Periodontitis Affects Skeletal Muscle Metabolism Through an Increase in Proinflammatory Cytokines

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Abstract

Periodontitis is an inflammatory disease of the oral cavity which attacks the gingival and periodontal tissue. One of the results of immune response activity in periodontitis is an increase in proinflammatory cytokines both locally and systematically. An increase in proinflammatory cytokines will affect tissue metabolism, including skeletal muscle tissue. The mechanism of periodontitis in affecting skeletal muscle is still being discussed and studied, this review will discuss the mechanism of periodontitis in affecting skeletal muscle metabolism. The interaction between bacteria and the immune system in periodontal tissues will activate the immune system and can cause an increase in proinflammatory cytokines such as IL-6, IL-1β, and TNF-α both locally and systemically. The presence of bacteria in the body's circulation and an enhancement of proinflammatory cytokines systemically can affect other tissues in the body, one of which is skeletal muscle. Several researchers have proven that periodontitis affects the regeneration process, glucose uptake, and recovery in skeletal muscle. An increase in IL-6, IL-1β, and TNF-α caused by periodontitis can reduce the process of muscle regeneration, reduce glucose uptake in skeletal muscle, and decreases the level of muscle responsiveness to training loads.

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Introduction

Periodontitis is an inflammatory disease characterized by inflammation of the soft tissues and the periodontal ligament and also alveolar bone damage.[1] Periodontal disease is mainly caused by infection from gram-negative bacteria such as *Porphyromonas gingivalis* (*P.gingivalis*).[2] Inflammation will triggered by the interaction between these bacteria and the host's immune systems, causing damage to collagen tissue as one of the tooth supporting tissue structures. [3,4] The process of recognizing bacterial components by the host immune system in the periodontal tissue will cause various immune cells to be activated in the inflamed area.[5] This causes an increase in the production of inflammatory mediators, such as chemokines, ROS, and proinflammatory cytokines where they can be the sign of disease progression level.[6,7,8,9] The activation of inflammatory mediators in periodontitis has a significant effect on the host response to systemic inflammation.[8] There are several cytokines such as IL-6, IL-1, IL-8, and TNF-α, prostaglandins, and MMP produced from periodontitis.[10,11] Bacteria and cytokines in periodontal tissues can enter the body's systemic circulation and cause a response from several tissues.[12,13,14] A study conducted in a systematic review has proven that periodontitis can affect physical fitness through its effects on muscles.[15] The increased level of cytokines can cause muscle wasting.[16] Proinflammatory cytokines such as IL-6, IL-1β, and TNF-α can trigger muscle damage.[17,18]

The anabolism and catabolism processes

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are such important factors that they can maintain muscle mass. Anabolic factors consist of physical and chemical factors, while catabolic factors consist of muscle that is rarely used, oxidative stress, proinflammatory cytokines, acidosis, and glucocorticoid hormones.[19] Structural changes such as a decrease in muscle mass and fiber can cause muscle weakness, reducing the muscles strength and endurance.[20,21] Immunological factors such as cytokines and myeloid cells also influence muscle metabolism. An increase in proinflammatory cytokines can cause an increase of lysis in muscle fibers and affect the process of differentiation of muscle cells.[22]

Until now, the mechanism of periodontitis in influencing muscle metabolism has not been thoroughly explained. The purpose of this article is to review the effect of periodontitis on the regeneration process, glucose uptake, and muscle recovery process seen from the aspect of increasing proinflammatory cytokines.

Review

In periodontitis, there is an increased level of IL-6 and TNF-α cytokines. The plasma levels of IL-6 and TNF-α are higher in people with periodontitis than people without it.[23,24] The increased levels of IL-6 experienced by patients with periodontitis occur in both plasma and saliva.[25] A study on experimented animals showed that rats induced by periodontitis using *P. gingivalis* bacteria experienced an enhancement in serum concentration of the proinflammatory cytokine IL-6 on day 15 which indicated a association between serum IL-6 levels and disease activity in periodontitis.[26] In periodontitis, there is also an increase in IL-1β, which can be detected through the gingival cervicular fluid (GCF) and saliva, periodontitis patients show higher IL-1β concentrations than people without it.[27,28] A study on an experimented rat in periodontitis model induced by *P.gingivalis* showed an increase in serum IL-1β.[26] This suggests that periodontitis can cause a systemic increase in IL-1β. In addition to IL-6 and IL-1β, there is also an increase in TNF-α concentration in patients with periodontitis. The study showed the results of an enhancement in TNF-α levels in the saliva of periodontitis patients.[29] An increase in TNF-α concentration also occurs in the serum of patients with periodontitis.[30]

There was a relationship between *P.gingivalis*-induced on experimented animals and sarcopenia.[31] The animals induced by *P.gingivalis* using doses adjusted to systemic *P.gingivalis* levels in periodontitis patients resulted in a decrease in skeletal muscle mass, especially in fast-type skeletal muscle.[31] A study by Visser *et al.* proved that there was a reduce in muscle mass and strength as IL-6 and TNF-α concentration increased.[32] Meanwhile, another study conducted by Sullivan indicates that IL-1β plays a role in suppressing myoblast fusion to become muscle fibers, resulting in a decrease in muscle regeneration.[33]

P.gingivalis bacterial infection in periodontal tissue can reduce skeletal muscle glucose uptake.[34] There is a possibility that the decrease in skeletal muscle glucose uptake due to periodontitis is caused by an increase in the IL-6 cytokine in response to an increase in the amount of bacteria. A study in experimental animals has proven that chronic exposure to IL-6 can cause insulin resistance by decreasing the translocation process from glucose transporter type 4 (GLUT4) to muscle cell membranes. The GLUT4 is needed when taking glucose from the blood circulation which then will be used as a source of energy formation for the muscles to contract and relax.[35,36]

The study conducted by De Souza *et al*. proved that periodontitis can affect the recovery process in rats' skeletal muscles which is given a treadmill exercise. Periodontal disease is able to change the leukocyte count and systemic interleukin levels so that it will contribute to the training load and have an indirect effect on muscle catabolism.[37]

Systemic increase in chronic proinflammatory cytokines can cause skeletal muscle atrophy.[38] Periodontitis induces an increase in TNF-α and IL-6 but in rats which were given treadmill exercise and induced periodontitis did not change the concentration of these cytokines.[37] This suggests that periodontitis may indirectly impair muscle responsiveness to training loads due to the presence of local TNF-α. The presence of an increase in local TNF-α triggers the catabolism process in muscle fibers in response to training loads, and this effect is very visible in type 2 muscle fibers because the gastrocnemius muscle shows a decrease in fiber hypertrophy in rats given training loads and induced periodontitis.[37]

Discussion

An Increase in Proinflammatory Cytokines in Periodontitis

In periodontitis, the process of recognizing the bacterial cell wall is carried out by Toll-like Receptors (TLRs).[39] Toll-like Receptor 4 is the main receptor for the LPS signaling process.[40] Lipopolysaccharide (LPS) which binds to TLR4 in gingival fibroblasts activates several second messengers and NF-B which play a role in the expression of inflammatory cytokines including IL-6.[40,41] Meanwhile, the increase in IL-1β production is triggered by the interaction between the host and microbiota and is widely induced by the expansion and activation of Th1 and Th2 cells.[42] LPS from bacteria will induce monocytes and macrophages to produce TNF-α and IL-1β.[43] Oral *poly morphonuclear leukocytes* (PMN) have mRNA for both TNF-α and IL-1β which are able to produce both types of cytokines in sufficient quantities without stimulation.[44,45]

Periodontitis - Skeletal muscle regeneration process

Interleukin-6 and IL-1β can affect the process of muscle regeneration through their action on IGF-1. In sufficiently low concentrations, IL-1β can suppress protein synthesis, myogenin expression and myoblast differentiation significantly. This will inhibit the work of IGF-1 in muscle to increase protein synthesis.[46] A study conducted by Li (2009) using rats proved that exposure to IL-1β for 2 days can reduce myotube width by 13%. In addition, there was a decrease in actin synthesis by 13% to 14%.[47] Interleukin 1β is able to inhibit Growth Hormone (GH) responses to the Serine protease inhibitor 2.1 (Spi 2.1). At 10 ng/ml, IL-1β has been shown to inhibit GH from expressing IGF-1 and Spi 2.1 mRNA in hepatocyte cultures.[48,49] A study by Bergad *et al.* even showed that at lower concentrations, ie 0.25 or 0.5 ng/ml, IL-1β could inhibit the expression of Spi 2.1 mRNA and its activity.[50] Growth hormone stimulation of IGF-1 and Spi 2.1 mRNA was inhibited by IL-1 by suppressing the JAK2/STAT5 pathway.[51] There was a decrease in the activation ability of STAT 5 which was phosphorylated and bound to DNA.[52] The target of IL-1 inhibition on STAT5 is histone acetyl transferase which plays a role in chromatin remodeling and it is a coactivator for the regulation of transcriptional activity of STATs.[53]

Interleukin-6 can cause a decrease in circulating IGF-1 while the production of IGF-1 in the liver and the number of acid-labeled subunits in the serum do not change, but the circulating levels of IGFBP-3 decrease along with the increase in proteolysis.[54] The binding between IGF-1 and its receptor will trigger phosphoinositide-3-kinase (P13-K) to produce hosphatidylinositol (4,5)-biphosphate (PIP2) which in turn stimulates the production of hosphatidylinositol 3,4,5-triphosphate (PIP3).[55,56,57] Hosphatidylinositol 3,4,5-triphosphate will bind to phosphoinositide-dependent kinase-1 (PDK1) which will then bind to the plextrin homology (PH) domain of Akt.[55,57] Akt activates mammalian target of rapamycin (mTOR).[57] The phosphorylation process of mTORC1 in mTOR^{2448} and mTOR^{2481} will cause muscle protein synthesis.[58,59] Therefore, a decrease in IGF-1 in the systemic circulation caused by an increase in IL-6 will inhibit muscle protein synthesis.

Several studies have shown that TNF-α triggers the breakdown of myosin heavy chain protein (MHCP).[60,61,62] Exposure to TNF-α for a long time can cause inhibition of cell differentiation and muscle regeneration.[63] Studies in muscle cells owned by humans, pigs and rats have shown that exposure to TNF-α and IL-1β prevents IGF-1 from stimulating protein synthesis.[64,65]

Periodontitis - Skeletal muscle glucose uptake

Chronic exposure to IL-6 attenuates insulin stimulation of glucose uptake and GLUT4 translocation at C2C12 and neonatal myotubes. Insulin activity in stimulating IRS-1 and AKT phosphorylation was inhibited by IL-6. The absence of AMPK and AS160 phosphorylation further highlights the negative effects of insulin signaling due to chronic IL-6 exposure.[66,67]

Insulin can increase glucose transport to peripheral tissues including muscle by increasing translocation of GLUT4 from intracellular to plasma membrane where this process is mediated by activation of PI3K, protein kinase B (AKT), and several isoforms of protein kinase C.[68] Skeletal muscle has a mechanism to increase glucose transport by activating AMPK which can be triggered in conditions of hypoxia, ischemia, or exercise, and it is an insulin independent mechanism.[69] AKT substrate 160 (AS160) is a 160 kDa protein which is an effector

for glucose transport and triggers GLUT4 translocation.[70] Interleukin-6 increases glucose uptake by activating the serine/threonine protein kinase 11 (LKB1)/AMP-activated protein kinase/protein kinase B pathway substrate of 160 kDa (AS160). The opposite effect occurred when miotube and rat experimental animals were exposed to IL-6 for a long (chronic) period where IL-6 decreased GLUT4 translocation to the plasma membrane, resulting in a decrease in insulin signaling on insulin receptor substrate (IRS-1). The three mechanisms involved include: activation of c-jun NH2-terminal kinase (JAK1/2), accumulation of suppressor of cytokine signaling 3 (SOCS3) mRNA, and increased activity of PTP1B.[35]

Periodontitis - Skeletal muscle recovery

When inflammation occurs in which TNF-α increases systemically, the skeletal muscle sarcolemma can function as receptors for TNF-α.[71,72] TNF-α can activate NF-κB which is a transcription factor and activation of NF-κB causing the degradation of skeletal muscle protein.[73,74] Nuclear Factor Kappa Beta is in the form of inactive homodimer or heterodimer complexes in the cell cytoplasm, when activated by cytokines, NF-κB dimers will translocate to the nucleus and increase the expression of several genes encoding proteins, including proteins that trigger muscle atrophy.[75]

The effect of muscle damage by TNF can occur through the activation of Janus Kinase. The activated Janus Kinase can inhibit the expression of IGF-1 mRNA, during inflammation and increase in cytokine IGF-1 signaling mechanisms and the interaction between TNF and IGF-1 can cause muscular dystrophy.[64]

TNF-α which binds to its receptor will activate JAK which then, as a signaling molecule, will inhibit the activation of Insulin Receptor Substrate 1 (IRS-1). Inhibited IRS-1 will not be able to activate Akt, causing inhibition of the muscle protein synthesis process.[76]

Conclusions

An increase in cytokines IL-6, IL-1β, and TNF-α in periodontitis can reduce the process of muscle regeneration by affecting the activity of IGF-1. IL-6 can decrease IGF-1 levels in the systemic circulation and IL-1β can reduce the ability of hepatocyte cells to express IGF-1. IL-1β and TNF-α are able to prevent IGF-1 from stimulating muscle protein synthesis. In addition, IL-6 can also reduce glucose uptake in skeletal muscle where the glucose is needed as a source of contraction for muscles. Periodontitis also indirectly affects the process of muscle recovery if given a training load, in which the effect is thought to be through TNF-α which reduces the level of muscle responsiveness to training loads.

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Declaration of Interest

The authors report no conflict of interest.

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