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Fetuin-A, Preptin, and Ceruloplasmin: A Possible Link Between Chronic Periodontitis and Diabetes Mellitus: A Review

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Abstract
Chronic periodontitis (CP) is a common inflammatory disease which is characterized by progressive destruction of the tooth supporting structures and ultimately, potential tooth loss. A relationship between CP and diabetes has been recognized for some time. Both diseases share several collective risk factors, however, recent research has provided greater insight into the relationship with evidence emerging for each disease being a co-factor in the pathogenesis of the other. This article focuses on some biochemical markers as valuable utility in risk assessment, clinical screening, diagnosis, and prognosis prediction of chronic periodontitis and diabetes mellitus.

Introduction:

Today, Diabetes mellitus (DM) is a major worldwide health problem leading to markedly increase mortality and serious morbidity. Every 30 seconds, one person in the world loses a leg due to lack of awareness of diabetes and diabetes controls. It's a clinically and genetically heterogeneous group of endocrine metabolic disorders characterized by consistent elevated levels of glucose in the blood with disturbance of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. and hyperlipidemia, which have a severe impact on public health [1].Insulin mediates its action through phosphorylation of the insulin receptor, insulin resistance associated with

enhanced hepatic glucose output and impaired insulin secretion due to a progressive decline of β-cell function[1-4].To a third of diabetic patients, scold of odontogenic abscesses, brilliantly mouth syndrome, xerostomia, gingivitis and periodontitis [5].

Periodontitis is considered to be a multifactorial, infectious disease that affects the periodontium and is caused by an impaired immune response to oral bacteria. It is considered to be one of the most common inflammatory diseases throughout the world and causes harm to both the connective tissue and bone. Periodontitis is a primarily infectious and inflammatory disease caused by anaerobic bacteria (Porphyromonas gingivalis, Treponema denticola, Prevotella intermedia, Prevotella nigrescens, Eikenella corrodens, Aggregatibacter actinomycete-mcomitans, among others) in association or not with other periodontopathogens, in dental biofilm. It affects teeth's protection and support tissues as gingiva and alveolar bone and can lead to dental mutilation [6].

The two main forms are aggressive periodontitis and chronic periodontitis (CP). The characteristic feature of latter is destruction of the supporting structures of the teeth [7]. CP is a major public health problem due to its high prevalence and because it may lead to tooth loss and disability.

1. Chronic periodontitis and Diabetes Mellitus

For decades, a significant close association between diabetes and periodontitis has been confirmed, where evidence suggests that diabetes is a contributing factor in worsening the condition of periodontal disease, on the same hand, periodontal disease has a higher incidence in diabetics, and is claimed to be more prevalent and severe in diabetics when compared to healthy individuals [8].

Coexistence of periodontitis in diabetic patients is attributed to failure of the body's immune system to completely eliminate the source of inflammation such as microorganisms, this in turn, keeps the inflammatory process continuously activated, therefore, a chronic inflammatory reaction is induced[9].This chronic inflammatory response is the main etiologic factor of systemic upregulation of different pro-inflammatory cytokines such as interleukins (IL-1β, 4, 6, 8, and 10) as well as tumor necrosis factor-α (TNF-α) [10,11].

2. Fetuin-A

Adipose tissue is a complex, essential, and highly active metabolic and endocrine organ. These tissues communicate with each other via secreted mediators, such as adipokines, hepatokines and myokines, to maintain metabolic homeostasis [12,13]. Among these mediators, fetuin-A is fetuin-A, also known as α2-Heremans–Schmid glycoprotein (AHSG), is a member of the cystatin superfamily. It is a 59 kDa glycoprotein is the only factor which is produced predominantly in the hepatocytes and secreted into serum that is an endogenous inhibitor of the insulin-stimulated receptor tyrosine kinase, protease inhibitory activity and subsequently decrease glucose clearance and enhance insulin resistance. In addition, fetuin-A could suppress adiponectin expression[2].Fetuin-A binds the β subunit of the insulin receptor; thus, it does not compete with insulin binding, reversibly binds the insulin receptor tyrosine kinase in peripheral tissues, thereby inhibiting the insulin-induced intracellular signal cascade and producing peripheral insulin resistance[14,15].To date, only 2 proteins are known to bind the ectodomain of the insulin receptor, insulin and fetuin-A; the former stimulates signal transduction and the later inhibits it[16].

Fetuin-A is a negative acute phase protein whose synthesis is down regulated by the inflammatory cytokines interleukin-1, interleukin-6, TNFα and interferon-ɣ [17,18].Fetuin-A is an enigmatic protein because of important for lots of pathways in mammalian, but its level is influenced by several factors including aging, high fat diets, calorie restriction, medication such as thiazolidinedione, niacin, omega-3 polyunsaturated fatty acids[19].

Epidemiological research confirmed that serum fetuin-A became associated with IR and its comorbidities, including metabolic syndrome and DM [20].

Whole saliva is a mixture of gingival fluids and secretions of the salivary glands which protects all the tissues of the oral cavity. Saliva is defined as an accessible bi-oxide which contains components derived from the oral mucus surfaces, gingival crevices, and tooth surfaces. It contains a large number of proteins that have maintain oral homeostasis metabolic, immune response, transporting, and several other cellular functions, as well as it contains microorganisms that colonise the mouth, and other exogenous substances, and can therefore provide a picture of the host's relation to the environment [21-23].
Determination of the saliva components levels reflect the microbial condition and severity of periodontitis [24]. Because of saliva's ready availability it is suitable for study. it is considered as the gold standard in biochemical assays and analysis [25].

3. Preptin

Preptin is a recently isolated [34- amino acid peptide hormone] from secretory granules that is co-secreted from the cells of pancreas along with insulin, amylin, and pancreastatin. Its precursor is Pro-IGF-II, which also produces insulin-like growth factor II (IGF-II). IGF-II is involved in the regulation of cell growth, differentiation, and metabolism [26].It is also expressed in the salivary gland, mammary tissue, and kidneys[27].

It is still controversial whether the cause of the increased insulin level seen as a result of resistance is due to increased capacity of the pancreatic cells or stimulation of insulin secretion by preptin. Preptin acts as a physiological amplifier of glucose-mediated insulin secretion through the activation of the insulin-like growth factor 2 receptor (IGF2R) linked to the protein kinase C (PKC)-phospholipase C pathway to induce calcium-dependent insulin secretion under high glucose conditions [28].

The association between preptin concentrations and the insulin that is increased in circulation due to insulin resistance in T2DM[29].

4. Ceruloplasmin

Human ceruloplasmin (Cp: EC 1.16.3.1: 132kDa) is one the important components of the multicopper oxidase family of enzymes[30].It is it binds six or seven copper ions per molecule that is expressed in several tissues, including liver, brain, retina and lung.). Although Cp is generally considered a secreted plasma protein, a membrane-bound isoform has been identified in the brain and in cavernosal tissue. It is an inflammation sensitive as well as an acute phase protein. It has ferroxidase property which contributes to its antioxidant nature·Ceruloplasmin acts as an antioxidant can catalyze the oxidation of Fe2+ ,and it also scavenges superoxide anion radical[31-33].

Uric acid

Uric acid is the terminal degradation product of purine catabolism generated after breaking of DNA, RNA, ATP and proteins, and may serve as a connective and vascular damage mediator. The rate-limiting step of UA production is an enzymatic reaction of the xanthine dehydrogenase / xanthine oxidase (XDH/XO) enzyme that oxidizes hypoxanthine-xanthine into UA. UA contributes to the antioxidant capacity of both blood and saliva. However, the enzyme responsible for its production also generates free radicals and several studies have shown that uric acid can act as a pro-inflammatory and pro-oxidant agent. Elevated uric acid concentrations favor the development of kidney problems and increase the chances of development of obesity, metabolic syndrome, diabetes, fatty liver, arterial hypertension and cardiovascular disease. It may also stimulate the production of CRP, known to be a predictive marker of progression of atherosclerotic cardiovascular disease [34,35].

Aim of the study

The present study aimed to spot the light on the possible role of serum and salivary levels of fetuin-A, preptin, ceruloplasmin, and UA as potential biomarkers of periodontitis in diabetic patients in an effort to understand their role in the link between both diseases.

Discussion

The adipose tissue actively secretes a variety of adipocytokines that are involved in inflammatory processes, unhealthy adipose tissue metabolism detected in DM was believed to adversely impact other organs including periodontal tissues, through creation of a variety of biomarkers such as, adipokines, TNF-α, IL-6, as well as other pro-inflammatory cytokines [36,37].
The influence of DM on CP is well-accepted, whereby there is also substantial evidence indicating that diabetes is a risk factor for CP (**38**).
The acidic pH of saliva leads metabolic acidosis which in turn loss the protective mechanism of saliva in diabetes patients. This acidic pH promotes the growth of aciduric bacteria and allows the acidogenic bacteria to proliferate creating an inhospitable environment for the protective oral bacteria. Oral environmental balance is changed and is favorable for cariogenic bacteria, lowers the PH further and the cycle is continues [39].

The persistent hyperglycemia alters both blood vessels and basement membrane permeability of salivary gland, leading to an increase of glucose percolation as well as other small molecules like urea, which are not secreted by salivary gland from blood to saliva through gingival crevices. The association of salivary glucose increase, and the salivary flow rate decrease was reported to be implicated in xerostomia for diabetic patients.

5. Fetuin-A, Chronic periodontitis and Diabetes Mellitus

Fetuin-A, a member of the cystatin superfamily of protease inhibitors, is secreted by the liver in adults and by various fetal tissues. It is associated with insulin resistance and metabolic syndrome. It binds to the β-subunit of the insulin receptor, thus activating insulin receptor kinase. Some studies have reported high concentrations of fetuin-A in patients with type 2 DM, and others have reported low concentrations.

Consequently, fetuin-A contributes to pathogenesis of diabetes mellitus and CP disease through its effects impairing the metabolism with the development of insulin resistance as well as fetuin-A induced inflammation[40].and induced suppression of Adiponectin production. Adiponectin as adipokine is associated to insulin resistance and inversely related to TNF-α[41]. Another reason for higher fetuin-A concentration in GCF and saliva in patients with dental calculus than in patients without dental calculus may be due to a higher affinity to hydroxyapatite, which is the major mineral of dental calculus [42].

6. Preptin, Chronic periodontitis and Diabetes Mellitus

Preptin is a recently identified adipocyte-derived hormone that has been shown to play a substantial role in the development of insulin resistance. It was hypothesized that preptin may be one of the links between obesity, insulin resistance, and diabetes.

1. Measurement of preptin in saliva is noninvasive, simple which could contribute to the explanation of the physiology and pathological role of preptin[43].

Increased counts of monocytes and macrophages in periodontitis which express higher concentration of preptin, could be held responsible for the increased value of preptin in group II. Another reason for this increased value could be that P gingivalis, being a keystone pathogen in periodontitis could stimulate release of preptin from neutrophils via LPS[44].

7. Ceruloplasmin, Chronic periodontitis and Diabetes Mellitus

Ceruloplasmin is part of a family of acute phase proteins with a response of

intermediate magnitude that typically plays a protective role in response to an immune infuriating incentive. It is a multifunctional copper containing protein that was first isolated in blood in 1948. One of its main roles is as an antioxidant, as it has substantial ferrooxidase activity and can sequester other free radicals [4546,].

The exact mechanism underlying this positive association between ceruloplasmin levels and progression of chronic periodontitis is largely unknown. One plausible explanation is that its role in the ferroxidase activity which is of greatest importance as it converts reduced (ferrous) linked with transferrin to oxidized (ferric) iron linked with ferritin. Fe^{+2} acts as a pro-oxidant agent because of its readiness to change from one valency state to another. In its free form, iron is one of the most effective antioxidant catalysts. There are several mechanisms which have been suggested for ceruloplasmin antioxidant activity, including the protecting the organism as a whole from within the possible ill effects caused by the release of free radical oxidation products[46].Considering that increased oxidative stress and oxidized LDL are known to be associated with progression of diabetic kidney disease, elevated ceruloplasmin level might reflect or augment progression of diabetic complication[47].This suggests that the organism might respond by raising the antioxidant efficiency of plasma by elevating ceruloplasmin levels [46].

8. Uric acid, Chronic periodontitis and Diabetes Mellitus

Uric acid (UA) is the most abundant antioxidant, non-enzymatic molecule of plasma origin in saliva, and its concentration in saliva is similar to that in serum [48].

There are several mechanisms that may be responsible for this association between diabetes mellitus type 2 and uric acid serum levels.

1. The elevated uric acid may promote endogenous aggression in canaliculi and hepatic joint capsules, and especially the collagen coating the periodontium.
2. Higher levels of serum insulin may decrease uric acid clearance by kidneys causing hyperuricemia, the mechanism behind this association remains obscure. The most conceivable hypothesis is that this occurs at the renal level. Renal tubular function is influenced by hyperinsulinemia, and urinary uric acid clearance decreases with decreasing insulin mediated glucose disposal. Thus, decreased uric acid excretion leads to hyperuricemia, So that the elevation of uric acid levels observed in patients group might reflect a compensatory mechanism to neutralize the oxidative stress associated with this disease [49].
3. Nitric oxide has various physiological properties including vasodilatation, inhibition of platelet aggregation, neutrophil adhesion, scavenging superoxide (O -2) radical, inhibition of xanthine oxidase activity and has a crucial role in glucose intake, therefore, its reduction will lead eventually to less intake of glucose in skeletal muscles. Induction of endothelial dysfunction through reduction of NO by high UA concentrations [50,51].

Conclusion:

Fetuin-A, preptin, ceruloplasmin, and UA levels are biomarkers which may be used as a possible non-invasive technique for periodontal disease diagnosis, suggesting a role of these marker in the pathogenesis of periodontal disease as well as in the connection between periodontal disease and diabetes.

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