Association between T1DM and Periodontal Diseases

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Gingivitis and periodontitis are chronic inflammatory diseases that affect the supporting tissues of the teeth. Although induced by the presence of bacterial biofilms, other factor, such as tobacco smoking, drugs, and various systemic diseases, are known to influence their pathogenesis. Diabetes *mellitus* and periodontal diseases correspond to inflammatory diseases that have pathogenic mechanisms in common, with the involvement of pro-inflammatory mediators. There seems to be an association between periodontal disease (PD) and Type 1 diabetes *mellitus* (DM1), and the prevalence and severity of PD was higher in DM1 patients when compared to healthy controls.

Keywords: periodontitis ; type 1 diabetes mellitus ; glycemic control

1. Introduction

Type 1 diabetes *mellitus* (DM1), also known as insulin-dependent diabetes or juvenile diabetes, has an idiopathic or autoimmune cause in which there is a destruction of the pancreatic β-cells [1][2][3][4]. It can be diagnosed at any age, but this type of diabetes often manifests itself in children, adolescents, and young adults [4]. According to the American Diabetes Association, type 1 diabetes represents about 5–10% of patients with diabetes [5][6].

Periodontal disease (PD) is a chronic inflammatory disease that causes the destruction of the tissues that support the tooth. This inflammatory process is caused by the presence of Gram-negative bacteria, which accumulate along the tooth margin, promoting a chronic and progressive local inflammatory response [5][7][8][9][10][11]. Gingivitis and periodontitis are the two forms of periodontal disease. Gingivitis is a superficial inflammation of the periodontium in which there is no attachment loss. When left untreated, it can reach the deep periodontium, evolving to periodontitis, which is an irreversible inflammation of the periodontium with tissue destruction and bone resorption [9][12]. The consequent loss of support structure can lead to loss of tooth parts and systemic inflammation [8][13].

Diabetes *mellitus* and PD correspond to inflammatory diseases that have pathogenic mechanisms in common, with the involvement of pro-inflammatory mediators [14]. According to some studies, the presence of elevated levels of pro-inflammatory mediators in the gingival tissues of diabetic patients, such as IL1-β (interleukin 1 beta), tumor necrosis factor (TNF-α), IL-6 (interleukin 6), matrix metalloproteinases (MMPs), prostaglandins (PGs), nuclear factor-kappa B receptor activator ligand/osteoprotegerin relationship (RANK-L/OPG), and oxidative stress, plays an important role in the initiation and progression of periodontal disease [14][15][16][17][18].

Type 1 diabetes *mellitus* is associated with elevated levels of systemic markers of inflammation. The elevated inflammatory state in diabetes contributes to both microvascular and macrovascular complications, and hyperglycemia can result in the activation of pathways that enhance inflammation, oxidative stress, and apoptosis [19].

The level of glycemic control is of key importance in determining increased risk of periodontal disease. The glycated hemoglobin (HbA1c) test is also widely used for the detection and control of diabetes mellitus. This test determines the amount of glucose that is irreversibly bound to the hemoglobin molecule of red blood cells and which will remain bound throughout its lifetime, around 30 to 90 days. The normal value for hemoglobin HbA1c is less than 6.5%; the higher the glucose level, the higher the percentage of glycated hemoglobin [19][20].

2. Association between T1DM and Periodontal Diseases

2.1. Glycemic Control

The evidence suggests that the level of glycemic control is of key importance in determining increased risk of periodontal disease [15][19][21]. For this reason, periodontal literature used categorical values for Glycated Hemoglobin (HbA1c) as seen in the new consensus report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant

Diseases and Conditions for the staging and grading of periodontitis [22]. The goal of research led by Dicembrini et al. [8] was to investigate the prevalence of PD in DM1 patients and its association with glycemic control and glucose variability. A significant correlation was found between mean Clinical Attachment Loss (CAL) and Glucose Coefficient Variation (CV) (r = 0.31, *p* = 0.002), but not with Glycated Hemoglobin (HbA1c) (r = 0.038 *p* = 0.673). Furthermore, mean Periodontal Probing Depths (PPD) were associated with CV but not with HbA1c (r = 0.27 and 0.044; *p* = 0.007 and 0.619, respectively). A positive correlation between the CV and DM1 was seen after adjusting for the main confounders.

Furthermore, Jindal et al. [23] investigated the relationship between the severity of PD and glycemic control in DM1 patients in a hospital-based study, and the DM1 patients with poor metabolic control (PMC) exhibited increased inflammation (*p* < 0.005), more dental plaque, and clinical attachment loss when compared to those with fair and good glycemic control (GMC).

2.2. Advanced Glycated-End Products

The presence of chronic hyperglycemia is related to the increased production of Advanced Glycated-End products (AGEs). AGEs are implicated in suppressed collagen production by gingival and periodontal ligament fibroblasts [3][24]. In addition, the binding of AGEs to a receptor increases the production of pro-inflammatory mediators, such as interleukin-1 β (IL-1β), tumor necrosis factor α (TNF)-α, and interleukin-6 (IL-6), involved in periodontal destruction [19][25].

The study of Zizzi et al. [24] attempted to evaluate the expression of AGEs in Diabetes-Mellitus-associated periodontitis. According to their findings, AGE-positive cells were not found either in fibroblasts or in gingival inflammatory cell infiltrates in subjects of the control group and in the group of systematically healthy individuals affected by chronic periodontitis. On the other hand, in the group of subjects with DM1 affected by chronic periodontitis, there was found a positive correlation between the duration of DM and the percentage of AGE-positive cells in epithelium (r: 0.610; *p*: 0.012), vessels (0.635; *p*: 0.008), and fibroblasts (r = 0.589; *p*: 0.016). A positive association was found between gingival expression of AGEs and the duration of DM1.

Periodontal disease is an inflammatory process caused by Gram-negative anaerobic bacteria that are present in bacterial plaque along the tooth margin, causing a chronic and progressive response. For this reason, the presence of inadequate oral hygiene might contribute to the development of periodontal inflammation and further tissue destruction [26]. Moreover, the results by Roy et al. [27] showed that the mean presence of plaque, GI, and BOP and the mean sites with GI score ≥ 1 were appreciably higher in the DM1 group than in the control group, which suggests that these subjects will be more susceptible to developing periodontitis in the future. However, concerning the diagnosis of periodontal disease, no significant differences were observed. Gingivitis was present in 68% of the diabetics and 60% of nondiabetic subjects.

2.3. Pro-Inflammatory Mediators

After the inflammatory stimulation, the pro-inflammatory cytokines such as IL-1β, IL-6, interleukin-8 (IL-8), and TNF-α and other pro-inflammatory mediators like prostaglandin E2 (PGE2) and Matrix Metalloproteinase (MMP) and the receptor activator of nuclear factor kB ligand (RANKL), as well as T cell regulatory cytokines (interleukin 18- IL-18) will increase, and periodontal destruction will occur [3][14][19][28][29][30]. There are eight studies that support that evidence [3][8][17][18][24][28][29][31]. The study by Keles et al. [29] targeted parameters such as gingival crevicular fluid IL-18 and TNF-α levels in diabetic children with gingivitis. The clinical periodontal parameters, gingival crevicular fluid IL-18 and TNF-α levels, were similar between diabetic and systemically healthy children (*p* > 0.05). The gingivitis subgroups showed a significantly higher PI, GI, PPD, GCF volume, and TNF-α total amounts than the healthy subgroups (*p* < 0.0001). However, the IL-18 concentrations were significantly higher in the periodontally healthy subgroups than in gingivitis subgroups. The TNF-α were positively correlated with PI, GI, PPD, GCF volumes, and IL-18 concentration (r = 0.552, *p* = 0.01; r = 0.579, *p* = 0.01; r = 0.534, *p* = 0.01, respectively). However, there was a negative correlation between the IL-18 concentration and the TNF-α (−0.524, *p* = 0.01). It is known that the presence of TNF-α in periodontal tissues acts as a risk factor for the beginning of alveolar bone destruction and periodontal connective tissue breakdown by increasing both secretion of matrix metalloproteinases and osteoclast formation [29][32]. The increased gingival crevicular fluid (GCF) TNF-α in DM1 children with gingivitis confirms that TNF-α is closely related to gingival inflammation [29].

The IL-18 belongs to the IL-1 superfamily and has been implicated in the pathogenesis of chronic diseases, including DM1. According to the scholars, despite of the fact that previous studies have reported that serum IL-18 levels in diabetic children were higher when compared to healthy controls, there is no evidence of the GCF IL-18 levels from diabetic and non-diabetic children [29].

Another aspect worth considering is the circulating levels of RANKL and osteoprotegerin (OPG) in the extent of periodontal destruction. According to the literature, the OPG and RANKL have been suggested to play an important role in the differentiation of osteoclasts and, furthermore, in periodontal-disease-associated bone loss [18]. The study by Antonoglou et al. [18] showed that DM1 patients with no or mild periodontitis had a total of 16 sites (16.4 ± 14.5) presented with bleeding and PPD ≥ 4 mm and 0.7 sites (0.7 ± 1.0) with attachment loss (AL) ≥ 4 mm. When compared to severe periodontitis, the corresponding figures were (39.6 ± 21.9) and (38.8 ± 18.5) respectively, which suggest that PPD and AL increase with the severity of periodontal disease in DM1 subjects.

The OPG was 135 pg/mL in subjects with severe periodontitis and 96.0 pg/mL in those with no or mild periodontitis. The results showed a positive association between AL ≥ 4 mm and severity of periodontitis and the level of serum OPG. However, when the analyses included only non-smokers, the positive association mentioned above showed a major drop in the strength and statistical significance. The results did not find any association between serum RANKL level or RANKL/OPG ratio and periodontal variables. The RANKL in the group of subjects with no or mild periodontitis was 18.1 pg/mL and 33.2 pg/mL for those with severe periodontitis. Concerning the RANKL/OPG ratio, the values were (0.2 ± 0.1) for the first group (no or mild periodontitis) and (0.1 ± 0.1) for those with severe periodontitis. According to their study, the serum OPG, which is a marker of systemic inflammatory burden, could also be an indicator of periodontal tissue destruction in DM1 subjects [18].

3. Conclusions

Periodontal disease was associated with glucose variability in DM1 patients. Furthermore, an increased periodontal inflammatory tendency corresponded to those individuals with poor metabolic control. DM1 subjects with increased HbA1c levels were associated with an increase in plaque index, gingival index, probing depths > 3 mm, and clinical attachment loss when compared to healthy subjects. According to some studies, longer durations of DM were associated with greater periodontal attachment loss.

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