.

Adiponectin has been shown to inhibit monocyte adhesion to endothelial cells and macrophage transformation to foam cells [39]. It also appears to be important in bacterial and viral infections. It was shown to negatively regulate mouse macrophage-like cell responses to Toll-like receptor (TLR) ligands [40]. Furthermore, it acted as an inhibitor of osteoclast formation stimulated by LPS from periodontopathic bacteria [16]. Collectively, these observations suggest that adiponectin may inhibit alveolar bone loss in periodontitis.

4. Leptin

Leptin is a 16-kDa non-glycosylated peptide hormone encoded by the *ob* gene and was initially thought to regulate body weight by inhibiting food intake and by stimulating energy expenditure. Mice with a mutated *ob* gene developed severe obesity related to the lack of signaling in the brain-gut axis. Leptin in humans is positively

correlated with body fat mass and is decreased upon weight reduction [41]. For example, insulin has been shown to stimulate leptin secretion during feeding, and starvation, to decrease leptin secretion in humans [42]. Leptin is a known regulator of energy homeostasis and modulates the inflammatory response and immune system [43].

The role of leptin in the immune response has been a subject of recent interest. It was shown that leptin synthesis is increased by a number of inflammatory stimuli, including IL-1, IL-6, TNF- α , and LPS [44]. An increase in leptin secretion during infection and inflammation strongly suggests that it is involved in the cytokine network that governs host defense mechanisms. Leptin receptors are known to be expressed in adipocytes, T lymphocytes, and vascular endothelial cells.

Karthikeyan and Pradeep reported that leptin concentrations in gingival crevicular fluid (GCF) were found to be higher in healthy gingiva than in tissues with periodontitis [15]. Conversely, serum leptin levels are increased in people with periodontitis [16]. The mechanism of these discrepancies between GCF and serum leptin levels with/without periodontitis remains unclear. One possible explanation is speculated that the secreted leptin may be used up as a substrate during inflammation. Furthermore, the levels of leptin in GCF were demonstrated to be significantly lower in smokers than in non-smokers [45].

Leptin may exacerbate auto-immune reactions such as type 1 diabetes and rheumatoid arthritis. It may reduce T regulatory cells, which constitute 5–10% of CD4⁺ T cells. Considering that in the initial and stable stages of periodontal inflammation, Th1 is the dominant cell type, leptin might contribute to periodontal inflammation concerning to T cell immune reactions.

5. Resistin

Resistin is a 12.5-kDa polypeptide hormone that was first identified as a gene responsive to antidiabetic drugs known as thiazolidinediones. It belongs to the found in the inflammatory zones (FIZZ) family, and FIZZ3/resistin is linked to obesity and diabetes. The administration of recombinant resistin decreased insulin responsiveness in mice and in an adipocyte cell line [46]. Resistin is expressed abundantly in adipose tissues of mice; however, in humans, resistin is expressed at very low levels in adipocytes, whereas at higher levels in circulating blood monocytes, mononuclear leukocytes, and macrophages [47]. The genes for human resistin and mouse resistin are located on different chromosomes and have an amino acid identity of only 60% [46].

Circulating resistin levels are elevated in patients with cardiovascular disease

[48]. The effect of resistin on inflammation was shown to be related to the expression of vascular adhesion molecules. Human resistin acts as a proinflammatory molecule and stimulates the synthesis and secretion of TNF- α and IL-12 [49]. LPS was shown to increase resistin mRNA levels in mouse adipocytes and human peripheral blood monocytes. In addition to TNF- α and IL-6, resistin may participate in inflammatory processes caused by bacterial infections [50].

We reported that periodontitis was significantly associated with increased levels of resistin, after adjustment for gender, smoking, fasting glucose, and BMI. This association was promoted under bleeding conditions of the periodontium (Table 1) [13, 14]. Other inflammatory cytokines such as IL-6, TNF- α and IL-1 β have an effect on the expression of resistin *in vitro*, suggesting that chronic periodontal inflammation may influence resistin expression. Furthermore, the administration of *E. coli* LPS in humans is associated with increased circulating resistin levels [51]. LPS originated from periodontal pathogens may influence adipose tissues and macrophages through inflammatory cytokines as described above. Moreover, a potential role for resistin in bone metabolism was suggested by increased resistin levels that coincided with osteoclast differentiation [52]. The physiological functions of resistin during periodontal inflammation remain unclear

and warrant further investigation.

6. Adipocyte and innate immunity

TLRs have emerged as a first line of defense against infectious diseases caused by bacteria. TLRs were shown to be critical for efficient innate and adaptive immunity. For example, TLR2 recognizes peptidoglycans found in Gram-positive bacteria, and TLR4 recognizes LPS. TLRs have been detected on many types of cells, including macrophages, T cells, and epithelial cells. Reportedly, leptin can induce TLR expression and responsiveness in both preadipocytes and mature adipocytes, which suggests that leptin immunomodulates adipocyte function and that adipocytes contribute to the innate immune system [53]. Also, adiponectin acts as a negative regulator of the inflammatory response induced by TLR in macrophage-like cells [40]. Nutritional fatty acids can affect TLR4 signaling in monocytes and adipocytes [54]. Mice lacking TLR4 are protected against insulin resistance induced by a high-fat diet. TLR4 in adipocytes that is activated by either LPS or free fatty acids enhances the expression of TNF- α and IL-6, which leads to systemic insulin resistance [55]. TLR4 is likely activated chronically in the obese state and could play an important role in metabolic syndrome. TLRs were

promoting inflammatory changes in adipocyte-macrophage co-culture systems [56].

LPS from *Aggregatibacter actinomycetemcomitans*, which is associated with progressive periodontitis, is recognized by TLR4 [40]. TLR4 activation in both adipocytes and macrophages regulates the production of various cytokines and therefore may be associated with periodontal inflammation.

7. Conclusions

TNF- α and IL-6 increased by the progression to severe forms of periodontitis may affect glucose metabolism. Hence, the elevation of these cytokines attributable to periodontitis could increase the risk for insulin resistance (Fig. 3). As low-grade inflammation is involved in the pathogenesis of systemic diseases such as type 2 diabetes, the dysregulation of cytokine secretion by adipose tissues or macrophages may be critical in disease pathogenesis. Decreases in the levels of C-reactive protein and TNF- α following antimicrobial periodontal treatment may effectively reduce the risk for coronary heart disease [18]. In addition to a *Porphyromonas gingivalis* LPS challenge, diet-induced obesity may also increase the risk for developing bacterial infections [57].

Although epidemiological studies concerned with adipokines and periodontitis were performed in cross sectional studies, the cause-effect relationship is not clarified at

present. Hereafter, prospective large cohort studies with adipokines levels in subjects with periodontitis and interventional studies by periodontal treatment, are needed to clarify the relationship between adipokines and periodontitis.

Periodontal inflammation may affect systemic inflammatory processes and immune function. Mechanistic insights revealed with state-of-the-art approaches will be useful for developing strategies to combat periodontal disease and other pathologies characterized by inflammation.

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Table 1 Summerized the relationship between adipokines and periodontitis

Authors and year	Study design	Major Result
Kamio et al. 2009 [12]	In vitro study	Globular adiponectin has an anti-inflammatory activity in periodontitis.
Furugen et al. 2008 [13]	Cross sectional study	Increased surum resistin is associated with periodontal condition considering bleeding on probing.
Saito et al. 2008 [14]	Cross sectional study	Resistin may mediate the relationship among obesity, type 2 diabetes, and periodontitis.
Karthikeyan BV et al. 2007 [15] [16]	Cross sectional study	Leptin levels decreased progressively in gingival crevicular fluid from health to periodontitis and increased in serum leptin levels.
Yamaguchi et al. 2007 [17]	In vitro study	Adiponectin inhibits osteoclast formation stimulated by LPS from <i>A.actinomyetemcomitans</i> .
Iwamoto et al. 2003 [18]	Clinical study	Periodontal treatment is effective in reducing TNF- α , and adiponectin is not influenced.

Table 2 Serum resistin and adiponectin levels in the subjects with periodontal conditions and control subjects (Ref.13, 14)

Periodontal status	n	Resistin (ng/mL)	<i>p</i>	Adiponectin (μg/mL)	<i>p</i>
Niigata study (Ref.13) ^a					
Control	74	4.9 ± 0.4 ^b	0.138	12.0 ± 0.6 ^b	0.248
Periodontitis	84	6.0 ± 0.3		11.0 ± 0.6	
Niigata study (Ref.13) ^a					
Control					
without bleeding	60	4.8 ± 0.4	0.037	11.7 ± 0.8	0.551
Periodontitis					
with bleeding	47	6.1 ± 0.5		11.1 ± 0.9	
Hisayama study (Ref.14) ^c					
Healthy gingiva	42	8.0 ± 5.2 ^d	0.037	12.4 ± 5.1	0.46
Periodontitis	34	9.9 ± 5.0		11.5 ± 5.0	

^a ANCOVA was performed adjusting for sex, BMI, fasting glucose, and smoking.

^b Data are expressed as the mean ± standard error of mean.

^c Mann-Whitney *U* test.

^d Data are expressed as the mean ± standard deviation.

Figure legend

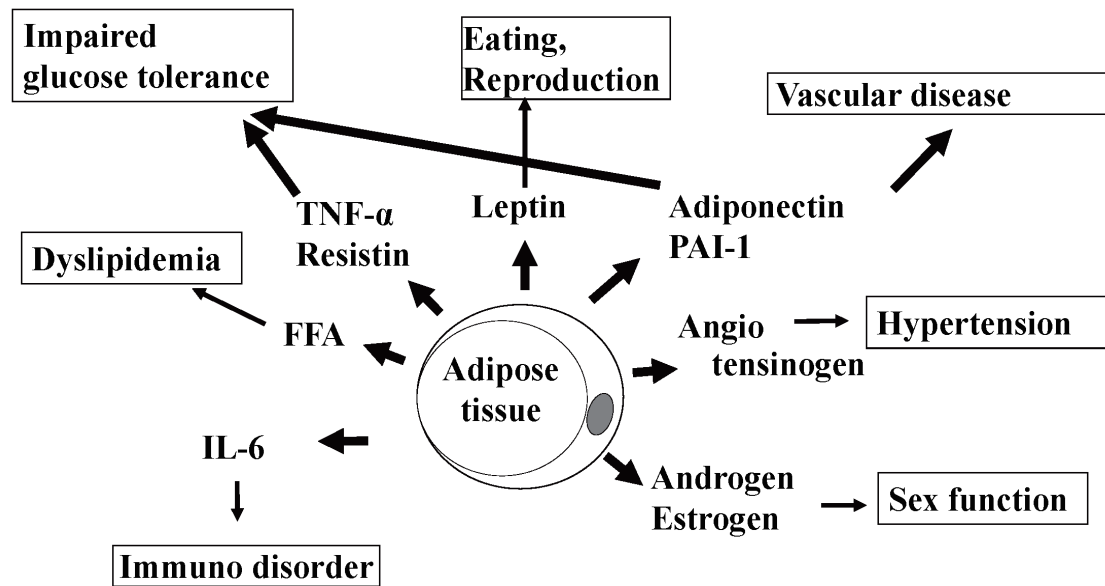


Figure 1. Adipokines are bioactive substances that are secreted from adipose tissue.

Adipose tissue is the main energy store in the body and is also a source of paracrine and endocrine factors that modulate the inflammatory response, vascular function, and insulin sensitivity.

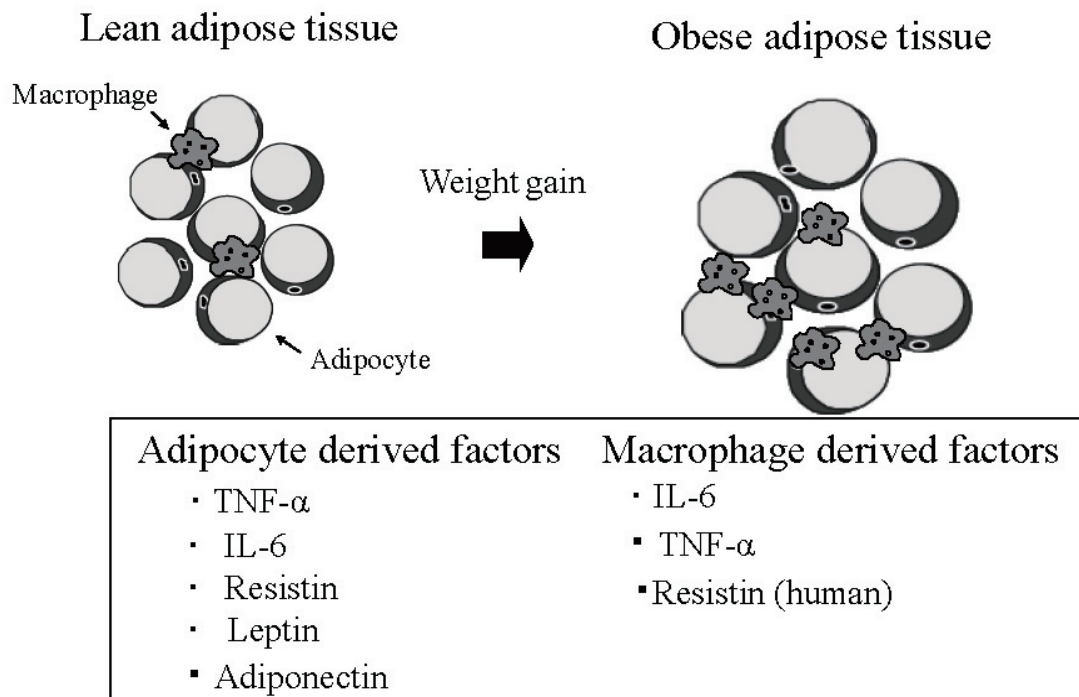


Figure 2. Adipocyte-macrophage interactions. Lean adipose tissue is composed of small adipocytes containing few macrophages, whereas large adipocytes in the obese state are associated with more macrophages. Lean adipose tissue secretes a high level of adiponectin and low levels of leptin and resistin. Conversely, in obese adipose tissues, the adiponectin level is low, and resistin levels are high.

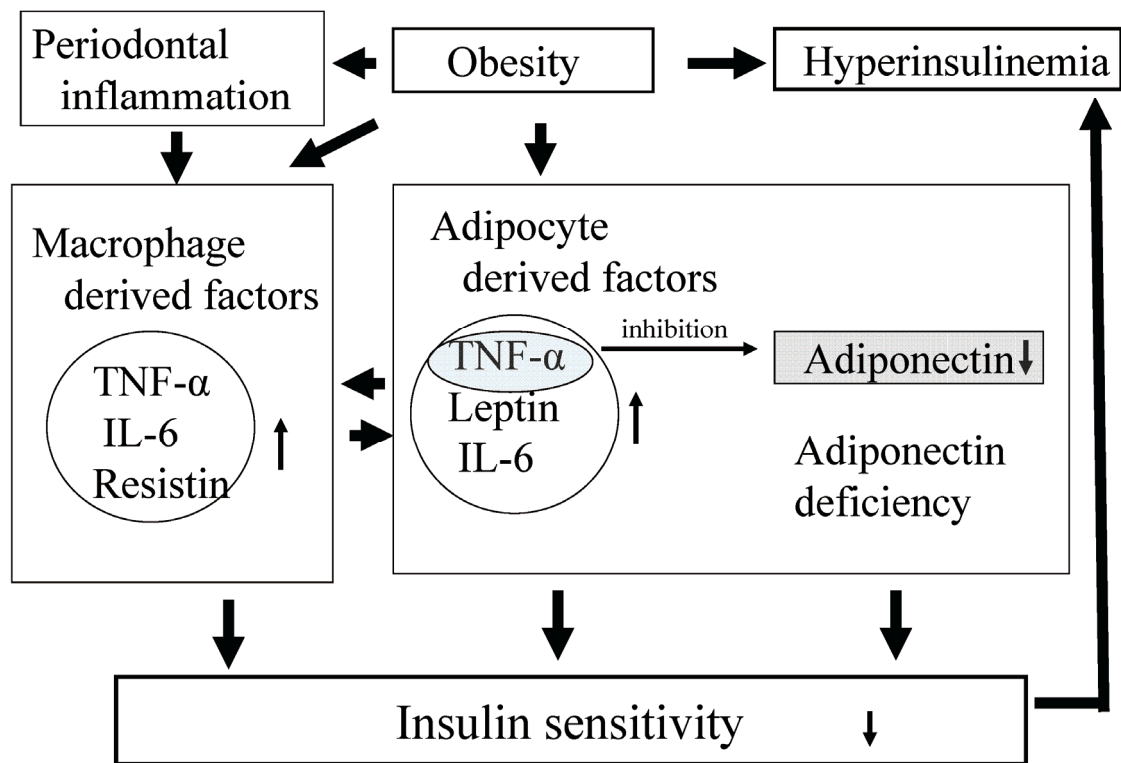


Figure 3. The relationship among periodontitis and adipokines