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Editorial

Oral Disease and Diabetes Mellitus: Local Health Links Systemic Health

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Diabetes Mellitus (DM or diabetes) is a heterogeneous chronic metabolic disorder with high blood sugar (hyperglycemia) resulting from defects in insulin secretion or insulin action. Type 2 diabetes mellitus (insulin resistance, or called non-insulin dependent diabetes mellitus, NIDDM, T2D) accounts for about 90%. Type 1 diabetes (lack of insulin, also called insulin dependent diabetes mellitus, IDDM or juvenile diabetes, T1D) and gestational diabetes mellitus (insulin resistance during pregnancy, GDM) account for about 10%. DM has been emerging as an epidemic disease around the world. There are 366 million people worldwide suffering from diabetes in 2011, and this number is predicted to increase by about 50% by year 2030 [1]. In the U.S. diabetes affects 25.8 million or 8.3% population [2]. The economic cost of diagnosed diabetes in the U.S. in 2012 is $245 billion, including $176 billion in direct costs and $69 billion in reduced productivity (disability, work loss, premature mortality) [3]. Its complications include retinopathy, nephropathy, neuropathy, cardiovascular disease and impaired wound healing.

Over the past decades oral disease has been recognized as in close connection with the systemic diabetes mellitus particularly among elder people [4-9]. Periodontal Disease (PD) has been acknowledged as the sixth complication of diabetes [10]. Oral mucosal lesions, xerostomia and other oral diseases are also reported in association with diabetes [11-14]. Oral disease is a major public health problem in both developed and developing countries [15-19]. According to the US Centers for Medicare and Medicaid Services report the expenditure for dental services in 2012 is $110.9 billion and projected to $167.9 billion in 2020 [20].

Accumulating evidence demonstrates that diabetes mellitus and oral disease have a bidirectional relationship [21-24]. Patients with oral disease have more prevalence of DM, and DM increases the risk for and severity of periodontitis and other oral diseases [25,26]. Treatment of oral diseases can significantly improve the glycemic control of DM patients and vice versa [21,27-29]. The tremendous amount of observations of the link between oral disease and diabetes mellitus deserve great attention in tackling these two highly prevalent and closely related chronic diseases.

People are investigating through pathological and biochemical ways to elucidate the mechanisms that are underlining the local oral disease and the interrelated systemic diabetes mellitus. Up to date the mechanisms by which oral diseases may affect diabetes mellitus are not well established. Several hypotheses have been postulated to describe the possible manifestations of these two interplaying epidemics.

Pro-inflammation is one mechanism for this pathogenic feed-forward loop [30-32]. Oral inflammation and pathogens and their toxins (especially lipopolysaccharide, LPS) may activate macrophages and T lymphocytes that trigger the production of pro-inflammatory cytokines (such as IL-1, IL-6, TNF-β, lymphotoxin, prostaglandins and high sensitivity C-reactive proteins) [33], enzymes (such as Paraoxonase-1, PON-1) [34] and oxidative stress molecules that have important effects on lipid, glucose and protein metabolism. These pro-inflammatory cytokines have been identified as a potent antagonist to the cell surface insulin-receptor protein needed for proper glucose transport and directly related to the impairing of insulin sensitivity or action. The resistance to insulin action results in the irreversible formation of advanced glycation end-products (AGEs) under hyperglycemic conditions [31]. AGE-RAGE axis has been proposed as playing an important role in tissue destruction and impaired repair in diabetes-associated periodontitis [22]. AGEs impart their pathogenic effects by interaction with their specific cellular receptor for AGE (RAGE) on macrophages and monocytes that induce a hyper-responsive state, leading to enhanced secretion of various proinflammatory cytokines to predispose to chronic tissue inflammation, progressive tissue breakdown, and diminished capacity for tissue repair, thus contributing to periodontitis.

One of the molecules formed by the nonenzymatic addition of glucose is glycated hemoglobin (HbA1c). Researches indicate that levels of HbA1c and fasting blood glucose (FBG) significantly correlated with periodontal health among individuals with T2D [35]. HbA1c within red blood cells (erythrocytes) circulates and persists in the bloodstream for up to 120 days, it forms the basis for a convenient clinical indicator of the degree of glycemic control. Prediabetic conditions, which include impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), might be associated with chronic gingival and/or periodontal inflammation [36-38].

Diabetes mellitus favors the occurrence of oral morbidity through gum's microvascular disorders, the selection and development of an aggressive bacterial plaque and through an exaggerating inflammatory response to the microflora within the oral cavity. *Actinobacillus actinomycetemcomitans*, *Campylobacter rectus*, *Helicobacter pylori Porphyromonasgingivalis*, human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV-1) have been reported as prevailing pathogens in oral diseases [39]. *A. actinomycetemcomitans* is associated with periodontitis in patients with diabetes while *P. gingivalis* in patients without diabetes [40,41].

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There are reports demonstrating that collagen molecules are more easily glycated under the hyperglycemic conditions, leading to excessive cross-linking, and collagenase is increased in the crevicular fluid of diabetic patients. This resulted in accumulation of abnormally glycated, highly cross-linked gingival collagen, thereby adversely affecting normal tissue turnover and healing in diabetic individuals [42-44].

Resistin is recently acknowledged as a biomarker that links periodontal disease with systemic diseases, such as DM. Resistin is a newly discovered adipocytokine and considered as a peptide hormone, initially thought to be produced by adipocytes alone, and later found also produced in abundance by various cells of the immunoinflammatory system, indicating its role in various chronic inflammatory diseases. A three-way relationship has been established between diabetes, obesity and periodontitis [45].

Human β-Defensins (hBDs) have been reported having a strong antibacterial action against various microorganisms, especially periodontal pathogens. HBD-1 and hBD-3 have been shown to be related to DM and periodontal disease [46].

DM can change the oral environment that affects the oral microbiota. That may account for the increased severity of aggressive oral infections and poorer glycemic control in DM patients [47-49].

Many other conditions can predispose and/or facilitate the occurrence of PD, such as smoking and obesity that are linked to diabetes mellitus. The best predictor for severe periodontal disease in subjects with T2D is smoking followed by HbA1c levels. T2D subjects should be informed about the increased risk for periodontal disease when suffering from T2D [50].

There are some controversies among the results of the link between PD and DM. In one report with periodontal treatment as predictor and the actual change in hemoglobin A1c level as the outcome, it showed that none was statistically significant [51]. Another research with Mexican-American population also showed that no statistically significant differences were found in the changes of HbA1c levels between test and control groups. Non-surgical periodontal therapy improved the magnitude of change in periodontal parameters as compared to the control subjects [52]. The causes of the discrepancy among the research results may come from sampling size, bias, analysis method, heterogeneity and the chronic properties of these two epidemic diseases [53].

Although there is a strong body of evidence that supports the relationship between oral health and diabetes, oral health awareness is lacking among patients with diabetes and other health professionals [54-56]. In future directions, there is a real need for larger, prospective, controlled, longitudinal and cross-sectional clinical studies, together with studies of animal models and cells/tissues in vitro [22,54] and emphasizes for more researches to define a clear relationship between these interplaying complications. More importantly this knowledge needs to be informed to the public about this interface, especially for patients with diabetes and/or oral diseases to be aware of the interrelationship of these two chronic epidemics.

We are aware that the mouth is an integral part of the body and as the Chinese saying goes, illness comes from the mouth, we should pay great attention to dental hygiene in order to improve our body health. Taken together, oral diseases have an adverse impact on the glycemic control of diabetes and diabetes increases the prevalence and severity of oral diseases . This calls for cooperative work between inter-professional health management in the provision of overall health care for patients with oral disease and systemic diabetes.

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