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Interrelationship between Periapical Lesion and Systemic Metabolic Disorders

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Abstract

Periapical periodontitis, also known as periapical lesion, is a common dental disease, along with periodontitis (gum disease). Periapical periodontitis is a chronic inflammatory disease, caused by endodontic infection, and its development is regulated by the host immune/inflammatory response. Metabolic disorders, which are largely dependent on life style such as eating habits, have been interpreted as a “metabolically-triggered” low-grade systemic inflammation and may interact with periapical periodontitis by triggering immune modulation. The host immune system is therefore considered the common fundamental mechanism of both disease conditions. An elevated inflammatory state caused by metabolic disorders can impact the clinical outcome of periapical lesions and interfere with wound healing after endodontic treatment. Although additional well-designed clinical studies are needed, periapical lesions appear to affect insulin sensitivity and exacerbate non-alcoholic steatohepatitis. Immune regulatory cytokines produced by various cell types, including immune cells and adipose tissue, play an important role in this interrelationship.

Keywords

periapical lesion; metabolic disorders; type 2 diabetes; hypertension; NAFLD; cytokines; inflammation; immunity

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1. Introduction

Infections of the dental pulp occur as sequelae of caries, unsuccessful operative dental procedures, and trauma. The pulpal infection is a polymicrobial infection, with predominantly gram-negative anaerobes. Once bacteria invade and colonize the dentin, their removal is very difficult. Although pulpal infection initiates an immune response in the dental pulp, the immune response is insufficient in eradicating the pathogens, because immune cells and molecules cannot reach into the dentin effectively. In addition, the dental pulp is uniquely situated in a low-compliance environment surrounded by dentin and lacks a collateral vascular supply. The dental pulp receives its blood supply from blood vessels entering/exiting through periapical foramen or foraminae. If the pulpal vascular system becomes dysfunctional, the pulpal infection typically progresses to cause total pulpal necrosis and infected root canal (endodontic infection).

The infected root canal is a persistent source of bacterial pathogens, which secondarily stimulate an immune/inflammatory response in the area surrounding the dental root apex, the so-called “periapical” region. Endodontic infection-induced inflammatory response is therefore commonly referred to as a periapical lesion, apical periodontitis, or periapical periodontitis. Characteristic features of the periapical lesion are bone resorption and subsequent incomplete wound healing (typically granulomatous tissue formation) in the periapical region. The periapical lesion is an unpleasant outcome of a protective response to the bacteria derived from the infected root canal system, resulting in a chronic inflammation.

If appropriate endodontic treatment is not provided, the infected root canal becomes an indissoluble source of bacteria, similar to deep periodontal pockets in periodontitis. In the early and middle 1900s, the focal infection theory was suggested periapical lesion as a cause in cases where considerable systemic conditions and dental infections occur in the same patient. According to the focal infection theory, microorganisms inhabiting the oral cavity cause infection and inflammation in different locations of the host via three potential mechanisms: 1. Metastatic infection due to transient bacteremia; 2. Metastatic inflammation due to immunological injury; and 3. Metastatic injury due to microbial toxins [1]. An example of the focal infection theory is palmoplantar pustulosis (PPP) caused by oral infections. In Asian patients (but not in worldwide populations), a causal relationship between PPP and oral/dental infection was demonstrated [2-7], and tonsillectomy and dental treatments are common measures for treatment of PPP [3, 8].

To date, the strong correlation between oral infections and systemic conditions, including cardiovascular disease, diabetes mellitus, and preterm low birth weight, was suggested in various studies [1, 9-14]. The focal infection theory seems to be attractive as the mechanism of these correlations. However, in 2012, the American Heart Association stated that past observational studies support only an association, not a *causal* relationship, between periodontal disease and atherosclerotic vascular disease [15]. In the same year, the American Association of Endodontists also released a statement that there is no valid, scientific evidence causally linking endodontically treated teeth and systemic diseases [16]. Collectively, the clinical association between oral infections and such systemic conditions

may depend on common risk factors such as insulin resistance and dysregulation of biological functions, including immune response, rather than on the focal infection theory.

Metabolic syndrome is a cluster of conditions, including increased blood pressure, a high blood glucose level, excess visceral fat accumulation, and abnormal cholesterol levels, occurring together in the same person. Metabolic syndrome is also a critical risk factor for cardiovascular diseases and type 2 diabetes. The clinical relationship between periodontal disease and cardiovascular diseases and/or type 2 diabetes is well-documented elsewhere [17-20] while there is limited available information about periapical lesions. This difference is probably in part due to the natural and clinical history of periapical lesions. Periodontitis is a silent disease and is highly prevalent in middle- to elderly-age populations [21]. Similarly, 63% of adult cases of diabetes (age range 18–79 years) are diagnosed between the ages of 40 and 64 years [22]. In contrast, dental caries, which is the primary cause of endodontic diseases, is prevalent in much younger ages compared to the age at diagnosis/presence of cardiovascular disease and type 2 diabetes. According to the Center for Disease Control and Prevention (CDC), 82.1% of U.S. adults aged 20-34 have already experienced dental caries [23]. Unlike periodontitis, some phases in dental caries and subsequent pulpitis are very symptomatic and often painful. About 56% of all non-traumatic dental emergencies are associated with periapical abscesses and toothaches [24]. These acute phases may increase the chance of therapeutic intervention even in lower-income populations [25-29]. Therefore, instead of discussing the frequency of coincident occurrence, considerations regarding how metabolic disorders affect established periapical lesions, or vice versa, will be more practical for the focus of this article.

It is now widely accepted that low-grade systemic inflammation causally links to the development of metabolic disorders and their complications [30]. Systemic inflammation associated with metabolic disorders is metabolically triggered inflammation. For instance, nutrients (*e.g.* fatty acids)-stimulated proinflammatory mediators such as TNF (tumor necrosis factor)- α in adipose tissue deteriorate insulin resistance, type 2 diabetes, fatty liver disease, atherosclerosis, hypertension, and stroke [30]. In contrast, the periapical lesion is an infection-stimulated chronic inflammation. The host immune system is the key element in these inflammatory responses. Metabolic disorders and dental infections in all likelihood share common fundamental mechanisms in the development of the chronic inflammatory state: *e.g.* the function of macrophages and macrophage-derived mediators are well-investigated in both metabolically triggered and infection-stimulated inflammation. In this review article, we mainly focus on the interrelationship between periapical lesions and metabolic disorders including type 2 diabetes mellitus, hypertension, and non-alcoholic fatty liver diseases (NAFLD), and their common pathological background in immunology/osteimmunology and cytokine biology.

2. Periapical lesion and type 2 diabetes mellitus

Diabetes mellitus is one of the most common metabolic disorders, affecting 387 million people of all ages in 2014 [31]. Diabetes mellitus is defined as a group of metabolic disorders characterized by chronic hyperglycemia with disturbances in carbohydrates, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both

[32, 33]. The disease is frequently associated with an increased susceptibility to infection, impaired wound healing, and increased morbidity and mortality associated with disease progression [34]. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs: eyes, kidneys, nerves, heart, and blood vessels. [35]. Similar to the periodontium, the dentin-pulp complex is also affected by diabetes mellitus.

To date, systematic investigation of the effect of diabetes mellitus on the structure of dental pulp has not been reported. However, Russell reported that angiopathy represented by a thickened basement membrane was observed in the dental pulp of diabetics [36]. According to previous studies focusing on the periodontium, an increase in basement membrane, thickening of the capillaries, and endothelial dysfunction are due to impaired nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, superoxide production, and protein kinase C signaling in diabetics vs. non-diabetics [37, 38].

Diabetes mellitus inhibits collagen fibril formation and also interferes with collagen cross-linking and may impair degradation of matrix proteins and subsequent tissue remodeling [39], leading to poor wound healing in diabetics [40]. Poor wound healing is similar in diabetic dental pulp, too. In a rat model of direct pulp capping using MTA (mineral trioxide aggregate), diabetic rats exhibited lower formation of MTA-induced restorative dentin bridge and elevated pulpal inflammation compared to non-diabetic animals with statistical significance [41].

Leptin receptor deficient diabetic (db/db) mice, fed a standard laboratory rodent diet and tap water ad libitum for 50 weeks, exhibited higher incidence of naturally occurring dental caries and subsequent periapical lesion compared to non-diabetic db/+ mice ($p<0.01$ and $p<0.001$, respectively) [42]. In addition, there was a trend in elevated severity of dental caries and periapical inflammation in db/db mice [42]. The susceptibility of leptin deficient (ob/ob) mice to periapical lesion is unknown. GK (Goto-Kakizaki) rats, a model for spontaneous non-insulin-dependent diabetes, fed a regular rodent diet and 30% sucrose solution ad libitum, exhibited significantly enlarged periapical lesions in weeks 2 and 4 post pulp exposure compared to groups of GK rats fed the regular diet and tap water and non-diabetic Wistar rats treated with the same diet regimens ($p<0.01$ in each observation period) [43]. Streptozotocin-induced diabetic rats, a model for type 1 diabetes, exhibited extended periapical lesions and elevated inflammation vs. control animals in two different studies [44, 45]. These results indicate that either type 1 or type 2 diabetes deteriorates periapical inflammation and bone destruction.

In humans, a retrospective cohort study suggested a significant association between the prevalence of periapical lesions and diabetic status [46]. This study also pointed out two important aspects. The first one is a high frequency of endodontically *untreated* periapical lesions in diabetics (5.5% of total examined teeth in diabetics vs. 2.7% in non-diabetics). The reason for the higher percentage of untreated teeth is unknown, but it may involve factors of oral health care behavior [47] and socioeconomic status [48]. Second, the data suggests that the higher prevalence of periapical lesions in diabetics in part depends on unsuccessful endodontic treatments. In this regard, Fouad and Buleso reported that the rate of successful treatment outcome was significantly lower in diabetics with pre-operative

periradicular lesions [49]. In addition, the success rate was reduced in non-surgical endodontic retreatments vs. primary treatment cases, especially in diabetics [49]. Furthermore, metabolic disorders including diabetes, hypertension, and cardiovascular disease resulted in an elevated rate of poor outcomes (tooth extraction) in non-surgical endodontic treatment subjects compared to corresponding control subjects [50]. These studies indicate that diabetes mellitus is a risk factor for poor prognosis in non-surgical root canal treatment, resulting in refractory periapical lesions or, in the worst case scenario, extraction of the diseased tooth.

Periapical immune response localizes the infection within the confines of the root canal system and prevents its systemic dissemination. In the host immune system, neutrophil is the first defense line when pathogens invade. In addition, the initial pulpal response to bacterial infection and/or to the diffusion of bacterial antigens comprises the infiltration of polymorphonuclear neutrophils (PMNs) and monocytes [51-53]. Diabetes mellitus seriously impairs the function and bactericidal activity of neutrophils [54, 55]. In particular, hyperglycemia can prime neutrophils via enhanced release of superoxide and protein kinase C activity, which are associated with the severity of periodontitis [56].

Macrophages are phenotypically categorized into proinflammatory M1 and pro-resolving M2 subsets [57]. In obese patients with type 2 diabetes, the macrophage population in adipose tissue is polarized to proinflammatory M1 macrophages, and the number of M2 macrophages in peripheral blood and bone marrow is markedly lower in diabetics compared to control subjects [58, 59]. These findings suggest that type 2 diabetes modulates host immunity to a hyperinflammatory state and/or vice versa.

As described earlier, a mixed infiltrate of myriad immune cells constitutes a complex immune response in the lesion. A number of cytokines derived from immune cells are involved in the regulation of periapical inflammation and bone loss. IL (interleukin)-1 α , IL-1 β , TNF- α , and IL-6 elevate inflammation, stimulate bone resorption by osteoclasts, and inhibit bone formation [60-63]. Of those, IL-1 is the central mediator in the network, because IL-1 expression is strongly associated with the severity of periapical bone loss [64, 65]. In the IL-1 family, IL-1 β plays a prominent role in periapical bone loss in humans depending on its expression level in lesions and the potency of osteoclast-stimulation, which is approximately 500-fold more potent than TNF [60, 63, 66, 67]. It is now known that osteoclast activity mediated by these cytokines is in part due to the ability of these mediators to induce the expression of RANKL (receptor activator of nuclear factor-kappa B ligand) by osteocytes, osteoblasts, stromal cells, lymphocytes, and fibroblasts [68-71].

In general, the expression and action of proinflammatory mediators are modulated by the network of other immune regulatory cytokines. This cytokine network is well-understood in the context of the four major subsets of CD4+ T-helper (Th) cells, which are Th1, Th2, Th17, and Treg (regulatory T cell) subsets. Proinflammatory Th1 cells produce IFN (interferon)- γ , IL-2, and TNF- α . In contrast, anti-inflammatory Th2 cells produce IL-4, -5, -6, -10, and -13. Th17 cells, another proinflammatory subset, are notably involved in autoimmune diseases and the major source of IL-17. Treg cells are the predominant anti-

inflammatory T-cell subset depending on the production of IL-10 and TGF (transforming growth factor)- β .

Our functional studies revealed that a cytokine network is activated in the development of periapical lesions. The level of IL-1 α is in part regulated by the Th1 pathway in chronic pathogenesis [72]. The importance of Th1 response in periapical lesions was further supported by a study that demonstrated that induction of Th1-biased response against an endodontic pathogen resulted in dramatic elevation of local production of IFN γ and IL-1 α and periapical bone destruction, compared to immunocompetent or Th2-based conditions [73]. In contrast, endogenous IL-10 produced by macrophages, Th2, and Treg cells has a strong and non-redundant inhibitory effect on periapical inflammation and bone destruction. Therefore, proinflammatory pathways predominate in the absence of IL-10 [74]. In the cytokine network, IL-10 strongly suppresses T cell response mediated by myeloid-derived IL-12, induced by Toll-like receptor (TLR)-4 signaling [75]. Another Treg-derived mediator, TGF- β 1, is also predominantly immunosuppressive in the development of endodontic lesions [76]. Although IL-17 and IL-6 are proinflammatory and bone destructive in rheumatoid arthritis [77, 78], IL-17RA (IL-17 receptor A) signaling may be protective in infection-stimulated bone destruction via alteration of neutrophil traffic [79, 80]. Endogenous IL-6 also suppresses periapical bone destruction in the development of periapical lesions via suppression of IL-1 α , but the potency is less than that of IL-10 [81].

As a consequence of systemic inflammation in diabetes mellitus, the serum level of proinflammatory mediators TNF- α , IL-1 α , IL-1 β , CRP (C-reactive protein), and IL-6 was significantly elevated in type 2 diabetes patients either recently diagnosed or with long-standing disease [82, 83]. Since these mediators play proinflammatory and bone destructive roles in periapical lesions, elevation of circulating proinflammatory mediators associated with type 2 diabetes may negatively impact local periapical inflammation similar to periodontal disease.

IFN γ expression in adipose tissue increases in obesity [84]. Serum level of IFN γ and its downstream chemokine IP-10 (CXCL10) was significantly higher in patients with type 2 diabetes and type 2 diabetic nephropathy [85, 86]. IFN γ facilitates M2 to M1 macrophage phenotypic conversion in obesity [57], contributing to a systemic hyperinflammatory state. IFN γ signaling causes suppression of insulin-dependent glucose uptake and lowering triglycerides in adipocytes via reduction of IRS-1 (insulin receptor substrate-1), which is a key molecule in insulin signaling [87]. Thus, IFN γ KO mice exhibited better insulin sensitivity and glucose tolerance compared to wild-type mice under a high fat diet treatment [84, 88].

In contrast, the association between type 2 diabetes and serum level of IL-10 is unclear [89-91]. There is no definitive information about circulating IL-4 in diabetics. It is therefore not clear whether high circulating levels of these anti-inflammatory mediators are favorable for protection from type 2 diabetes. However, in the Leiden 85-Plus study, the capacity of IL-10 production by whole blood cells upon LPS (lipopolysaccharide) stimulation was significantly lower in diabetics vs. non-diabetics ($p=0.001$) [92], probably leading to a hyperinflammatory state.

Diabetes mellitus also alters local cytokine expression profile. Uncontrolled type 2 diabetes subjects exhibited more inflammatory cytokine profile in GCF (gingival crevicular fluid). Up-regulation of proinflammatory mediators including eotaxin, MIP (macrophage inflammatory protein)-1 α , GM-CSF (granulocyte/macrophage-colony stimulating factor), IL-6, and TNF- α and down-regulation of IL-10 were observed even in healthy periodontal sites compared to non-diabetic subjects [93]. Moreover, GCF levels of IL-17 were higher in poorly controlled type 2 diabetes subjects compared to well-controlled diabetics [94].

Taken together, diabetes mellitus is a risk factor for infection-stimulated bone destruction due to induction of systemic proinflammatory cytokine expression profile, consisting of elevated TNF- α , IL-1, IL-6, Th1 type IFN γ , and impaired IL-10 production. Such alterations may lead the cytokine expression profile in periapical lesions to further proinflammatory/bone destruction in diabetics compared to non-diabetics.

Is endodontic treatment beneficial in control of diabetes mellitus? IL-1 β is a critical mediator in the development of insulin resistance through inhibition of insulin signaling and amplification of TNF [95]. Thus, IL-1 β is a potential therapeutic target of type 2 diabetes [96]. A recent study suggested that, during the onset of type 2 diabetes, glucose-targeted treatments have to be complemented by adjuvant anti-inflammatory therapies targeting IL-1 β in order to stop or decelerate disease progression [97]. As periapical inflammation elevates circulating CRP, IL-1, IL-2, and IL-6 [98], periapical lesions potentially impair the insulin secretion by β cells in the pancreatic islet and the insulin sensitivity remotely [99, 100]. In a case of a combined endodontic-periodontic (endo-perio) lesion in a moderately controlled diabetic, insulin demand of the patient was associated with an exacerbation of the lesion, and the insulin sensitivity of the patient was drastically improved after endodontic treatment [100], suggesting the importance of endodontic treatment as a potential adjuvant anti-inflammatory/-insulin resistance therapy in diabetics with endodontic complication/s.

As reviewed, diabetes and periapical pathosis shares fundamental mechanisms in up-regulation of systemic and local inflammation (summarized in Figure 1). Diabetes is one of the most prevalent diseases in medically compromised dental patients [101, 102]. An epidemiologic projection targeting the U.S. population suggests that total diabetes prevalence, both diagnosed and undiagnosed cases, will increase from 14% in 2010 to 21% by 2050. Diabetes mellitus may further increase a risk of total pulp necrosis and subsequent periapical pathosis, and unsuccessful endodontic treatment cases due to altered wound healing, vascular and immune functions.

3. Hypertension and periapical lesions

Evans and Rose described that hypertension should be defined in terms of blood pressure level above which investigation and treatment do more good than harm [103]. Essential hypertension may occur as an outcome of interaction between genetic factors and lifestyle. In contrast, secondary hypertension has a clear cause, such as renal disorder. In general, a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg, or both, will be diagnosed as hypertension [104].

Although hypertension does not affect the prevalence of periapical lesions [105], hypertension is the most frequent comorbid condition in patients hospitalized for periapical abscess (24.6%), which is an advanced form of endodontic infection/inflammation [106]. Also, multiple epidemiologic studies indicate an association between periodontal disease and hypertension [107]. These data suggest a clinical association between hypertension and immune/inflammatory response caused by oral infection. We should mention here that the immune system is probably not a primary cause of hypertension, because immunity-related risk alleles were not found in hypertension-associated gene loci in multi genome-wide association (GWAS) studies [108]. The contribution of immunity to hypertension is thought to be a secondary factor following initiation of pre-hypertension, a modest elevation of blood pressure about 135 to 140 mmHg mainly caused by genetics and lifestyle. Pre-hypertension and subsequent vascular injuries lead to the production of damage-associated molecular patterns (DAMPs), neoantigens, and immune regulatory mediators that promote immune and inflammatory response [109,111].

TLR4 signaling is the key proinflammatory signaling in the induction of hypertension, target organ damages and periapical lesions [112-115]. Here, we focus on the TLR4 signaling as a common mechanism linking hypertension and periapical inflammation. TLR4 also recognizes damage-associated molecular patterns (DAMPs) such as HMGB1 (high-mobility group protein B1), and S100 proteins, which will be released by macrophages and damaged vascular cell walls [116-119]. In addition, the western diet is a major source of food-derived TLR4 stimuli including free fatty acids, oxidized LDL (low-density lipoprotein), and triglycerides [120]. In hypertension, angiotensin II is also a TLR4 agonist [121, 122]. Activation of TLR4 by these ligands in either macrophage-lineage cells or resident cells increases PKC (protein kinase C) activity, leading to the phosphorylation and activation of IKK (I kappa B kinase). IKK mediates phosphorylation of I κ B, resulting in the translocation of NF- κ B into the nucleus. The activation of NF- κ B ultimately promotes the transcription of inflammatory cytokines such as TNF- α and IL-1. These inflammatory factors are critical in endothelial dysfunction, vasoconstriction and vasodilation, which increase peripheral resistance and ultimately elevate blood pressure. Other chronic inflammation such as rheumatoid arthritis contributes to immune activation in the development of hypertension [123]. In addition to DAMPs, low-grade infections such as periodontitis and periapical lesions may generate circulating bacteria and pathogen-associated molecular patterns (PAMPs) [124,126]. TLR4 deficient mice are therefore resistant to hypertension induced by chronic hypoxia and infusion of angiotensin II [127, 128] and periapical inflammation [115]. Interestingly, inhibition of TLR4 within the paraventricular nucleus attenuates blood pressure and inflammatory response in the spontaneously hypertensive (SHR) rat [129], which is a model of essential hypertension, suggesting neuroinflammation mediated by innate immunity is a potential regulating factor of low-grade systemic inflammation.

Activation of the innate immune response leads to induction of the adaptive immune response mediated by lymphocytes. However, the incidence of hypertension in HIV/AIDS (human immunodeficiency virus/ acquired immunodeficiency syndrome) subjects exhibiting reduced CD4+ T cell count was significantly lower than non-infected subjects [130], suggesting the importance of T cells in the development of hypertension. In addition, a SCID (severe combined immunodeficiency) mouse strain, the RAG-1 deficient mouse

lacking functional lymphocytes, is resistant to induction of hypertension by angiotensin-II infusion and DOCA-salt (deoxycorticosterone acetate plus salt) challenge [131]. The renin-angiotensin axis is a major regulatory mechanism in control of blood pressure, and angiotensin converting enzyme (ACE) mediates a key proteolytic step in the induction of angiotensin receptor signaling [132]. Blocking angiotensin II by ACE inhibitors or inhibition of angiotensin receptor type 1 strikingly resulted in significant reduction of proinflammatory Th1 and Th17 cells, producing IFN γ and IL-17, respectively. In contrast, blocking ACE promoted anti-inflammatory Treg cells [133], producing TGF β and IL-10. This study demonstrated a critical role for angiotensin II in differentiation of proinflammatory T cell subsets. Although deficiency of IL-17 did not affect initial hypertensive response to angiotensin II infusion vs. wild-type mice, angiotensin II-induced hypertension was not sustainable in IL-17 deficient mice while wild-type mice were hypertensive for four weeks [134].

Immune regulatory cytokines systemically and/or locally mediate inflammatory response. Hypertensive human subjects exhibit elevated circulating TNF- α and IL-6 [135, 136]. Correlation between serum IL-17 and hypertension is not clear [137]. However, as described above, TNF- α , IL-6, and IL-17 are most likely involved in the development of hypertension. In addition, these mediators are involved in periapical pathosis [138-140]. However the major role of these mediators may not always be in bone destruction [80, 81, 141].

On the other hand, IL-10 is an important anti-inflammatory cytokine in hypertension. Systemic overexpression of IL-10 induced by an AAV (adeno-associated viral) vector prevented hypertension-induced damage and inflammation in the target organs in SHR rats [142]. As described above, ACE blockage augmented Treg population, leading to suppression of autoreactive Th1 and Th17 cells via inhibition of NF- κ B in SJL/J mice [133]. In cardiovascular disease patients, improvement in the ratio of IL-10/CRP in serum is associated with amelioration of systemic endothelial vasoreactivity [143]. In addition, serum IL-10 level in women with preeclampsia was significantly decreased compared to subjects with normal pregnancies [144]. The number of IL-10 positive trophoblasts was lower in preeclampsia tissue samples (0.75-fold), whereas there was a trend in increased TNF- α positive cells (1.79-fold; $p = 0.09$) in the same study [144]. In addition, the ratio Tregs to Th17 cells is significantly lower in preeclampsia compared to normal pregnancies [145]. Hypertensive disorders of pregnancy, including inflammation, endothelial dysfunction, and blood pressure, were attenuated by administration of IL-10 in DOCA/saline-treated pregnant rats [146]. Hence, IL-10 is a common counter-regulatory axis in the development of hypertension and periapical lesion. The potential interrelationship between hypertension and periapical lesions was summarized in Figure 2.

4. Non-alcoholic fatty liver disease (NAFLD) and periapical lesions

NAFLD is a disease spectrum, which ranges from simple steatosis (pure fatty liver), non-alcoholic steatohepatitis (NASH; resulting in liver fibrosis), to cirrhosis and ultimately hepatic carcinoma. NAFLD is the representation of metabolic syndrome in the liver. Fatty liver exhibits insulin resistance [147, 148], overproduction of glucose [148] and VLDL (very low-density lipoprotein) [149, 150], leading to metabolic abnormalities such as

hyperglycemia, hypertriglyceridemia, and a low HDL (high-density lipoprotein) cholesterol concentration [151]. The clinical relationship between NAFLD and dental inflammation has not been systematically examined.

However, elevated serum γ -glutamyltransferase (GGT) level is associated with periodontal disease (> 4 mm periodontal pockets) in adults without drinking habit [152]. GGT is a deviation enzyme mainly present in liver, kidney and pancreatic cells. Greater than normal level of serum GGT is frequently observed in subjects with abdominal obesity [153-156] and is considered as a hepatic biomarker of steatosis [157]. In addition, the rate of colonization of *Porphyromonas gingivalis*, which is a common pathogenic species for both periodontitis and periapical lesion, in the oral cavity is significantly higher in both NAFLD and NASH patients compared to non-NAFLD control subjects (46.7%, 52%, and 21.7%, respectively) [158]. Moreover, within NASH patients, the level of fibrosis scores was significantly higher in *P. gingivalis* positive subjects compared to *P. gingivalis* negative subjects [125]. These findings suggest a hypothetical association between the progress of NAFLD/NASH and *P. gingivalis* infection. This hypothesis was tested in two studies. One study determined the status of the grade of NASH and related biomarkers in *P. gingivalis*-injected mice treated with a high fat diet. As a result, the injected mice exhibited an advanced grade of NASH with up-regulated proinflammatory cytokines [158]. The other study demonstrated that endodontic infection of *P. gingivitis* accelerated exacerbation of high fat diet-induced NASH to cirrhosis [125].

An advanced hypothetical model of the development of NASH is the multiple parallel hits model, in which metabolic disorders such as lipotoxicity, insulin resistance, and dysbiosis lead to proinflammatory processes mediated by different proteins and immune components [159]. Extra-hepatic tissues, including adipose tissue and gut, are major sources of inflammatory mediators and the site of dysbiosis [160]. *P. gingivalis* is a keystone pathogen in dysbiotic microbiota in the oral cavity [161, 162]. As a part of the alimentary canal, we expect that dysbiosis in the oral cavity and the subsequent elevated immune response are probably involved in the exacerbation of NAFLD/NASH. To prove this hypothesis, further well-designed clinical studies are essential to determine the existence of dysbiosis associated with NAFLD/NASH (metabolic syndrome in perspective) in human oral microbiota.

Recent studies highlight the importance of inflammasomes in the development of NASH. NLRs (NOD-like receptors) are cytoplasmic receptors that detect microbial components (PAMPs) and host danger signals (DAMPs). Upon stimulation by PAMPs and DAMPs, NLRP3 (*NOD-like receptor family, pyrin domain containing 3*) changes its conformation, associates with ASC (apoptosis-associated speck-like protein containing a CARD) and caspase-1, and finally assembles inflammasome in the cytoplasmic domain. In response to PAMPs and DAMPs, inflammasome will activate caspase-1, resulting in elevated production of proinflammatory cytokines IL-1 β and IL-18 [163]. The NLRP3 inflammasome is involved in activation of immune response in adipose tissue and insulin resistance. Therapeutic interventions influence the expression of NLRP3 and IL-1 β gene in adipose tissue in obese/diabetic subjects, leading to ameliorated inflammation and insulin sensitivity [164]. Nlrp3 deficient mice fed a high fat diet exhibited attenuated immune response and better insulin signaling in fat depots and liver compared to corresponding controls [164].

Thus, the effect of the therapeutic intervention is in part dependent on inactivation of the NLRP3 inflammasome – IL-1 axis [164].

In obesity/metabolic syndrome/type 2 diabetes, the activation of NLRP3 inflammasome will be primarily induced by obesity-associated danger signals such as palmitic acid (a saturated fatty acid), ceramides, impaired autophagy, or mitochondrial dysfunction [95, 164-166]. In addition, palmitic acid and bacteria endotoxin co-stimulate hepatocellular inflammasomes in immune activation and the development of NAFLD/NASH [167]. TLR4 is the key receptor of endotoxin-induced activation of inflammasomes [168]. In contrast, endodontic infection of *P. gingivalis* in high fat diet treated mice resulted in up-regulated TLR2 expression, activation of inflammasomes in liver, and finally exacerbation of NASH [168]. Unlike other Gram negative species, *P. gingivalis* triggers TLR2 signaling [169]. Thus, in addition to TLR4 signaling, *P. gingivalis* seems to activate the TLR2 – inflammasome pathway, which promotes the progression of NASH via overproduction of TNF- α and IL-1 [125, 158, 170].

On the other hand, recent studies revealed the importance of the TLR-inflammasome axis in pulpal and periapical inflammatory response [171, 172]. Although macrophage-derived IL-1 is the central mediator in the development of periapical lesions [72, 141], an increased number of NALP3 positive cells, including an influx of myeloids, was quite apparent with the progression of periapical inflammation [172]. The number of NALP3 positive cells was also significantly associated with the level of inflammatory cell infiltration, ASC, caspase-1, IL-1 β and IL-18 [172], suggesting that inflammasomes play an important role in production of IL-1 in periapical lesions. In a mouse *P. gingivalis*-induced periodontitis model, macrophage is an important source of proinflammatory mediators including nitric oxide (NO), IL-1 β , IL-6, IL-10, IL-12 p70, eotaxin, G-CSF (granulocyte-colony stimulating factor), GM-CSF, MCP (monocyte chemoattractant protein)-1, MIP- α and - β , and TNF- α [173]. Depletion of macrophage using clodronate liposomes in this disease model resulted in suppression of *P. gingivalis*-induced immune response such as pathogen-specific IgG (immunoglobulin G) and serum cytokine levels [173]. A three-month periodontal treatment of NAFLD patients with > 5 mm periodontal pocket/s significantly improved the serum level of AST (aspartate aminotransferase) and ALT (alanine transaminase), which signify hepatic damage and/or injury [158]. In summary, oral inflammation mediated by *P. gingivalis* is a possible “hit (risk factor)” and may be involved in the aggravation of NAFLD/NASH through the TLR – Nlrp3 inflammasome axis.

NASH is now a common cause of cirrhosis, ranking with alcohol abuse and HBV/HCV (Hepatitis B virus/hepatitis C virus) infection [174]. Up to 10% of patients with NASH develop cirrhosis, which is the end stage chronic liver disease [174, 175]. In liver transplant candidates with cirrhosis, the frequency of periapical lesions is significantly higher in the candidates (79%) than that in control subjects (50%) ($p=0.008$; OR=3.7; C.I. 95%=1.4 - 9.5) [176], suggesting a clinical association between end-stage liver disease and periapical inflammation.

Interestingly, vitamin B6 deficient diet in rhesus monkeys resulted in coincident occurrence of atherosclerosis, endodontic infection spectrum, and cirrhosis [177, 178]. Vitamin B6 (Pyridoxal 5'-phosphate) is important in the metabolism of homocysteine, which is a

predictor of steatohepatitis in NAFLD patients [179]. Homocysteine and LPS synergistically elevate differentiation of proinflammatory M1 macrophages and also conversion of pro-resolving M2 macrophage to M1 phenotype [179], contributing to the development of a proinflammatory state.

In the Boston Puerto Rican Health Study (361 men and 861 women; mean $\pm$ SD age: 52 ± 7 y), more metabolic syndrome and type 2 diabetes subjects had vitamin B6 inadequacy compared to corresponding control subjects (12% of metabolic syndrome subjects vs. 7% of control subjects ($p=0.0016$); 13% of diabetics vs. 9% of non-diabetics ($p=0.014$)). The conclusion of this study is that low vitamin B6 concentrations are associated with inflammation, higher oxidative stress, and metabolic conditions in older Puerto Rican adults [180]. In a study in rats, supplementation of vitamin B6 (1 mg per animal, daily) to a hyperlipidemic diet significantly suppressed increase of body weight, degree of fat deposition in liver, and serum level of cholesterol compared to the conditions of an ordinary diet and the hyperlipidemic diet alone in 14 days observation period [181]. A recent cross sectional study indicates that daily intake of the calcium, sodium, potassium, vitamins B6 and C did not meet the recommended values in most NAFLD patients [182]. Therefore, these findings suggest that the inadequacy of vitamin B6 is a potential “hit” in the progress of NAFLD. According to the clinicaltrials.gov [183], several clinical trials are currently ongoing to determine the effect of B6 on inflammation and oxidative stress caused by liver diseases. Future studies are essential to answer the interesting question of whether vitamin B6 supplementation is a potential adjuvant anti-inflammatory therapeutic approach in dental inflammation. The potential interrelationship between NAFLD/NASH and periapical lesions was summarized in Figure 3.

5. Effect of metabolic disorders on systemic and local bone metabolism

The teeth are supported by alveolar bone. Therefore, the status of bone metabolism may impact dental health. Osteoclasts are responsible for bone resorption. The differentiation and activity of osteoclasts largely depends on RANKL. Binding of RANKL to RANK (a receptor expressed on the surface of osteoclast precursors) initiates a signaling cascade that ultimately results in activation of NF- κ B and differentiation and activation of osteoclasts. RANKL-RANK interaction can be inhibited by an endogenous decoy receptor named OPG (osteoprotegerin). Thus, the ratio of RANKL to OPG is a critical factor in regulation of differentiation and activity of osteoclasts. Here, we briefly review how the metabolic disorders affect systemic and local bone metabolism.

Serum levels of OPG are significantly elevated in subjects with type 2 diabetes mellitus compared to healthy controls. RANKL expression, on the other hand, is similar in both diabetics and control subjects [169]. Although a lower RANKL/OPG ratio seemingly suggests that diabetics will be protected from bone loss, diabetes mellitus negatively affects skeletal homeostasis by dysregulating the coupling of bone formation to bone resorption. In fact, poor glycemic control results in lower bone formation with increased bone resorption [184], which ultimately causes bone loss. Local RANKL/OPG ratio in periodontium is also affected by systemic metabolic disorders. RANKL/OPG ratio in GCF (gingival crevicular fluid) derived from diseased sites is higher in type 2 diabetes subjects than in non-diabetics

[185]. This tendency is further accentuated in poorly controlled diabetics vs. well-controlled diabetics [185]. Angiotensin II, a peptide hormone that causes hypertension, can activate osteoclasts by up-regulating RANKL expression in osteoblasts [186]. In line with this observation, ligature-induced periodontitis caused an elevation in the RANKL/OPG ratio (a more “osteoclast-forming” environment) in SHR rats (a strain that is genetically hypertensive) compared to normotensive controls [187], suggesting a potential effect of hypertension on local RANKL/OPG ratio.

Recent studies revealed that metabolic syndrome and diabetes mellitus increase a risk of bone fracture [188-190]. Reduction of bone mineral density (BMD), a key determinant of future fracture risk, is a well-known complication in type 1 diabetes [191]. In contrast, the effect of type 2 diabetes mellitus on systemic BMD is unclear [184, 191]. In a human cross-sectional study, hip BMD was lower in diabetics than that in non-diabetic subjects, whereas the anterior-posterior spine BMD was significantly higher in diabetics [192]. These data uncover the complexity of diabetes-mediated skeletal dysregulation [190] and suggest that the effect of metabolic disorders on BMD may be site-specific. Hypertension also may negatively affect BMD due to abnormal metabolism of 1,25-dihydroxyvitamin D₃, a key regulator of calcium homeostasis and bone metabolism, intestinal calcium transport, and angiotensin II-mediated osteoclast activation [186, 193]. What are the effects of metabolic disorders on alveolar bone? In a streptozotocin-induced diabetes model, the volume of bone formation and the number of osteoclasts in alveolar bone were significantly lower in diabetic rats than in the controls, indicating lowered turnover of alveolar bone under diabetes [194]. Insulin treatment, on the other hand, rescued the impaired alveolar bone turnover observed in diabetic rats [194].

Insulin and IGF(insulin-like growth factor) are osteo-anabolic factors [195, 196]. Insulin signaling is essential for production of osteocalcin [197] and expression of RANKL by osteoblasts [198]. Insulin resistance, on the other hand, has a negative effect on bone turnover. This negative effect is mediated by impaired osteoblast differentiation and proliferation, induction of osteoclastogenesis and low bone turnover, which ultimately leads to osteopenia. Low levels of 1,25-dihydroxyvitamin D₃ are also associated with insulin resistance [199]. In addition, bone turnover and quality is negatively affected by impaired collagen cross-linking, significantly reduced PTH (parathyroid hormone), and microangiopathy in bone marrow [200-202].

Taken together, metabolic disorders, in particular diabetes mellitus, negatively affect skeletal homeostasis, causing bone destructive conditions like rheumatoid arthritis [203], periapical/marginal periodontitis [204], an increased the risk of bone fractures, [190] and delayed fracture healing [205, 206].

6. Conclusion

Metabolic disorders are dependent on low-grade systemic inflammation caused by metabolically triggered immune response. The elevation of proinflammatory cytokines (such as IL-1 and TNF- α) is the key condition in the development of metabolic disorders. Also, metabolic disorders systemically and/or locally impact bone regulatory cytokines. Anti-

proinflammatory cytokine therapies will be a potential option in control of type 2 diabetes and probably other metabolic disorders. In contrast, the primary cause of periapical lesions is endodontic infection. PAMPs-triggered immune response induces proinflammatory cytokines and subsequent periapical pathosis, including chronic inflammation and bone destruction. The primary cause of periapical lesions does not overlap with metabolic disorders. However, in terms of cytokine biology, immune regulation mediated by cytokines is the common fundamental mechanism linking periapical lesion and metabolic disorders. Although it is not definitive, some studies suggest that periapical inflammation makes the metabolic disorder worse. Given the poor endodontic treatment outcomes in type 2 diabetes patients and the potential benefit of the treatment in control of insulin sensitivity, research and development of novel therapeutic approaches are essential for more effective treatment regimens for infected root canals.

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Figure 1. Potential interrelationship between type 2 diabetes mellitus and periapical lesions
Diabetes mellitus is accompanied by elevated systemic chronic inflammation and angiopathy, resulting in increased susceptibility to infection and poor wound healing. Such alterations would negatively affect on a refractory state of periapical lesions, leading to a marked deterioration in the rate of successful endodontic treatments. In the opposite direction, endodontic treatment might be a potential adjuvant anti-inflammatory/-insulin resistance therapy in diabetics with endodontic complication/s.

Figure 2. Potential interrelationship between hypertension and periapical lesions

Pre-hypertension is primarily triggered by genetics and life style and activates TLR4 signaling and T cell response, leading to a proinflammatory profile of immune regulatory cytokines. This overactive inflammatory state advances the development of hypertension and might be involved in the formation of periapical abscess. However, the effect of periapical inflammation on the development of hypertension is unknown at the present time.

Figure 3. Potential interrelationship between NAFLD/NASH and periapical lesions

Inadequate nutrition and life style are major causes of metabolic syndrome, generating multiple risk factors (hits) for the development of NAFLD/NASH. NAFLD/NASH activate NLRP3-TLR4 pathway, induce a proinflammatory macrophage profile, and result in elevated circulating level of proinflammatory mediators. Periapical lesion is an indissoluble source of bacteria/PAMPs. *P. gingivalis* derived from periapical lesions exacerbates NAFLD/NASH, suggesting that *P. gingivalis* is a potential hit. Vitamin B6 seems to be a key vital nutrient in regulation of both NAFLD/NASH and periapical inflammation.