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ADIPOKINES IN PERIODONTAL DISEASE–CULPRITS OR ACCOMPLICE?

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ABSTRACT

Periodontitis is a disease of periodontium resulting from pathogenic microorganisms combined with other risk factors. For many years, the relationship of obesity with periodontal disease has been discussed and it has been shown that obesity may act as a risk factor for periodontitis. Adipokines are bioactive molecules secreted by adipose tissue. Along with regulating energy expenditure and insulin sensitivity they also modulate the inflammatory and healing process. Recent studies have also shown adipokines, such as leptin, adiponectin and visfatin are could play a role in periodontal disease progression and may be used as biomarkers for the same. Understanding the role of adipokines may help illuminate the relationships among obesity, periodontitis, type 2 diabetes, and cardiovascular diseases.

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INTRODUCTION

Adipose tissue plays a very important role in the regulation of energy homeostasis. It is an active endocrine organ that secretes more than 600 biologically active substances, collectively termed adipokines [1]. The well-investigated biologically active molecules among these are pro-and anti-inflammatory cytokines including IL-1β, TNF-α, IL-6, IL-10, growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), chemokines such as monocyte chemotactic protein-1 and interleukin-8 and hormones such as leptin, adiponectin, visfatin, and resistin. These molecules play a wide variety of overlapping roles in inflammatory diseases among which periodontitis is very common. However, at present, there is not much research literature available on the relationship between adipokines and periodontitis. The present article is focused on highlighting this relationship and also discusses whether adipokines may be used as biomarkers for periodontal disease progression.

Etiopathogenesis of periodontitis: Periodontitis is a multifactorial disease with microbial etiology being its primary etiology. It is an inflammatory disease that leads to slow and progressive degradation of the periodontium. Many putative periodontopathogens have been implicated in the etiopathogenesis of periodontal diseases. Some of these pathogens include Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Aggregatibacter actinomycetemcomitans, and Fusobacterium nucleatum.

The host-microbial interactions result in the release of various immunological mediators which cause the destruction of periodontal tissues [2, 3]. The most important mediators among these include IL-1β, IL-6, IL-8, TNF-α, PGE2, and matrix-degrading proteases, such as matrix metalloproteinases (MMPs). Along with this, environmental factors like stress, smoking, and genetics play an important role in periodontal disease progression [4]. The periodontal disease progression can be halted if the microbial load in the periodontal arena is reduced by non-surgical periodontal therapy and a balance is restored between pro and anti-inflammatory cytokines. Along with this, various host modulation therapeutic agents may be used to reduce the periodontal destruction caused by the host immune response.

Associations of periodontitis with obesity: Initially, periodontitis was considered as a separate disease entity. But, with time it was demonstrated that periodontitis is related directly or indirectly to many systemic conditions like diabetes mellitus, coronary heart diseases, pregnancy, etc. At present various meta-analyses have proposed a strong association between periodontitis and coronary heart diseases [5] and diabetes mellitus [6]. Also, many studies have indicated that periodontitis is associated with obesity. Perlstein and Bissada in 1977 for the first time demonstrated in an experimental periodontitis rat model, that obesity contributes to the severity of periodontal disease [7]. In humans, the relationship between obesity and periodontitis was first demonstrated by Saito et al in 1998 [8].

The authors conducted this study on 241 Japanese healthy individuals, 20–59 years of age (172 women and 69 men). Out of 241 individuals, 96 had periodontitis. The study population was divided into four groups depending on their body mass index (<20, 20–24.9, 25–29.9, ≥30 kg m^{-2}). The relative risk of periodontitis in each group was calculated. The results of the study demonstrated that the relative risk of periodontitis was 3.4 in subjects with body mass indexes of 25–29.9 kg m^{-2}, and 8.6 in those with body mass indexes of ≥30 kg m^{-2}, compared with subjects with body mass indexes of<20 kg m^{-2}. These findings suggested that obesity can be considered as a risk factor for the development of periodontitis. In a subsequent study, Saito et al. [9] demonstrated that at distribution pattern(high waist-hip ratio) plays a critical role in the association between periodontitis and obesity. The association between periodontitis and obesity was also demonstrated in the united states National Health and Nutrition Examination Survey/ NHANES III with a sample size of 13,665. The study subjects were stratified by age: younger (18–34 years), middle-aged (35–59 years), and older (60–90 years) adults. In this survey, it was found that there was a significant association between periodontal disease and the measures of body fat was found among the younger adults, but not middle-aged or older adults. Some longitudinal studies have also been done to find out the association between obesity and periodontitis. In a longitudinal study, Gorman et al. (2012) demonstrated that both overall obesity and central adiposity are associated with an increased hazard of periodontal disease progression events in men [10].

Adipokines and metabolism: In humans, there are two types of adipose tissues: brown adipose tissue and white adipose tissue. The brown adipose tissue has multilocular adipocytes with abundant mitochondria, responsible for the thermogenic activity of the tissue and the white adipose tissue is responsible for fat storage. White adipose tissue (WAT), is the major adipose tissue in humans that stores energy. It is composed of specialized cellsfor lipid storage (adipocytes) embedded in a highly vascularized and innervated loose connective tissue. Along with this, WAT contains multiple cell types including adipocyte progenitor cells, macrophages, leukocytes, fibroblasts, and endothelial cells. Our primary reserve energy source is triglycerides which are stored in white adipocytes. Along with the major hormones including insulin and glucagon, adipose tissue produces andsecretes several proteins including adhesion molecules, growth factors, adipokines, cytokines, chemokines, and complement and coagulation factors. In the present discussion, we shall focus on leptin, adiponectin, resistin, visfatin, apelin, omentin 1, and plasminogen inhibiting factor 1.

Leptin: Leptin is a 16 kDa non-glycosylated peptide hormone. It has been classified as a cytokine because it shows structural similarities to the long-chain helical cytokine family, specifically IL-6, IL-12, and granulocyte colony-stimulating factor [11]. It regulates T lymphocyte proliferation, activation, and cytokine production [12, 13]. The mixed lymphocyte reaction demonstrates the induced proliferation of naive CD4+CD45RA+ T cells and reduced proliferation of memory $CD4^{+}CD45RO^{+}$ T cells [14]. Various effects of leptin on adaptive and innate immune response have been summarized in table 1.

Table 1 Effects of Leptin on the innate and adaptive immune response

Leptin (Pro-inflammatory activity)	Innate immunity	Adaptive immunity
	↑ TNF [15, 16]	↑ Lymphopoiesis
	↑ IL-6[15]	↑ Thymocyte survival
	↑ IL-12[15]	↑ T-cell proliferation
	↑ Neutrophil activation (CD11b) [17]	↑ TH1 response (IL-2 and IFNγ)
	↑ Reactive oxygen species [17]	↓ TH2 response (IL-4)
	↑ Chemotaxis[17]	
	↑ NK-cell function [18]	

It must be noted here that Leptin is secreted in proportion to the size and number of adipocytes. Thus, plasma levels of leptin are enhanced in obesity and diminished after weight loss [19]. It performs multiple metabolic activities including inhibiting appetite, stimulating energy expenditure, and modulating lipid and bone metabolism, coagulation, hematopoiesis, affecting the function of pancreatic β-cells and insulin sensitivity. Along with this, leptin regulates immunoinflammatory processes, primarily, proinflammatory actions [20]. It has been demonstrated that Leptin enhances pro-inflammatory cytokine production and phagocytosis by macrophages [21]. Inflammatory and infectious stimuli such as lipopolysaccharide and cytokines increase leptin levels in the acute phase [22]. Multiple studies have reported that during active periodontitis, the levels of leptin in the gingival crevicular fluid are increased [23, 24]. Also, the plasma levels of leptin have been found to be increased in patients with periodontitis and these levels reduce after periodontal treatment [25, 26]. In a study done on type-II diabetic patients with periodontitis, it was observed that the serum levels of leptin significantly decreased ($P < 0.05$) during a 3-mo follow-up period after non-surgical periodontal treatment [27]. However, another study done on Japanese type 2 diabetic patients demonstrated that acombination of periodontal treatment with periodontal antibiotics improved the periodontal status of the patients without dramatically affecting the serum leptin level [28]. One more study done on periodontitis patients that failed to show that periodontal therapy could change the level of leptin as well as those of other adipokines in serum was conducted by **Teres** et al. [29]. Hence, it can be concluded from the above discussion that leptin may reflect systemic inflammatory conditions but may not be a good predictor for local inflammatory conditions like periodontitis.

Adiponectin: Adiponectin is also known as Acrp30, apM1, or GBP28. It is an important polypeptide adipokine (molecular weight of 30-kDa) that plays a very important role in homeostasis control of glucose, energy, and lipid metabolism. It participates in regulating glycemia, lipidemia, endothelial dysfunction, and proinflammatory mechanisms [30]. It must be emphasized that adiponectin levels are inversely correlated with obesity, hyperlipidemia, and insulin resistance [30]. The gene for adiponectin is located on chromosome 3 at 3q27 [31]. Serum levels of adiponectin are markedly decreased in individuals with visceral obesity and states of insulin resistance, such as non-alcoholic fatty liver disease, atherosclerosis, and type 2 diabetes mellitus [32]. Adiponectin was first cloned from mice and subsequently from humans. The human adiponectin shares 83% amino acid identity with mouse adiponectin.

This polypeptide circulates in the blood in trimeric (low molecular weight, LMW), hexameric (medium molecular weight, MMW), and multimeric (high molecular weight, HMW) forms [33]. Adiponectin plays a very important role in immunomodulation. It has been shown to attenuate the effects of TNF-α [34], inhibit nuclear factor-kB, inhibit IL-6 production, and induce anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist [35]. TNF-α downregulates the levels of transcription of adiponectin in an adipocyte cell line, which might explain the reduced levels of serum adiponectin in individuals who are obese [36]. Weight loss is an important up regulator of adiponectin synthesis. Circulating levels of adiponectin, however, are affected by many other factors including gender, age, and lifestyle. The association of serum adiponectin with periodontitis has been studied in many investigations. Many studies have demonstrated no relationship between periodontal conditions and serum adiponectin levels [37-39]. However, it has been demonstrated that HMW adiponectin is pro-inflammatory and it may have a direct correlation with an inflammatory condition like periodontitis. Another important effect of adipokine is that it has been shown to downregulate monocyte adhesion to endothelial cells and macrophage transformation to foam cells. Also, it has been shown to downregulate osteoclast formation stimulated by LPS from periodontopathic bacteria [40]. Hence, it can be concluded from the above discussion that adiponectin may inhibit alveolar bone loss in patients with periodontitis. However, its association with active periodontal disease progression has not been demonstrated in the literature so far.

Resistin: Resistin is a 12.5 kDa cysteine-rich secretory protein consists of 108 amino acids. The name 'Resistin' has been given to this molecule because the original observations showed that it induced insulin resistance in mice. Recent human studies have suggested that resistin is primarily expressed in monocytes, macrophages [41,] and bone marrow [42]. A very little resistin is expressed in adipocytes. These findings explain its importance as an immune modulator molecule. Increased expression of resistin in the peripheral blood mononuclear cells (PBMCs) are stimulated by IL-1β, IL-6, and TNF-α [43, 44,] and the effects of resistin are mediated through the NF-κBsignaling pathway. On the other hand, resistin acts as a proinflammatory molecule and stimulates the synthesis and secretion of proinflammatory cytokines: tumor necrosis factor (TNF)-a, interleukin (IL)-6, IL-12, and monocyte chemoattractant protein (MCP)-1 [44].Also, the bacterial lipopolysaccharides (LPS) have been shown to increase resistin mRNA levels in mouse adipocytes and human peripheral blood monocytes. Circulating resistin levels are elevated in patients with cardiovascular disease [45]. The effects of resistin on innate and adaptive immune response have been elucidated in Table 2.

Table 2. Effects of resistin on the innate and adaptive immune response

Resistin (Pro-inflammatory)	Innate immunity	Adaptive immunity
	↑ TNF[44, 46]	Not described yet
	↑ IL-1β[46]	Not described yet
	↑ IL-6 [46]	Not described yet
	↑ IL-12 [46]	Not described yet
	↑ NF-κB[44]	Not described yet
	↑ Endothelial adhesion molecules (VCAM1 and ICAM1) [47]	Not described yet

Many investigations have been done to evaluate the associations of serum/GCF levels of resistin and periodontitis. A study demonstrated a positive correlation with bleeding on probing (BOP) and serum levels of resistin in patients with chronic periodontitis [37]. Another study evaluated GCF levels of resistin in experimental gingivitis cases. The results of the study demonstrated resistin in GCF as an inflammatory mediator during the induction and resolution of experimental gingivitis in humans [48]. Thommesen et al. demonstrated a potential role for resistin in bone metabolism because they observed that increased resistin levels coincided with osteoclast differentiation [49]. However, at present, the exact role of resistin during periodontal inflammation remain unclear and warrant further investigation.

Visfatin: Visfatin was identified in 2005 by Fukuhara et al. [50]. It is a well-established pre-B-cell colony-enhancing factor. It has cytokine-like effects and a role in energy metabolism. It is a 52-KDa protein that increases pre-B-cell colony release from lymphocytes and improving the maturation of B-lymphocytes [51]. It is secreted by visceral adipose tissue and macrophages. Along with this, it has also been isolated from muscle, dendritic cells, and bone marrow. During infection and inflammation,Visfatin induces the release of IL-1 β, TNF-α, and IL-6 [52]. Visfatin is also known as nicotinamide phosphoribosyltransferase, an enzyme inhibiting the biosynthesis of nicotinamide adenine dinucleotide [53]. Visfatin is present in both GCF and saliva and its levels vary depending upon the physiological and pathological condition. One study investigated the levels of Visfatin in GCF of healthy individuals and patients with periodontitis. It was observed in the study that there was a possible relationship between GCF levels of Visfatin and the presence and levels of Porphyromonasgingivalis, Prevotella intermedia, Prevotellanigrescense, and the Epstein-Barr virus (EBV). Further, the presence of EBV was found to be associated with increased Visfatin levels [54].

The role of Visfatin in periodontal diseases is poorly established. There are only a handful of studies describing if any association of salivary or GCF Visfatin and periodontal health and disease. One study evaluated the relationship between serum and GCF concentrations of visfatin and periodontal diseases. It was found in this study that concentrations of visfatin in the serum and GCF progressively increased with the severity of periodontal disease starting from gingivitis to severe periodontitis. Along with this, visfatin levels were found to be higher in patients with periodontal disease and type 2 diabetes mellitus as compared to that with periodontitis and without type 2 diabetes [55]. In another study, it was demonstrated that the levels of visfatin were higher in patients with gingivitis and periodontitis as compared to healthy individuals [56].Özcan et al. evaluated the levels of visfatin, NF-κB (NF-κB1 and NF-κB2), PI3k, TNF-α, and IL-1 β in the tissues of patients with periodontitis and healthy individuals. It was concluded in this study that increased visfatin levels were associated with the expression of NF-κB and PI3k [57]. This finding explains the possible role of visfatin in immunomodulation during the inflammatory process. The effects of visfatin on innate and adaptive immune response have been summarized in table 3.

Table 3. Effects of visfatin on the innate and adaptive immune response

Visfatin (Activity not established)	Innate immunity	Adaptive immunity
	↑ IL-6[58]	Not determined
	↑ IL-8 [58]	Not determined
	↓ Apoptosis ofneutrophils[59]	Not determined

Some other studies have evaluated the changes in visfatin levels before and after periodontal treatment in periodontitis patients. Raghavendra et al. [60]reported a decreased level of visfatin in both serum and GCF in periodontitis patients after periodontal treatment. The effect of non-surgical periodontal treatment on GCF and salivary visfatin levels was evaluated by Abolfazli et al. in one study [61]. The authors observed that after non-surgical periodontal therapy, mean salivary and serum levels of visfatin significantly decreased ($P<0.05$). Also, the changes in salivary visfatin levels were more prominent. These results were supported by another recent study [62] that evaluated the effects of non-surgical periodontal therapy on GCF levels of visfatin in periodontitis patients with and without Type 2 Diabetes Mellitus (T2DM). The results of the study concluded that thosevisfatin levels are highest in individuals with both periodontal disease and diabetes, even after periodontal therapy. Individuals with T2DM may be at higher risk of developing periodontal disease. Still many aspects of the association of visfatin and periodontitis are obscured and more research is required in this field to establish the association if any.

Apelin: Apelin is a short peptide released from adipocytes upon stimulation. Three forms of Apelin have been identified consisting of 13, 17, or 36 amino acids, all originating from a common 77-amino-acid precursor. Insulin stimulates apelin synthesis and its plasma levels are increased in obesity-associated insulin resistance and hyperglycemia. Apelin is known to exert different physiological effects on different systems, mainly on the cardiovascular system. Apelin not only acts on glucose and lipid metabolism but also modulates insulin secretion. It has been observed that its plasma concentration is usually increased during obesity and type 2 diabetes [63]. Its receptors are expressed in several vital tissues such as the heart, skeletal muscle, lungs, brain, etc.

Apelin has been shown to play a role in the inflammatory process. Koguchi et al. reported apelin to be an anti-inflammatory cytokine [64]. They observed that apelin effectively suppressed the expression of inflammation factors such as TNF-α and IL-1β protein. In an animal study, Leeper et al. demonstrated that apelin treatment significantly reduced the amount of macrophage colony-stimulating factor. Also, levels of monocyte chemoattractant protein-1, macrophage inflammatory protein-1a, IL-6, and TNF-a mRNA were found to be reduced [65]. The authors further highlighted that apelin inhibits the down-modulation of vascular endothelial cadherin by the vascular endothelial growth factor, which intern leads to suppression of hyperpermeability. This explains the anti-inflammatory action of apelin. These findings were supported by Visser et al. [66]who advocated the therapeutic use of apelin in suppressing inflammation. Similarly, Leal et al. also suggested a possible association between apelin and inflammation. However, some studies have demonstrated a pro-inflammatory role of apelin. Heinonen et al. [67]reported that apelin promoted inflammation in patients with metabolic syndrome after a diet-induced weight loss.

At present, the role of apelin in inflammation is not much clear and more investigations are required in this field.

Omentin 1: Omentin (intelectin) is another product of adipose tissue stromal cells. It was identified while by examination of a visceral adipose tissue cDNA library. It consists of 313 amino acids and weighs 40 kDa, exhibiting a variety of biological properties that are anti-inflammatory, anti-atherogenic, and anti-diabetic in nature [68]. In humans, two forms of omentin are found: omentin-1 and omentin-2. Omentin-1 is the key form circulating in human blood. Omentin exhibits anti-inflammatory, anti-atherogenic, and anti-diabetic characteristics.It has been shown to enhance the action of insulin by increasing insulin-facilitated glucose uptake by subcutaneous tissue and omental adipocytes [69].

Omentin-1 is an immune modulator and its role in inflammatory diseases has been investigated. It has been shown to inhibit the TNF-α-induced cyclooxygenase (COX2) expression [70]. The circulating omentin-1 concentration has been found to be inversely correlated with the levels of pro-inflammatory factors, such as IL-6 and TNF-α in individuals with impaired glucose regulation [71]. The role of omentin-1 has been investigated in rheumatoid arthritis by Senolt et al. [72] and in Crohn's disease by Schäffleret al. [73].Another important biological function of omentin-1 is the modulation of bone metabolism. However, the present research work has provided us evidence that it has ambiguous effects on bone mass. Some studies have found that omentin-1 prevents bone loss and osteoporosis by suppressing bone resorption and promoting bone formation in mice and in multiple sclerosis patients [74, 75]. Other studies have found that omentin-1 has a negative effect on bone mass at different skeletal sites, and on bone turnover markers through inhibiting bone formation [76-78]. Still, other studies have found that omentin-1 does not has any significant relationship with bone mass and osteoporosis [79, 80]. Hence, it is presently a matter of research to find out the exact role of omentin-1 on bone metabolism.

There are only a few studies done to find out any association between omentin-1 and periodontitis. One study has described the levels of omentin in the GCF of periodontally healthy and chronic periodontitis patients with and without type 2 diabetes mellitus before and after non-surgical periodontal therapy. It was concluded by the authors that omentin may be used as an inflammatory marker of diabetes, periodontal disease, and their treatment outcome [81].

Adipocyte-derived plasminogen activator inhibitor-1 (PAI-1): Adipose tissue also releases plasminogen activator inhibitor-1 (PAI-1) which is a crucial inhibitor of plasminogen activators. It belongs to the serine proteinase inhibitor family. Along with inhibiting fibrinolysis, PAI-1 also has a complex interaction with cellular matrices, and further participates in inhibiting proteolysis. PAI-1 levels in the plasma are related to overall fatness [body mass index (BMI)], particularly the omental fat and are elevated in obese subjects. It has been demonstrated that PAI-1 is associated with metabolic syndrome in obesity [82-84] which is characterized by dyslipidemia, hypertension, and glucose intolerance. It must be noted here that the major tissue source of PAI-1 is white adipose tissue, specifically visceral adipose tissue, accounting for significantly more PAI-1 compared to subcutaneous adipose tissue.

During inflammation, the adipose tissue is infiltrated by macrophages that cause increased lipolysis through cytokines. It also causes increased release of PAI-1 which has been related primarily to increased TNF-α expression during inflammation [85, 86].

Biological significance of adipokines in periodontal disease progression: As already discussed in the previous sections, adipokines are bioactive molecules that have an active role in the genesis of inflammation and insulin resistance associated with obesity. At present there is evidence that obesity-related diseases could be cause due to the dysregulated production of adipocytokines. TNF-α, leptin, and resistin affect insulin sensitivity in the whole body. It is a well-established fact now that increased production of TNF-α is associated with insulin resistance. Hence, it is clear from the above discussion that certain risk factors for type 2 diabetes mellitus and periodontitis are the same. The association of adipokines and periodontal disease progression has been a focus of research for the last few years now. Multiple observations have been made by different researchers and at present, there is insufficient data to establish a well-defined relationship between various adipokines and periodontitis. As already stated, there are multiple adipokines in white adipose tissue. Only a few of them have been studied so far. Hence, this field is wide open for research.

CONCLUSION

Periodontal diseases are primarily inflammatory diseases and have multifactorial etiology. Various biological mediators such as cytokines, chemokines, and locally secreted enzymes by various immune cells play a vital role in periodontal disease progression. As various adipokines are biologically active molecules and are associated with insulin resistance and the development of type 2 diabetes mellitus. Hence, these may also participate in periodontal disease progression. The role of leptin, adiponectin, resistin, visfatin, apelin, and omentin 1 have been described in the inflammatory process. Only a few studies have been done to find out any association between these mediators and their possible role in the periodontal inflammatory process. Thus, in the future more research is desired to clarify various aspects of adipokines in periodontal health and disease.

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