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ORAL DISEASE AND NUTRITION (F NISHIMURA, SECTION EDITOR)

The Link Between Periodontal Inflammation and Obesity

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Abstract

Purpose of Review Obesity is a trigger for multiple diseases such as diabetes mellitus, hypertension, and cardiovascular diseases. Epidemiological studies have shown that obesity may be a risk factor for periodontal disease. Recently, there have been reports of presumed mechanisms of the associations between periodontitis and lipid metabolism or thermogenesis. This review aims to discuss the link between periodontal disease and energy regulatory function based on recent findings.

Recent Findings It has been demonstrated that activation of the C–C motif chemokine ligand/C–C chemokine receptor 7 pathway in adipose tissue induces inflammation and impairment of lipid metabolism and energy regulation in mice. *Porphyromonas gingivalis* administration has been shown to induce further weight gain and increased adipose tissue in diet-induced obese mice. Additionally, it has been reported that *Porphyromonas gingivalis*–induced endotoxemia potentially affect obesity by altering endocrine functions in brown adipose tissue in mice. Several cohort studies have shown that obesity is associated with tooth loss 5 years later, and periodontal conditions of obese individuals are significantly worse 2 and 6 months after the treatment compared with those of non-obese individuals. It has also been reported that body mass index is positively associated with the periodontal inflamed surface area index, a measure of periodontal inflammation. These results suggest that not only the enhancement of inflammation due to obesity but also the activation of inflammatory signaling may affect energy regulation.

Summary Loss of adipose tissue homeostasis induces increase and activation of immune cells in adipose tissue, leading to impaired immune function in obesity. Various cytokines and chemokines are secreted from obese adipose tissue and promote inflammatory signaling. Some of these signaling pathways have been suggested to affect energy regulation. The combination of obesity and periodontitis amplifies inflammation to levels that affect the whole body through the adipose tissue. Obesity, in turn, accelerates the exacerbation of periodontitis.

Keywords Periodontitis · Obesity · Inflammation · Energy metabolism

Introduction

Periodontal disease is a chronic inflammatory disease that is accompanied by periodontal tissue destruction. Low-grade inflammation, such as periodontal disease, affects glucose metabolism [1]. In a new classification of periodontal disease published by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) in 2018, diabetes mellitus (DM) was added as a risk factor for the progression of periodontal disease [2, 3]. Obesity is an important risk factor for type 2 (T2) DM, which accounts for 90% of DM cases, and the number of obese individuals is also increasing worldwide. In 2016, 39% of adults were overweight (25 kg/m^2 ≤ body mass index [BMI] < 30 kg/m^2) and 13% were obese (BMI ≥ 30 kg/m^2) [4]. Animals, including humans, can sustain life by storing excess energy in the form of fat and using it during starvation. This is an ingenious biological mechanism acquired during the course of a long evolution. However, excessive energy intake and lack of exercise induce obesity, leading to health threats. Epidemiological studies have shown that obesity may be a risk factor for periodontal disease [5]. Recently, associations between periodontitis and lipid

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metabolism or thermogenesis have been reported [6•]. This review aims to discuss the link between periodontal disease and energy regulatory function based on recent findings.

Energy Metabolism and Thermogenesis

Fat is not only taken directly from the diet, but also newly synthesized mainly in the liver and adipose tissue using excess energy. The fat obtained is stored in adipocytes. In obesity, adipocytes become hypertrophied, but when they can no longer be stored, fat is released as free fatty acid (FFA). Elevated blood FFA is taken up by skeletal muscle and liver and accumulates mainly as triglyceride, causing lipotoxicity [7]. Adipose tissue is roughly classified into white adipose tissue (WAT) and brown adipose tissue (BAT). White adipocytes store fat, while brown adipocytes are thermogenic adipocytes that play a role in maintaining body temperature and increasing basal metabolism in cold environments. In humans, brown adipocytes are abundant in newborns, but decrease after infancy. BAT activity in human adults is characterized by inducibility and reversibility [8]. In recent years, beige adipocytes that emerge in response to certain environmental cues, such as chronic cold exposure, have been found in WAT [9]; it has been shown that the tissue called BAT is composed primarily of beige adipocytes [10]. Thermogenesis in brown adipocytes and beige adipocytes occurs through the uncoupling of oxidative phosphorylation of mitochondrial uncoupling protein 1 (UCP1).

Biogenesis of beige adipocytes is induced in response to external stimuli, such as cold exposure, exercise, and treatment with β3-adrenoreceptor (β3-AR) agonists [11]. Adenosine monophosphate-activated protein kinase (AMPK) deletion in adipocytes results in cold intolerance and reduced thermogenesis in response to β3-AR stimulation [12]. AMPK activity in adipose tissue is diminished in humans and rodents with obesity and insulin resistance [13–16]. Activation of adipocyte AMPK improves obesity-induced insulin resistance [17]. AMPK also regulates mitochondrial biogenesis by activating peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) [18]. PGC1α is a critical transcriptional activator that regulates the number of genes involved in various metabolic pathways, such as fatty acid synthesis, oxidation, and gluconeogenesis. PGC1α stimulates UCP1 expression and increases the number of mitochondria and mitochondrial oxidative capacity [19, 20]. Suppression of adipose PGC1α results in systemic insulin resistance and obesity-associated inflammation [21]. Recently, ceramides and their metabolites, sphingolipids, have attracted attention as lipotoxic substances. Systemic and adipose tissue-specific inhibition of ceramide synthesis induces browning of subcutaneous WAT in obese mice [22]. M2 macrophages, known to enhance cold-induced thermogenesis [23], were increased in adipose tissue due to the inhibition of ceramide synthesis [22].

Inflammation and Energy Metabolism in Adipose Tissue

Adipocytes secrete multiple biologically active molecules, such as hormones and cytokines (known as adipokines). Normal adipocytes secrete anti-inflammatory adipokines to attenuate inflammation and play essential roles in the control of whole-body metabolism [24, 25]. The pathophysiological features of obesity include adipose tissue inflammation and infiltration of activated immune cells, such as macrophages [24]. Abnormal adipokine secretion is observed in hypertrophied adipocytes [24, 25]. Infiltration of immune cells such as macrophages is enhanced in obese adipose tissue, and the interaction with adipocytes promotes abnormal secretion of adipokines [24]. The coronavirus disease 2019 (COVID-19) pandemic has provided an opportunity for widespread public awareness that infectious diseases are more likely to become severe in metabolic disorders such as obesity. In obesity, the lack of adipose tissue homeostasis increases and activates immune cells in adipose tissue and promotes the production of inflammatory cytokines and chemokines [26–29]. It has also been suggested that such changes in immune cell response impair cell-mediated immune function, leading to enhanced activation of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome and increased susceptibility to infection [30].

Intake of a high-fat diet (HFD) changes the gut microbiota, which induces endotoxemia followed by chronic inflammation in various tissues, including adipose tissue [31–33]. Changes in the composition and number of gut microbiota lead to an increase in toll-like receptor 4 (TLR4) ligands that flow into the liver via the portal vein [34], which has been suggested to be relevant to multiple diseases such as obesity, cardiovascular disease, inflammatory disease, and diabetes [32]. We hypothesized that lipopolysaccharide (LPS) from the gut microbiota activates monocytes in the portal vein and accumulates in the adipose tissue. A comprehensive analysis of the gene expression in adipocytes co-cultured with macrophages stimulated with low concentrations of LPS was performed to examine the factors involved in chronic inflammation of adipose tissue. As a result, it was observed that co-cultured adipocytes promoted the expression of genes such as LPS-binding protein (LBP) and CD14, which are required for the action of LPS [35]. In the culture medium of the co-culture system, a marked increase in the secretion of proteins such as LBP, soluble CD14, C–C motif chemokine ligand 5 (CCL5), and serum amyloid A (SAA) was observed compared with those of adipocytes and macrophages individually cultured or without LPS stimulation. In addition,

the amount of interleukin 6 (IL6) produced from adipocytes increased significantly via macrophage-derived tumor necrosis factorα (TNFα) [36, 37], suggesting the induction of acute phase proteins such as C-reactive protein (CRP) and SAA [38]. SAA induces IL6 production in dendritic cells and promotes T helper 17 (Th17) cell differentiation [39]. Th17 cells secrete inflammatory cytokines, such as IL17, and have been suggested to be involved in periodontal disease [40, 41].

Based on the results of the adipocyte-macrophage co-culture system, it has been suggested that IL17 promotes Th17 cell infiltration through increased CCL20 production in adipose tissue in a chronically inflamed state, thereby exacerbating inflammation [42]. A comprehensive analysis of the gene expression in adipocytes co-cultured with macrophages showed a marked increase in gene expression of many CC chemokines, such as monocyte chemoattractant protein (MCP1), CCL5, and CXC chemokines, in adipocytes. Among them, CCL19 contributes to the attraction of dendritic cells and T cells. Serum CCL19 levels were markedly increased in both hereditary (ob/ob) and diet-induced obese mice. Therefore, we investigated the effects on inflammation and metabolism in mice lacking the CCL19 receptor, CC chemokine receptor 7 (CCR7) gene. Compared with wild-type mice, *Ccr7*$^{-/-}$ mice showed an increase in UCP1 expression in BAT, high rectal temperature during cold stimulation, and a significant increase in thermogenesis. In addition, they were resistant to HFD-induced obesity, adipose tissue and liver inflammation, fatty liver, and dyslipidemia, and insulin response and glucose tolerance were maintained normally [43]. Subsequently, for further investigation of the effects of CCL19/CCR7 axis, adipocyte-specific *Ccl19* knock-in (KI) mice were generated. *Ccl19* KI mice demonstrated that activation of the CCL19/CCR7 pathway in adipose tissue induced inflammation and that adipocyte CCL19 inhibited AMPKα by activating extracellular signal-regulated kinase 1/2 (ERK1/2), resulting in impaired lipid metabolism and energy regulation (Fig. 1). In addition, a 40% HFD enhanced these pathological changes and induced insulin resistance and weight gain [44•].

López-Cotarelo et al. reported that MEK1/2/ERK1/2 signaling induced by CCR7 ligands had an inhibitory effect on AMPK activity in human mature dendritic cells. In their experiments, both CCL19 and CCL21 were used as CCR7 ligands [45]. Our results of a comprehensive analysis of the gene expression in adipocytes co-cultured with macrophages showed a marked increase in *Ccl19* gene, but not in *Ccl21* gene. The expression level of *Ccl19* was one of the highest of the expression of all chemokines produced from adipocytes. Epidemiological studies have shown that serum CCL19 levels are elevated in individuals with obesity [46]. Furthermore, it has also been reported that adipose tissue CCL19

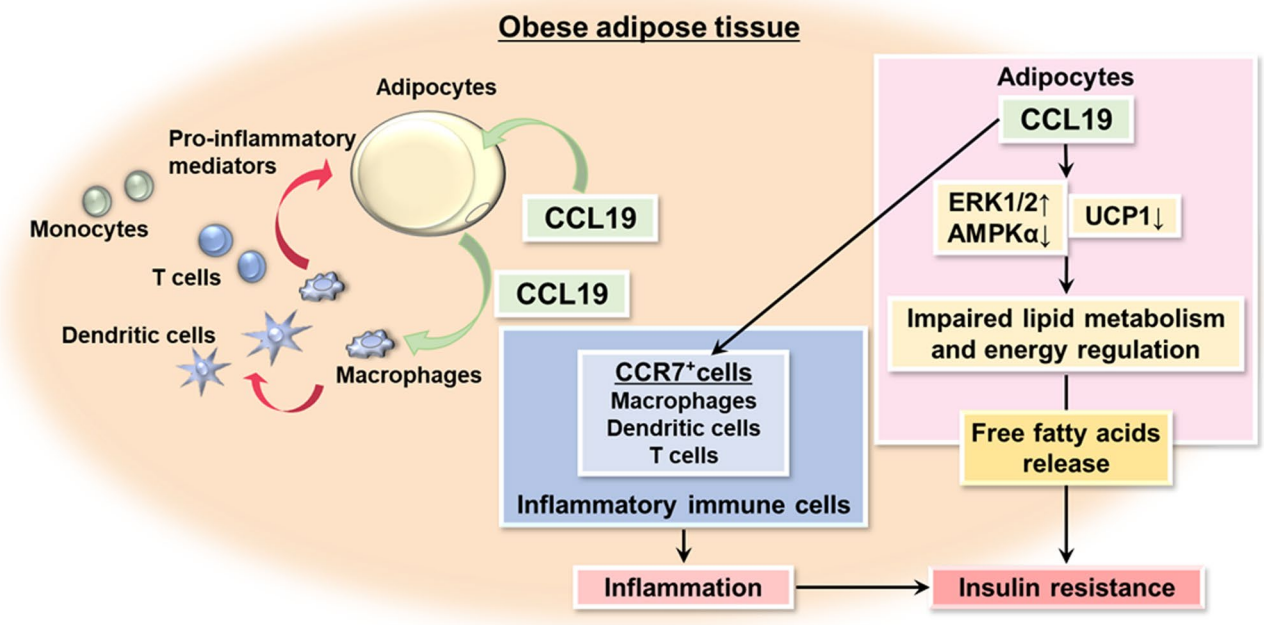

Fig. 1 Possible mechanisms of influences of the CCL19/CCR7 pathway in obese adipose tissue. Activation of the CCL19/CCR7 pathway induces inflammation and that adipocyte CCL19 inhibits AMPKα by activating ERK1/2, resulting in impaired lipid metabolism and energy regulation. The enhancement of these pathological changes induces insulin resistance

expression correlates with BMI, HbA1c, CRP, homeostasis model assessment of insulin resistance (HOMA-IR), IL12, and CCL5 [47]. A previous report exists regarding the down-regulation of AMPKα through the activation of ERK1/2 in muscle cells. Hwang et al. demonstrated that endoplasmic reticulum stress induced by thapsigargin and tunicamycin increased the phosphorylation of ERK1/2 and suppressed AMPKα activation in muscle cells [48]. Several publications have also shown that ERK1/2 activation is promoted in adipose tissues of humans and mouse models with obesity and diabetes and in 3T3-L1 adipocytes treated with TNFα or insulin [49–51]. However, the relationship between ERK and AMPK was not examined in these studies.

As shown in these results, various cytokines and chemokines are secreted from obese adipose tissue, promoting inflammatory signaling. Some of these signaling pathways have been suggested to affect energy regulation.

Association of Periodontal inflammation and Obesity

In periodontal disease, fimbriae, endotoxin, and proteases, which are the main virulence factors of periodontal pathogens, act on monocytes, macrophages, and gingival fibroblasts in the periodontal tissue. These cells induce an inflammatory response in the periodontal tissue via inflammatory mediators, such as IL1β, TNFα, prostaglandin E2 (PGE2), and matrix metalloproteinases (MMPs), and tissue destruction progresses. This chronic periodontal inflammatory reaction leads to leakage of host- and microbial-derived factors into the bloodstream. Once in the systemic circulation, these factors could contribute to the pathophysiology of systemic diseases, either directly or indirectly [52]. Multiple studies have shown the presence of periodontal bacteria in atherosclerotic coronary arteries [53–55]. Non-hematogenous dissemination of periodontal bacteria has also been suggested. Swallowed periodontal bacteria may translocate via the oro-digestive route and colonize ectopically in the gut. Periodontal bacteria have been detected in the gut of patients with inflammatory bowel disease [56, 57]. Although the presence of periodontal bacteria in extra-oral tissues may be transient, the release of virulence factors like endotoxin and toxic proteases [58, 59], or inflammatory mediators, can be important, given the chronicity of periodontitis and the frequency of bacteremia. In fact, serum levels of TNFα are elevated in patients with periodontitis [60, 61].

Our previous study demonstrated that administration of low-concentration LPS (1 ng/mL/g body weight) significantly upregulated the serum levels of LBP, CCL5, and SAA in hereditary obese (ob/ob) mice and diet-induced obese mice compared with those in the control group (ob/+ mice and normal diet-fed mice) [38]. This result suggests that local inflammation, such as periodontitis, is more likely to have a systemic effect in obese patients than in non-obese patients. As mentioned earlier, immune cells are activated in the obese adipose tissue. Also, some of the immune cells activated by bacterial products or host inflammatory factors may migrate to the adipose tissue via the circulation. In the combination of obesity and periodontitis, local inflammation is inferred to be amplified to levels that affect the whole body through adipose tissue. Thus, obesity may exacerbate periodontal disease.

Several recent animal model studies have demonstrated the relationship between the exacerbation of periodontitis and obesity. Saturated fatty acids induce inflammation and promote alveolar bone resorption in mice [62, 63]. In obese rats, it has been shown that protein kinase C (PKC) activation and oxidative stress may induce insulin resistance in gingiva leading to periodontal disease progression [64]. Furthermore, caloric restriction has been reported to prevent alveolar bone loss in experimental periodontitis in obese rats [65]. Sato et al. reported that HFD-induced changes in the gut microbiota exacerbated alveolar bone resorption via uric acid elevation [66]. Other researchers have reported that *Porphyromonas gingivalis* (*P. gingivalis*) administration induced further weight gain and increased adipose tissue in diet-induced obese mice [68]. Furthermore, it is also indicated the possibility that *P. gingivalis*–induced endotoxemia potentially affects obesity by altering endocrine functions in BAT [6•]. These results suggest that not only exacerbation of inflammation due to obesity but also activation of inflammatory signaling may affect energy regulation. It should be noted that administration of a single periodontal pathogen or endotoxin to animals, as in these animal studies, does not exactly reproduce human periodontitis associated with multiple pathogens [62, 63]. In addition, care must be taken in interpreting the results depending on the method and period of administration, strains, and bacterial species [6•, 66, 69]. Considering that the microbiota changes with oral and intravenous administration of *P. gingivalis* [66, 70, 67•], the indirect effect of *P. gingivalis* can also be said to be large. Further clarifying the mechanism of the relation between periodontal disease and obesity may reveal new and effective treatment strategies that will contribute to the improvement of periodontitis and obesity-related diseases in the future.

Clinical Studies on the Association of Periodontitis and Obesity

Several cohort and intervention studies related to obesity and periodontitis have been conducted. Recent cohort studies indicated that obesity is a risk factor for tooth loss [71] and that obesity is associated with worse mean probing pocket depth following periodontal therapy [72•]. Several reports

have investigated the association between the degree of obesity and systemic effects of periodontal inflammation. Munenaga et al. reported that Japanese patients with T2DM accompanied by severe periodontal disease and BMI around 25 kg/m^2 showed slightly increased systemic inflammation as assessed by high-sensitivity (hs)-CRP (hs-CRP levels over 500 ng/mL). In contrast, subjects with low hs-CRP levels (< 500 ng/mL) were characterized by a significantly lower BMI (approximately 23 kg/m^2) than that in the group with hs-CRP levels ≥ 500 ng/mL [73]. Other researchers have suggested that periodontal disease has a significant impact on systemic inflammation in patients with normal BMI, but not in patients with a BMI of around 35 kg/m^2 [74]. These studies suggest that systemic influences of local inflammation may be enhanced by mild obesity but largely masked by severe obesity. Therefore, it is considered that whether the systemic effects due to local inflammation, such as periodontal disease, manifest or not depends on the degree of obesity.

In recent years, clinical studies have been performed using the data of periodontal inflamed surface area (PISA), which is a measure of the amount of inflamed periodontal tissue. PISA is a quantified value of the surface area of the bleeding pocket epithelium [75, 76]. As the correlation between PISA and glycated hemoglobin (HbA1c) has been reported [76–78], it can be said to be an index for understanding the degree of systemic influence due to local periodontal inflammation. Recently, it has been reported that BMI is positively associated with PISA [79]. On the other hand, Takeda et al. reported that PISA in T2DM patients was not related to obesity parameters [77]. However, it is necessary to establish a larger control group to evaluate the relationship between PISA and obesity. Other researchers also reported that although obesity is not an independent risk factor for the progression of periodontitis, obesity and periodontitis have many common risk factors for each progression [80]. At present, there is limited clinical evidence on the association between periodontal disease and overweight/obesity. Further studies are required to clarify this association.

Conclusions

Loss of adipose tissue homeostasis induces increase and activation of immune cells in adipose tissue, leading to impairment of immune function in obesity. Various cytokines and chemokines are secreted from obese adipose tissue, promoting inflammatory signaling. Some of these signaling pathways may affect energy regulation. The combination of obesity and periodontitis amplifies inflammation to levels that affect the whole body through the adipose tissue. Obesity, in turn, accelerates the exacerbation of periodontitis.

Further understanding of the link between periodontal disease and energy metabolism disorders is expected to lead to new and more effective therapeutic strategies for both diseases. Obesity is a risk factor for many diseases, including DM, hypertension, and cardiovascular disease. Therefore, improving periodontitis and controlling body weight can contribute significantly to the maintenance of health and future life.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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