Interaction of Adipokines with Diabetes Mellitus and Dental Implants

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Abstract
Diabetes mellitus is a chronic metabolic disease defined by the persistence of hyperglycemia leading to an inflammatory effect and a negative impact on bone formation and remodeling and impedes the osseointegration of dental implants. Dental implant surgery is a widely used procedure to replace missing teeth in patients who have diabetes. The success of an implant is dependent on osseointegration following placement. Adipokines are biologically active proteins secreted from adipose tissues, and they are considered to be involved in several functions like metabolism, immune response, inflammation. In the following article, we will describe the role of adipokines such as adiponectin, leptin, resistin, diabetes mellitus, and osseointegration of dental implants.

Keywords: Diabetes mellitus, leptin, adiponectin, resistin.

Introduction
Diabetes mellitus (DM) is a chronic metabolic disorder marked by a defect in insulin secretion associated or not with peripheral insulin resistance, resulting in hyperglycemia. The different types of diabetes can be classified as immune-mediated (Type 1 Diabetes Mellitus – dependent only on insulin therapy), insulin resistance (Type 2 Diabetes Mellitus), gestational or other forms (genetic, infections, and due to some drugs). It is associated in particular with a higher or easier deterioration of the metabolism of carbohydrates, lipids, and proteins resulting from disorders in insulin secretion, its action in tissues, or both. This metabolic disorder is prevalent worldwide. According to the International Diabetes Federation, in 2017, 425 million people have been diagnosed with diabetes worldwide, representing about 8.8% of the adults, with equal rates in both women and men [1]. According to the World Health Organisation, by 2030, diabetes is going to be the 7th dominant cause of mortality [2]. The long-term complications associated with diabetes, if not controlled, comprise cardiovascular diseases, diabetic nephropathy, foot ulcers, diabetic retinopathy, and oral diseases. Oral complications are frequent, especially periodontitis, and lead to tooth loss, delayed wound healing, and impaired response to infection. Diabetes therapy is mainly aimed at keeping blood sugar levels within normal limits and can be accomplished with a balanced diet, exercise, weight loss, and use of medications (oral anti-diabetics or insulin therapy).

Diabetes mellitus and periodontitis have been biologically related. The ubiquity of periodontitis in diabetic patients is predicted to be double or triple as compared to non-diabetic patients; therefore, it is attributed as the sixth complication of diabetes [3]. Inadequate diabetes control results in rapid and severe periodontal tissue destruction due to increased oral microbial flora, leading to an excessive immune-inflammatory response to periodontal pathogens [4]. Dental implants can be an adjunctive treatment to missing teeth as a result of periodontal disease, an injury, tooth decay, or some other reason. The paucity of bone osseointegration and primary stability of the implant is contemplated to be
the leading cause of implant failure. The constant hyperglycemia results in diminished bone formation, as it impedes osteoblastic activity and modifies the action of the parathyroid hormone, reduces collagen formation during callus formation, promotes apoptosis in lining cells of bone and boosts the osteoclastic activity [5]. As a result, bone formation is reduced. The benefits of dental implants appear to be satisfying in a diabetic patient with adequate treatment planning, prophylactic therapy, and appropriate postsurgical care only when glycemic levels are in normal limits.

The adipose tissue has significant capacity in energy storage and is also considered the largest endocrine organ that releases a number of biologically active proteins known as adipokines into the circulation. Adipokines function both locally and systematically and exhibit a range of receptors. Adipokines have a vital role in metabolism, different immune responses, and inflammation. In this review, we will describe the role of adipokines such as adiponectin, leptin, and resistin in diabetes mellitus and osseointegration of dental implants.

**Leptin**

Leptin is a non-glycosylated peptide hormone, synthesized and released from adipocytes. It has an impact on energy homeostasis, immune, and neuroendocrine functions [6] and was discovered in 1994 by Friedman and colleagues. In normal physiological conditions, leptin binds with specific receptors on appetite-modulating neurons and the arcuate nucleus in the hypothalamus. This leads to a decrease in appetite and to an increase in the energy expenditure, which, therefore, decreases adipose tissue mass and body weight, promotes glucose utilization, and ameliorates insulin sensitivity. The degree of adiposity can be observed by the level of leptin, and this is why it is also known as an “adipostat”.

Insulin secretion is inhibited by leptin in a negative feedback loop, whereas insulin provokes leptin secretion. Thus, impairment of the adipoinsular axis may increase the progression of insulin resistance. Leptin provokes fatty acid oxidation in the following way: it activates adenosine monophosphate-activated protein kinase (AMPK), particularly in muscle, resulting in a reduction of non-adipose tissue lipid stores [7]. Studies have shown higher leptin levels in persons with diabetes mellitus, probably reflecting leptin resistance. Leptin has the ability to improve or conversely induce insulin resistance as it mediates the release of insulin from pancreatic β cells. Martins et al. observed a significant correlation between leptin and obesity, hyperinsulinaemia, and insulin resistance [8]. According to Piyali and colleagues, in agreement with Ko, the leptin/adiponectin ratio is a more accurate tool for insulin resistance than adiponectin or leptin levels alone [9].

Thomas et al. stated in 1999 that leptin could increase osteogenesis differentiation in mesenchymal stem cells from the bone marrow [10]. Bone osseointegration is an inflammatory and reparative process. Therefore, leptin levels are predicted to be higher during osseointegration. Leptin stimulates osteoblastogenesis and inhibits osteoclastogenesis through stimulation of osteoprotegerin and inhibition of receptor activator for nuclear factor-κB ligand (RANKL) expression in osteoblasts [11]. In 2010, Dilsiz et al. demonstrated an increase in leptin levels after 168 hours of orthodontic force application to teeth during orthodontic tooth movement [12]. Hassani et al., in 2017, stated the presence of leptin in the peri-implant sulcular fluid (PISF) and gingival crevicular fluid (GCF); but 60 days after the dental implant procedure, its levels did not show statistically significant changes [13]. Studies have submitted the positive effect of leptin on bone mineral density (BMD). Campos et al. described that increased levels of leptin: adiponectin ratio stimulate decreased BMD and bone mineral content (BMC) in obese adolescent girls [14].

**Adiponectin**

White adipose tissues synthesize and secrete a 30 kDa protein, known as adiponectin that circulates in high concentrations (5–30µg/ml) and represents about 0.01% of the total plasma proteins. Human adiponectin is found on chromosome 3q27. It is known to have anti-atherogenic and anti-inflammatory properties, and it also regulates insulin sensitivity. Adiponectin operates using two receptors located on skeletal muscles (Adipo RI) and liver (Adipo R2) [15]. Enhanced insulin sensitivity has been shown in both rodents and humans, when treated with thiazolidinediones, an anti-diabetic drug, as adiponectin is stimulated through peroxisome proliferator activating receptor - γ (PPAR-γ) agonists [16]. Several cross-sectional studies have documented that patients with obesity, insulin resistance, or Type 2 Diabetes Mellitus (T2DM) have low levels of plasma adiponectin [17, 18]. It was observed that females have statistically significantly increased values of serum adiponectin when compared with male’s counterpart, and this can be attributed to the distinctive body fat
distribution and the response of sex hormones on the production of adiponectin, as androgens inhibit adiponectin secretion [19].

Adiponectin modulates insulin sensitivity via numerous metabolic processes. Globular adiponectin activates adenosine monophosphate-activated protein kinase (AMPK), mediated by Adipo R1, and peroxisome proliferator-activated receptor-α (PPAR-α), mediated by Adipo R2, thereby enhancing phosphorylation of acetyl-CoA carboxylase, fatty acid oxidation, glucose uptake. It also inhibits hepatic gluconeogenesis by impeding the hepatic enzyme phosphoenolpyruvate carboxylase, hence, decreasing tissue triglyceride amount in muscle and liver. Furthermore, adiponectin has an impact on the number–ber of mitochondria and types of oxidative fibers [20]. Yamauchi et al. observed an absolute reversal of insulin resistance in lipomatropic mice when treated with leptin and adiponectin together, in contrast to adiponectin or leptin alone [21].

Adiponectin improves bone formation and also inhibits bone resorption, as its receptors are expressed in osteoblastic and osteoclastic cells. In vitro studies have corroborated that adiponectin acts on osteoclasts to inhibit osteoclastogenesis and bone resorption and increases osteoblasts proliferation and differentiation. Adiponectin regulates bone turnover by stimulating the receptor activator of nuclear factor-κB ligand (RANKL) expression and inhibiting the production of its decoy receptor, osteoprotegerin (OPG) [22]. The preliminary study performed by Bai et al. indicated that systemic administration of adiponectin (2.5 μg of mouse recombinant globular adiponectin per day) is expected to stimulate osteogenesis around peri-implant surface [23]. According to these observations, it could be proposed that adiponectin might lead to a significant decrease in the incidence of hyperglycemia and could enhance bone osseointegration in dental implant cases. Intake of soy protein, fish oils, and linoleic acid might lead to higher adiponectin levels [24].

Resistin

Resistin is an adipocyte-secreted polypeptide discovered in obese mice in 2001, and it has the capacity to interfere with the action of insulin, increasing insulin resistance in tissues. Human resistin is a cysteine-rich peptide of 12.5 kDa, with a sequence of 108 amino acids. In mice, resistin is secreted from white adipose tissue, while in humans, other than adipocytes, it is mainly secreted by peripheral blood mononuclear cells, TNF-α-induced macrophages, with the highest concentration in bone marrow cells. Resistin levels in human serum range from 7 to 22 μg/ml. Thiazolidinediones drugs down-regulates the expression of murine adipocytes through activating peroxisome proliferator-activated receptor – γ (PPAR-γ). Resistin has been associated with insulin resistance and inflammation. In rodents, resistin impairs glucose tolerance and insulin action, whereas, administration of an anti-resistin antibody improves glucose levels and insulin action [25].

Tokuyama et al. and Fujinami et al. illustrated significantly high resistin values in diabetic subjects compared to the control group [26, 27]. Al-Harithy and Al-Ghamdi also observed similar findings in obese diabetic subjects [28]. On the contrary, Heilbronn et al. and Takeishi et al. reported no significant changes in resistin concentrations among normal-weight subjects, obese non-diabetic subjects, and obese patients with diabetes mellitus [29, 30]. For these reasons, the role of resistin in human obesity is disputed. Chen et al. and Schwartz et al. interpreted that high serum resistin level subjects have a significantly higher risk of developing T2DM [31, 32].

Resistin stimulates osteoblastic and osteoclastic cells and enhances their differentiation. It influences the osteoclastic differentiation directly via activation of nuclear factor-kB promoter and proliferation of MC3T3-E1 cells in a protein kinase A (PKA)- and protein kinase C (PKC) dependent manner and expression of interleukin-6 in the cells. An increase in osteoclastic activity is indirectly through stimulation of interleukin-6 (IL-6) [33].

An inverse correlation is observed between resistin levels and osteocalcin levels in subjects having osteoporotic hip fractures [34]. The role and function of resistin in obesity, diabetes, and pathogenesis of osteoporosis is still not certain, probably due to the limited studies existing until now.

Conclusion

Uncontrolled diabetes on dental implants can have an inflammatory effect and impedes the osseointegration of bone around implants. Adipokines play a major role in insulin sensitivity and inflammation. Also, adipokines can be useful in developing new medical strategies for prevention and treatment interventions in order to upgrade the success rate of dental implants in diabetic patients. However, further studies should be performed on the role of biomarkers in dental surgical therapy in the case of diabetic patients.
Conflict of Interest

The authors declare no conflict of interest.

References


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