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**Effect of periodontal treatment on adipokines in type 2 diabetes**

Ogawa H *et al*. Adipokines and periodontal treatment

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**Abstract**

The association between adipokines and inflammatory periodontal diseases has been studied over the last two decades. This review was intended to explore the observation that periodontal therapy may lead to an improvement of adipokines in diabetic patients. In summary, substantial evidence suggests that diabetes is associated with increased prevalence, extent and severity of periodontitis. Numerous mechanisms have been elucidated to explain the impact of diabetes on the periodontium. However, current knowledge concerning the role of major adipokines indicates only some of their associations with the pathogenesis of periodontitis in type 2 diabetes. Conversely, treatment of periodontal disease and reduction of oral inflammation may have positive effects on the diabetic condition, although evidence for this remains somewhat equivocal.

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**Key words:** Adipokines; Diabetes; Periodontal disease; Periodontal therapy

**Core tips:** Several adipokines could serves as the monitoring molecules that reflect overall and oral disease conditions include periodontitis. Because they are rapidly change upon the change in body and oral conditions. The treatment response and disease activity progression may also predicted using these kinds of molecules. Moreover, the method to collect and analyse adipokines is relatively simple because they can be detected in gingival crevicular fluid and analysed using general ELISA technology. Collectively, clinicians include medical doctors and periodontists should take the concern regarding adipokines into their routine periodontal treatment plan and management.

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**OVERVIEW OF PERIODONTITIS AND INFLAMMATION IN TYPE 2 DIABETES**

Periodontal disease refers to the processes of destruction of the peri-tooth structures that support the teeth. These comprise the gingiva, the periodontal ligament, the cementum and the alveolar bone. The chronic destruction of these supporting tissues leads to the eventual loss of teeth. Epidemiological studies have revealed that more than two-thirds of the world's population suffers from one of the chronic forms of periodontal disease[1].

Periodontal destruction is host-mediated by locally produced pro-inflammatory cytokines in response to the bacterial flora and its products[2]. It is possible that the production of local cytokines[3] and or low-level asymptomatic bacteremia or endotoxemia[4] affects the plasma concentration of pro-inflammatory biomarkers.

Significant differences in the plasma concentrations of such biomarkers have been described[5-8]. Periodontitis may have an even greater influence on the systemic inflammatory condition in individuals with diabetes. Elevated circulating levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and high-sensitivity C-reactive protein, which can worsen insulin resistance and thereby impair glycemic control, have been shown in several studies[9,10]. Thus, periodontal disease may have a significant impact on the metabolic state in diabetes[11]. TNF-α has been reported to play a key role in the pathogenesis of type 2 diabetes, and the correlation of this cytokine with insulin resistance has also been shown in metabolic syndrome[12].

Several studies have reported the effects of periodontal treatment on glycemic control as well as systemic inflammatory mediator levels in patients with type 2 diabetes. In some cases, positive effects such as improving HbA1c or serum level of adiponectin have been indicated[13,14]; however, such phenomena regarding adipokines are still unclear due to several confounding factors. Adipokines are molecules mainly produced and exocytosed from adipocytes. These molecules are a large family composed of members such as leptin, adiponectin, resistin, visfatin, adipsin, interleukin, monocyte chemotactic protein-I and retinol-binding protein.

Accordingly, this review focuses on providing a concise summary and dealing with recent advances regarding the potential of selected adipokines as therapeutic tools or targets of periodontal treatment (Figure 1).

**ADIPOKINE MOLECULES AND PERIODONTAL TREATMENT**

***Leptin***

Leptin, a molecule that acts as an obesity-regulatory hormone, has the cytogenetic location of 7q32.1[15]. The gene encoding leptin is named the *LEP* gene or the obese (*Ob*) gene, which produces a 16-kDa protein secreted by white adipose tissue. By interaction with leptin receptor[16], it leads to appetite regulation, control of body energy expenditure and maintenance of bone mass. The actions of leptin mainly occur in the hypothalamus[17]; however, the production of leptin has also been found in bone marrow, placenta, skeletal muscle and stomach[17-20]. Recently, it has been found that leptin could reduce adipose tissue inflammation *via* activation of the macrophage histone deacetylase HDAC4[21]. In an animal model, namely, mice without the *LEP* gene, which are dramatically obese, leptin injection led to weight loss due to food intake reduction and increased energy expenditure[16,22].

The relationship between leptin and insulin is still not well established. At present, it has been demonstrated that leptin suppresses insulin production *via* a negative feedback loop, but insulin stimulates the production of leptin[23,24]. These interplays occur in an axis named the adipo-insular axis, and progression of insulin resistance was shown to be correlated with dysregulation of this axis[25]. Recent evidence in an in vitro model has demonstrated that leptin influenced insulin by regulation of insulin-like growth factor-binding protein 2 (IGFBP-2)[26], and this regulation occurred through signal transducers and activators of transcription (STATs), especially STAT-3, as well as phosphoinositol-3 phosphateand the AKT signaling pathway[26,27].

***Leptin and periodontal treatment***

Inflammation of periodontal tissue results in an increased serum leptin level, but leptin significantly decreased (*P* < 0.05) during a 3-month follow-up period in type 2 diabetic patients who received non-surgical periodontal treatment[28]. Even though this study and a study by Teres *et al*[29] found that leptin correlates with inflammatory condition because they found a positive relationship between IL-6 and leptin but a negative relationship between vitamin D and IL-6, the latter study failed to show that periodontal therapy could change the level of leptin as well as those of other adipokines in serum. Recent evidence has also suggested that the combination of periodontal treatment with periodontal antibiotic treatment could improve the periodontal status of Japanese type 2 diabetic patients without dramatically affecting the serum leptin level[30]. From all of the above studies, it seems that leptin is not a sensitive marker for periodontal tissue change or improvement. This molecule may reflect the systemic inflammatory conditions rather than local ones.

***Adiponectin***

Adiponectin (also known as Acrp30, apM1 or GBP28) is a 3-kDa adipokine secreted mainly by adipocytes, which plays important roles in the homeostasis control of glucose, energy and lipid metabolism. The adiponectin gene (*Adipoq*) is located on chromosome 3 at 3q27[31]. Although this protein is secreted mainly by adipocytes, it is also secreted by other cell types include cardiomyocytes[32,33]. Unlike other adipokines, adiponectin exerts anti-inflammatory, anti-diabetic as well as anti-arthrogenic activities[34-36]. Attempts have been made to utilize this molecule as a therapeutic agent or for obese patients. Adiponectin exerts its activity *via* two types of receptor, namely, ADIPOR1 and ADIPOR2[37]. Both of these are widely expressed in diverse cell types, include cardiovascular and immune cells. ADIPOR1 is expressed markedly in skeletal muscle cells, whereas ADIPOR2 is expressed mainly in liver cells[37,38]. When adiponectin binds to its receptor, the signaling pathway *via* activation of peroxisome-proliferator-activated receptor-γ (PPAR-γ), AMP-activated protein kinase (AMPK) or p38 mitogen-activated protein kinase (MAPK) has been shown to be active[27]. Among these, AMPK acts as a major downstream molecule of the adiponectin signaling pathway[39].

Chronic low-grade inflammation and oxidative stress in obesity have been shown to downregulate *Adipoq* gene and protein expression[40]. TNF-α and IL-6, two main inflammatory molecules, are capable of downregulation of adiponectin *via* protein kinase C[41] and MAPK signaling[42], respectively. Moreover, adiponectin inhibits monocyte adhesion to endothelial cells as well as inhibiting macrophage function, collectively contributing to inflammatory cascade regulation[43]. In addition, adiponectin was shown to significantly induce anti-inflammatory cytokines (*P* < 0.05), for instance, IL-10 and IL-1 receptor antagonist, in human monocytes and macrophages[44]. Recently, it was also found that adiponectin could induce the pro-inflammatory function of isolated CD4+ T cells and macrophages by enhancing T-cell differentiation and the induction of interferon gamma (IFN-γ) production[45]. This suggests a new role of adiponectin in the induction of selected inflammatory stimulation for desensitizing these cells to further stimuli.

In liver, adiponectin reduces gluconeogenesis in concert with insulin and improves insulin sensitivity[46,47]. The plasma level of adiponectin in isolated human subjects is also inversely related to fasting insulin level (r = -0.63) and insulin resistance (r = -0.38)[48]. From these lines of evidence, adiponectin has been studied for the possibility of using it as a target for diabetic drugs, especially in type 2 diabetes, and also in cardiovascular diseases.

***Adiponectin and periodontal treatment***

In elderly patients with chronic periodontitis, serum adiponectin level is similar to that in periodontally healthy subjects, but females have a higher serum adiponectin level than males[49]. In addition, non-surgical periodontal treatment given to adult patients with mild to moderate periodontitis did not affect the serum adiponectin level[29]. This may be explained by the fact that adiponectin has different isoforms (low, middle and high molecular weight)[50] with different functions. In addition, it was suggested that only the ratio of high-molecular-weight adiponectin to total adiponectin was significantly lower in subjects with periodontitis[51]. Furthermore, diabetic patients with periodontitis who received periodontal treatment without or with topical antibiotics showed significant elevation of serum adiponectin compared with an untreated group (*P* < 0.05)[28,30]. Effective control of inflammation by periodontal treatment with local antibiotics may contribute to increase systemic anti-inflammatory markers such as adiponectin and hence improve overall health status[14].

***Resistin***

Resistin (also known as adipocyte-specific secretory factor and found in inflammatory zone) is a 12.5-kDa protein said to play a role as a mediator of insulin resistance[52]. The name resistin comes from the finding that this molecule provides resistance to insulin. The gene that encodes this molecule, named Retn, is located on chromosome 19 at p13.3[53]. Interestingly, in humans, resistin is predominantly secreted by macrophages, rather than adipocytes[54]. Bone marrow, peripheral mononuclear cells, lung[55], placenta tissue[56] and pancreatic β-cells[57] can also express this molecule. Murine adipocytes, when cultured in the presence of insulin-sensitizing drugs, for example, thiazolidinediones, appeared to exhibit suppressed resistin secretion[53]. Circulating resistin was shown to decrease upon the administration of anti-diabetic drugs such as rosiglitazone, and to be increased in diet-induced and genetic forms of obesity. From these lines of evidence, it has been postulated that resistin may function as a link between obesity and diabetes, especially type 2 diabetes. However, one study did not find any relationship between resistin and obesity or insulin resistance[54]. This controversial finding may be explained in part by the fact that resistin has at least 2 isoforms: a high-molecular-weight (HMW) hexamer form and a more bioactive but less prevalent low-molecular-weight (LMW) trimer form, which exerts a different biological function[27,58]. Numerous clinical studies have demonstrated a possible relationship of resistin and insulin resistance in obese people with or without diabetes. The possible contributing factor that links resistin to insulin resistance may be hyperresistinemia. In addition, recent clinical studies have shown that individuals with a high serum resistin level have a significantly increased risk of developing T2DM[59,60].

Resistin may play a pivotal role in monocyte-macrophage function and inflammation due to the finding that the expression of resistin was increased in concert with the maturation of monocytes into macrophages[55]. At present, the concrete mechanism of resistin-mediated inflammation has not yet been established due to the resistin receptor not being identified yet, but an isoform of decorin and tyrosine kinase-like orphan receptor 1 were proposed as functional resistin receptors that may modulate glucose homeostasis or regulate enlargement of white adipose tissue in rodents[61,62]. Many pro-inflammatory stimuli and cytokines including lipopolysaccharide, TNF-α, IL-6 and IL-1β are capable of inducing resistin expression and function[63-65]. One line of evidence suggested that resistin could also induce the secretion of pro-inflammatory cytokines, for instance, TNF-α, IL-6, IL-12 or monocyte chemoattractant protein (MCP)-1 in peripheral blood mononuclear cells and macrophages[65,66]. Collectively, these findings show that resistin is a molecule that is closely related to systemic inflammation.

***Resistin and periodontal treatment***

The relationship between serum resistin and periodontal condition was investigated by Furugen *et al*[49], who found that serum resistin and total leukocyte count in subjects with periodontitis were higher than those in subjects without 6-mm pocket depth or without bleeding on probing, with an odds ratio of 2.0 or more. Saito *et al*[67] also found an association between increased severity of periodontitis and increased serum resistin level both in bivariate (OR = 3.0; 95%CI: 1.2-7.6) and multivariate analyses (adjusted OR = 3.1; 95%CI: 1.1-8.6) analyses, and concluded that the increased levels of serum resistin in middle-aged women might affect their systemic health. After non-surgical periodontal treatment, the serum resistin level in periodontitis patients who have no underlying disease decreased to some extent[68]. Recently, periodontal treatment with antibiotics in type 2 diabetic patients was shown to result in no difference of serum resistin level compared to that of healthy counterparts[30]. However, this study was performed in only a small number of subjects (21 subjects) and all subjects were categorized into mild periodontitis. The effect of periodontal treatment on serum resistin needs to be more clearly elucidated in a larger sample.

***Visfatin***

Visfatin, a 52-kDa protein, is another adipokine secreted by adipocytes and mimics the effect of insulin[69]. This molecule was found to be enriched in visceral adipose tissue, which is the reason for its name. It was also known as pre-B-cell colony-enhancing factor (PBEF)[27] or nicotinamide phosphoribosyltransferase (Nampt)[70] PBEF or Nampt, with the gene located on chromosome 7 at q22.3[71]. Visfatin is essential for nicotinamide adenine dinucleotide biosynthesis and hence is related to cell metabolism. In humans, visfatin is mainly expressed in bone marrow (highest expression in leukocytes), liver and muscle cells. It is also expressed in various tissues, including heart, lung, kidney and placenta. Visfatin has 2 isoforms: intracellular and extracellular ones. The intracellular isoform mainly functions in energy production in cells, while the extracellular isoform is related to increased inflammatory cytokines, such as TNF-α, IL-1β, IL-16 and TGF-β1, and the chemokine receptor CCR3[72].

Visfatin has insulin-mimicking effects, for example, increasing glucose uptake and enhancing triglyceride biosynthesis, because it binds to the insulin receptor (IR), although at a different site from insulin[69]. In type 2 diabetic individuals, it was demonstrated that visfatin impaired vascular endothelial function as well as creatinine clearance[73], which probably leads to atherosclerosis and chronic kidney disease. Additionally, the visfatin level in this type of patient was found to be enhanced, which positively correlated with increased homocysteine, an endothelial dysfunction marker[74]. It seems that visfatin levels are positively associated with a series of inflammatory conditions, independently of other potential metabolic implications[75].

Research has mainly focused on the role of visfatin in cardiovascular diseases. As mentioned earlier, it was shown to induce inflammation of endothelial cells and vascular smooth muscle cells. It also induced TNF-α and IL-8 production from peripheral mononuclear cells[76]. Additionally, macrophage survival was promoted by visfatin[77]. Exogenous visfatin could stimulate inducible nitric oxide synthase (iNOS), which is a pro-inflammatory cytokine that contributes to endothelial dysfunction and vascular injury in diabetes-related vascular complications[78,79].

***Visfatin and periodontal treatment***

Because visfatin exerts pro-inflammatory functions in several organs, this molecule also correlates with chronic inflammation of periodontal tissue. In periodontitis, it was reported that visfatin concentration was increased in such patients and the more severe the periodontitis, the higher the level of visfatin observed in serum and gingival crevicular fluid (GCF)[80]. Another study was performed on an observational basis in healthy subjects, those with periodontitis without diabetes and those with periodontitis with diabetes; it was found that the mean visfatin in both serum and GCF was markedly increased in diabetic patients concurrently burdened by periodontitis[81]. The periodontal ligament cells (PDL) could produce visfatin and *Fusobacterium nucleatum*, one of the periodontopathic bacteria, enhanced the level of visfatin, which supports the assertion that bacteria exert an inflammatory bioburden on periodontal tissue. This effect could be reversed by biomechanical loading[82]. The effect of non-surgical periodontal treatment on serum and GCF visfatin level in periodontitis patients was reported by Raghavendra *et al*[83], who found that periodontal treatment given to periodontitis patients could decrease a high visfatin level in the active disease stage to a nearly normal level, as in periodontally healthy individuals both GCF (*P* < 0.001) and serum (*P* = 0.008). Although no study has yet been conducted on the effect of non-surgical periodontal treatment on the level of visfatin in periodontitis patient with diabetes, it seems that this molecule is associated with inflammatory conditions and can be used as an inflammatory marker or periodontal disease activity marker at both local and systemic levels.

***Adipsin***

Adipsin, also known as complement factor D, factor D and adipocyte trypsin, is one of the adipokines secreted by adipocytes into the bloodstream. The adipsin gene in humans is located at p13.3 on chromosome 19[84]. Adipsin belongs to the serine protease family and functions in cleavage of the bond between complement factor 3 and factor B[85]. Human adipsin is a 24-kDa molecule that stimulates acylation-stimulating protein and is then involved in the stimulation of glucose transport, enhancement of fatty acid re-esterification and facilitation of lipid lipolysis[86]. In humans, plasma levels of adipsin are not different or slightly increased in the obese population compared with the non-obese one[87,88], but this remains controversial. Recently, it has been demonstrated in vitro that high glucose promoted adipocyte-derived molecules including adipsin and resistin, but inhibited osteogenic differentiation in osteosarcoma (MG-63) cells[89]. Recently, adipsin level was increased and positively correlated with lung fibrosis (rho = 0.412, *P* < 0.001) and pleural plaque (r = 0.245, *P* = 0.043), in asbestos-exposed workers[90]. This suggested the role of adipsin in inflammation enhancement.

***Adipsin and periodontal treatment***

Concerning the role of adipsin in periodontitis, it was suggested that it exerted the same activity as *P. gingivalis*, resulting in the breakdown of periodontium[91]. The effect of periodontal treatment on the change of adipsin in human subjects has not been reported yet, but we hypothesize that this molecule might be decreased as a result of inflammatory reduction after periodontal therapy.

**PERSPECTIVES**

Adipokines are much more complex and involved in many systems, include immune and endocrine systems, and these molecules influence the pathogenesis of obesity-related diseases, particularly type 2 diabetes and cardiovascular diseases, as well as inflammatory diseases, especially periodontitis. A growing number of molecules have been identified to be secreted from adipocytes and more are yet to be discovered. Unravelling their orchestrated roles in controlling obesity, inflammation and periodontal health may lead to successful management of pathological conditions. Some markers, especially visfatin, are molecules that are closely related to inflammation, diabetic condition and periodontitis. With the recent development of sophisticated means to study molecules, we now aim to detect, analyze and make use of a number of molecules simultaneously to screen, explain and monitor the therapeutic outcome of disease conditions. This is due to no single molecule being able to reflect the nature of complex multifactorial diseases such as periodontitis and diabetes. Thus, the disease profile should be set as a template from several integrated adipokines, not only quantitatively for each molecule but also qualitatively. Here, single-nucleotide polymorphisms of each gene controlling these adipokines should be taken into account for periodontitis staging in diabetic patients and evaluating the disease response.

Not only data from serum but also data from non-invasive methods, for instance, analyses of gingival crevicular fluid and saliva, should be utilized as robust confirmation of local periodontal health. An ideal marker for periodontitis will not only demonstrate a clear relationship with periodontitis, but also be linked to systemic conditions that are influenced by periodontitis. To develop an adipokine candidate to use as a periodontal disease-specific biomarker or therapeutic compound, we also need to perform experiments mainly in human subjects to complete our understanding of the mechanism of such substances.

Robotic science has emerged as an important field in medicine. In the next century, in vitro robot-assisted synthesis of therapeutic molecules that combines the advantages of each adipokine will probably be launched on the market and make a major contribution to the treatment of severe periodontal breakdown, more effectively than contemporary therapeutic modalities. At that time, periodontitis in diabetic patients may no longer be a major oral health problem.

**CONCLUSION**

Current knowledge concerning the roles of major adipokines provides only a partial understanding of their associations with the pathogenesis of periodontitis in type 2 diabetes. This is probably due in part to the limited number of studies conducted on an acceptable number of human subjects. More studies regarding the effect of periodontal therapy on several adipokines should be performed. Nevertheless, we saw potential to develop visfatin as a tool for drug discovery and to generate more specific therapeutic targets. A novel cocktail of adipokine-related therapeutic strategies may offer opportunities for the successful management of periodontitis concomitant with diabetes.

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**Figure 1 Relationship between type 2 diabetes and periodontal disease (hypothesis).**

