Apical periodontitis, inflammation and insulin resistance

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Apical periodontitis (AP) is an immunoinflammatory process characterized by the participation of different cell types such as lymphocytes, neutrophils, osteoclasts, and macrophages that are important sources of pro-inflammatory cytokines. Studies have found that localized inflammation in different tissues can eventually lead to systemic disorders. However, the mechanisms involved in these changes are not fully understood. It is known that high concentrations of proinflammatory cytokines such as TNF-α, derived from oral inflammation are associated with decreased insulin signal and insulin resistance, which are important risk factors for type 2 diabetes mellitus. This review aims to discuss the role of proinflammatory cytokines and the mechanisms involved in the development of insulin resistance in AP models.

Introduction

Studies have shown an association between AP, an inflammatory process developed from bacterial infection of the root canal¹ and type 2 diabetes mellitus (T2DM), a chronic disease characterized by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response², ³, ⁴. Although mechanisms involved in the development of insulin resistance in patients with AP are unknown, a possible explanation for this alteration is that an oral infectious process can induce the host to produce pro-inflammatory cytokines that eventually reach the blood circulation ⁵. These cytokines can impair the insulin signal and promote insulin resistance in peripheral tissues.

Thus, it is essential to discuss the inflammatory mechanisms involved in the insulin resistance pathogenesis associated with AP.

Insulin action and diabetes mellitus

Insulin is an anabolic hormone essential for several metabolic functions such as maintenance of glucose homeostasis, stimulation of lipogenesis, synthesis of glycogen and protein, inhibition of lipolysis, glycogenolysis and protein degradation, as well as cellular growth and differentiation. This hormone is secreted by the β cells of the pancreatic islets in response to increased circulating glucose, amino acids and free fatty acid levels after meals⁶, ⁷. Insulin acts in different tissues, such as muscle, adipose tissue and liver to stimulate glucose uptake, promoting the maintenance of glycemic homeostasis ⁸. The interaction of insulin with its receptor promotes receptor autophosphorylation and pp185 (IRS-1 / IRS-2) phosphorylation in tyrosine residues that stimulate the recruitment and activation of the phosphatidylinositol 3-kinase (PI3K) ⁹, ¹⁰ and protein kinase B (Akt). Akt induces Glucose transporter type 4 (GLUT4)
translocation to the plasma membrane, resulting in glucose uptake in insulin-sensitive tissues [11]. Impairments in the insulin signaling pathway can trigger insulin resistance, which plays an important role in the pathogenesis of T2DM [12].

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that can be triggered by defects in insulin secretion and action [2]. Chronic hyperglycemia is the most important causal factor in the development of late complications and mortality related to DM [13, 14]. Progression of the disease can lead to damage to various organs including eyes, kidneys, nerves, blood vessels, heart, and periodontal tissues [2, 15].

DM is an important public health issue in several countries especially in developing countries [16]. Based on recent data from the International Diabetes Federation, over 387 million people worldwide are carriers of the disease. It is estimated that the diabetes prevalence will exceed 592 million in 2035 [17]. This disease is classified into two main types: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is more frequently developed in childhood and arises from autoimmune destruction of pancreatic β cells. T2DM is related to disorders in insulin function and secretion and it is often associated with obesity, since this condition can promote peripheral resistance to insulin action [18].

**Insulin resistance in inflammatory processes**

Insulin resistance is defined as the inability of peripheral tissues to adequately respond to circulating concentrations of this hormone [19]. Several studies reported that inflammation is strongly associated with insulin resistance [20, 21]. Inflammation is characterized by local and systemic increased levels of pro-inflammatory cytokines and high infiltration of leukocytes in the inflammatory site. Infiltration of neutrophils usually occurs in the acute phase; while there is prevalence of macrophages during the chronic inflammation phase [22]. This inflammatory process is usually observed in obesity conditions. Studies have shown that obese subjects have an increased number of resident macrophages in adipose tissue and among the functions performed by macrophages, TNF-α production stands out [23].

TNF-α impairs the insulin signal by decreasing IRS-1 tyrosine phosphorylation [24]. In addition, TNF-α can stimulate some serine kinases, including IκB kinase (IKK) and c-Jun N-terminal kinase (JNK) which promote IRS-1 serine phosphorylation, resulting in attenuation of the insulin signal [25].

Increased prevalence of insulin resistance has been observed in patients with inflammatory diseases that show excessive production of pro-inflammatory cytokines, such as TNF-α [26]. Interestingly, treatment with TNF-α antagonists improves glycemic control in patients with inflammatory diseases, such as rheumatoid arthritis, psoriasis and Crohn's disease [27, 28, 29, 30]. Another pathology that shows high levels of pro-inflammatory cytokines is Alzheimer's disease [31]. A recent study reported the existence of a bidirectional relationship between Alzheimer's disease and T2DM, suggesting that inflammation is the link between these diseases [32].

Finally, oral inflammatory diseases, such as periodontal disease, may increase TNF-α plasma levels, impair the insulin signal and cause insulin resistance [33]. These data suggest that locally produced pro-inflammatory cytokines may eventually reach the systemic circulation and impair insulin action.

**Apical periodontitis, inflammation and diabetes**

Relationship between oral inflammation and diabetes has been extensively reported, especially in relation to periodontal disease [4]. However, there are few studies correlating AP and DM.

AP occurs as a sequence of several aggressions to the dental pulp, including infection, physical and iatrogenic trauma following endodontic treatment. Regulation of periapical inflammation is extremely complex consisting of several types of cells, intercellular messengers, antibodies and effector molecules. As a consequence of these processes and the inability of host defense mechanisms to eradicate infection, chronic periapical lesions are formed, with the aim of restricting microbial invasion [34, 35]. Kohsaka et al. (1996) [36] investigated the histological changes in the pulp and periapical tissues after pulp exposure in diabetic rats. The results demonstrated that diabetic rats with AP showed greater alveolar bone resorption compared to control rats. Garber et al. (2009) [37] investigated the impact of diabetes on pulp healing of inflamed pulp in rats and concluded that hyperglycemia can impair the healing process. These data showed that diabetes can worsen AP, complicating the treatment. Similarly, studies have shown that AP can worsen diabetes. Cintra et al. (2014) [38] evaluated the effects of oral infections on blood glucose and glycated hemoglobin in diabetic rats. The authors observed an increase of these parameters in rats with AP compared with control animals, suggesting that this inflammatory process can impair glucose homeostasis in rats. A recent clinical study investigated the relation between the prevalence of AP and glycemic control in type 2 diabetic patients. It was observed that the periapical
status had a significant correlation with glycated hemoglobin levels (HbA1c) of these patients [39]. These findings show that there is a bidirectional relationship between DM and AP in which one can negatively affect the other.

Although the mechanisms are not fully understood, studies suggest that locally produced cytokines may eventually reach the systemic circulation [40, 41, 42] and promote insulin resistance in peripheral tissues [40, 43]. Pro-inflammatory mediators such as interleukin-1 (IL-1) and Interleukin-6 (IL-6) are increased in AP models [42] and can be associated with insulin resistance.

There is controversy on the IL-6 role in the etiology of insulin resistance [44]. Studies show that IL-6 reduces hepatic glycogen synthesis stimulated by insulin [45, 46] and decreases the transcription of IRS-1 and GLUT4 in adipocytes, reducing glucose uptake in adipose tissue [47]. In the skeletal muscle, IL-6 is able to increase glucose uptake and to stimulate glycogen synthesis [48, 49]. Moreover, the skeletal muscle can produce IL-6 in response to exercise, and in this case IL-6 has an anti-inflammatory effect due to its ability to inhibit TNF-α production and induce the increase of interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10), which are anti-inflammatory factors [50].

IL-1β contributes to the development of T2DM by impairing the function and stimulating apoptosis of pancreatic beta cells [51]. In vitro studies demonstrated that adipocytes treated with IL-1β showed insulin signaling disorders and decreased GLUT4 translocation [52, 53]. Furthermore, inhibition of IL-1β using antibodies or IL-1ra was able to reverse these effects [54].

Some studies have also suggested that increase in the levels of other cytokines, such as Interleukin 17 (IL-17) can play an important role in insulin resistance pathogenesis [55]. The possible mechanism through which IL-17 may cause insulin resistance is the cross-talk between IL-17 and the renin-angiotensin system, specifically involving the AT1 receptor. This receptor can induce insulin resistance by increasing cellular oxidative stress, leading to impaired insulin signaling and insulin-stimulated glucose transport activity [56]. Moreover, IL-17 neutralization with antibodies improved glucose intolerance in rats [57].

Astolphi et al. [40, 43] investigated the effects of AP on insulin sensitivity and insulin signaling in insulin-sensitive tissues. The results showed that AP promoted insulin resistance, and reduced pp185 tyrosine phosphorylation status in muscle and adipose tissues, but not in the liver. These authors suggested that higher TNF-α plasma concentrations found in the adopted experimental model can explain these changes in insulin signaling. This data reinforce the importance of the AP treatment, since apicectomy [58] and dental extraction [59] are related to reduction in plasma pro-inflammatory cytokine concentrations. Therefore, it is necessary that health professionals are aware of the aspects related to insulin resistance in order to recognize this condition as a possible systemic manifestation in patients with endodontic disease.

Conclusions

Oral inflammation, such as AP releases pro-inflammatory cytokines that can impair the insulin signal and cause insulin resistance. However, further studies are needed to verify which systemic inflammatory pathways are activated in response to oral inflammation. These questions are important as they contribute to the understanding of how local inflammation can cause metabolic disorders, for example in insulin resistance. This reinforces the importance of prevention and treatment of AP to prevent insulin resistance.

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Conflict of interest

The authors declare that they have no Conflicting interests.

List of abbreviations

AP: Apical periodontitis; T2DM: Type 2 diabetes mellitus; PI3K: phosphatidylinositol 3-kinase; T1DM: type 1 diabetes mellitus; DM: Diabetes mellitus; HbA1c: Glycated hemoglobin; IL-1: Interleukin-1; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor- alpha; IL-1ra: Interleukin-1 receptor antagonist; IL-10: Interleukin-10; IKK: IκB kinase; JNK: c-Jun N-terminal kinase; IL-17: Interleukin-17.

Author contributions

Renato Felipe Pereira - performance of literature review; writing of the manuscript and final approval of the version to be submitted. Fernando Yamamoto Chiba - performance of literature review; writing of the manuscript and final approval of the version to be submitted. Maria Sara de Lima Coutinho Mattera - performance of literature review; writing of the manuscript and final approval of the version to be submitted. Doris Hissako Sumida - conception of review; writing of the manuscript and final approval of the version to be submitted.
References


