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OPINION
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Depression and Inflammatory Periodontal Disease Considerations—An Interdisciplinary Approach

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INTRODUCTION

Periodontal disease, a bacterially mediated inflammatory disease of the gingival and adjacent periodontal attachment apparatus, represents, after dental caries, the leading cause of tooth loss among adults in developed countries due to the destruction of the periodontal ligament and the loss of the adjacent supporting bone, the tissues which support the teeth (Pihlstrom et al., 2005).

Depressive disorders, the most commonly diagnosed conditions in psychiatry (Ustün et al., 2004; Kessler and Bromet, 2013), include, according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5): disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode) an extensive prevalent disorder ranked third among the primary causes of global illness (Mathers and Loncar, 2006), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder (American Psychiatric Association, 2013; Patten, 2013).

The aim of this article is to summarize the current knowledge about the periodontal disease—depression relationship and to discuss the plausible mechanisms underlying this possible bidirectional association, by which each disease may contribute to the other (**Figure 1**).

THE PERIODONTAL DISEASE-DEPRESSION ASSOCIATION'S STUDIES

An extensive body of clinical research (Monteiro da Silva et al., 1996; Moss et al., 1996; Genco et al., 1999; Ronderos and Ryder, 2004; Dosumu et al., 2005; Klages et al., 2005; Saletu et al., 2005; Johannsen et al., 2006, 2007; Rosania et al., 2009; Ababneh et al., 2010; Li et al., 2011; López et al., 2012) and experimental animal models (Breivik et al., 2006) documents the causal relationships between periodontitis and depression. Moreover, it has been revealed that clinical depression may also have a negative effect on periodontal treatment outcomes (Elter et al., 2002), paralleling other research indicating that psychosocial factors are predictive not only of surgical outcome, but also play a significant role in postoperative recovery (Rosenberger et al., 2006). Furthermore, antidepressants, such as fluoxetine, a selective serotonin reuptake inhibitor, have demonstrated suppressive effects on the inflammatory response and on periodontal disease severity not only in a rat ligature-induced periodontitis model (Branco-de-Almeida et al., 2012; Aguiar et al., 2013; Galli et al., 2013), but also in patients with periodontitis with clinical depression (Bhatia et al., 2015). In contrast, several clinical studies (Anttila et al., 2001; Persson et al., 2003; Solis et al., 2004, 2014; Castro et al., 2006; Cakmak et al., 2014) and experimental animal model studies (Soletti et al., 2009)

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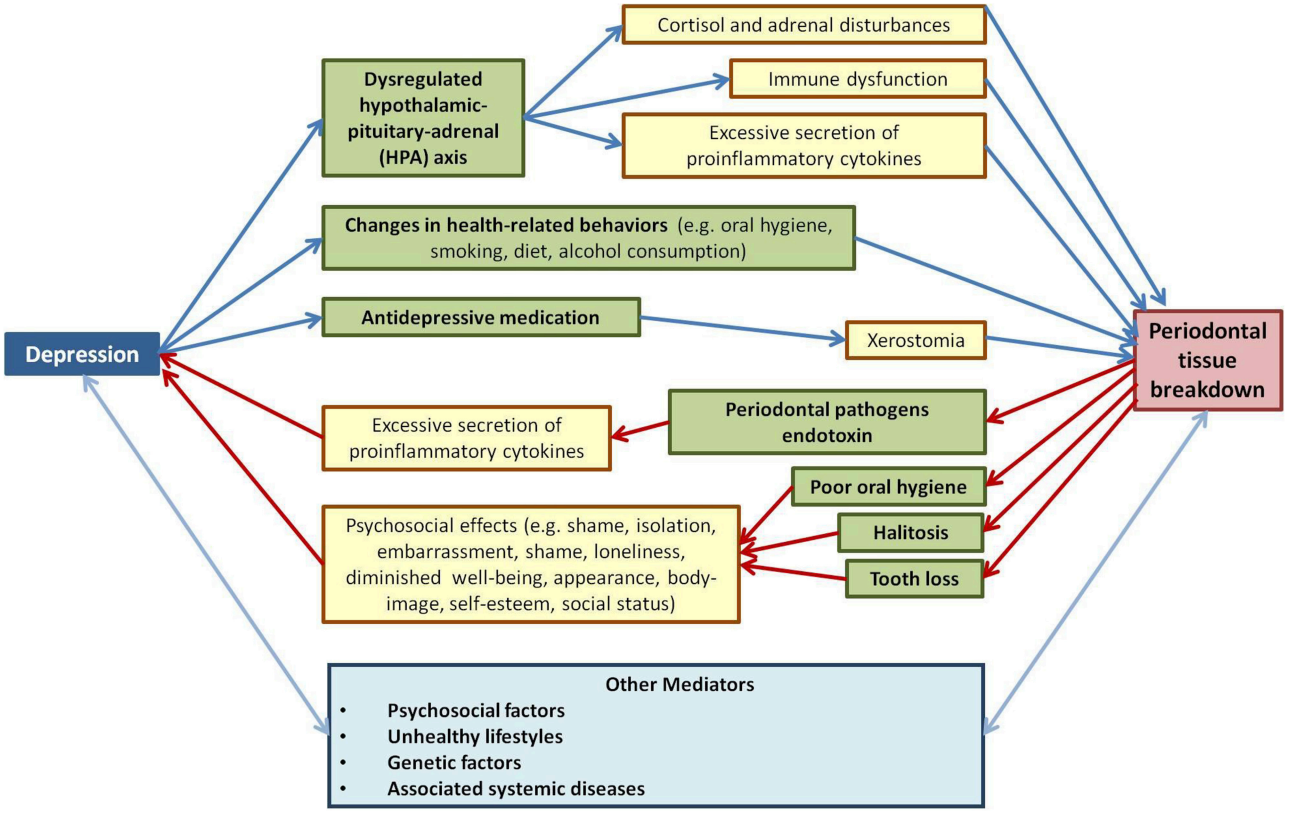

FIGURE 1 | Review of reported results related to the biological and psychosocial mechanisms underlying the depression-periodontal disease bidirectional connection.

failed to demonstrate the periodontal disease—depression connection, possibly because of the lack of consideration for relevant common mediators.

RELEVANT MEDIATORS OF THE PERIODONTAL DISEASE-DEPRESSION ASSOCIATION

Periodontal disease and depression are sharing common risk factors within the context of the wider socio-environmental milieu and adopting a collaborative approach (e.g., the common risk factor approach) is more rational than one that is disease specific (Sheiham and Watt, 2000; Watt, 2007; Petersen and Ogawa, 2012; Thomson et al., 2012; Watt and Petersen, 2012; Watt and Sheiham, 2012; Bentley et al., 2014).

The prevalence and severity of both periodontitis and depression, are associated with several social determinants such as older age (Holtfreter et al., 2009; Genco and Borgnakke, 2013; Allan et al., 2014; Kassebaum et al., 2014a), low socioeconomic status (Haustein, 2005; Borrell and Crawford, 2012; Haas et al., 2012; Thomson et al., 2012), low educational level (Kocher et al., 2005; Boillot et al., 2011; Eke et al., 2012; Hong and Tian, 2014), and ethnicity (Dunlop et al., 2003; Eke et al., 2012).

Unhealthy lifestyles, such as smoking and alcohol consumption have been shown to be risk factors for periodontal disease (Pitiphat et al., 2003; Tezal et al., 2004; Chambrone et al., 2013; Genco and Borgnakke, 2013; Fiorini et al., 2014) and also for depression (Paperwalla et al., 2004; Luger et al., 2014; Klimkiewicz et al., 2015). Moreover, scientific reports have shown that poor diet and a lack of exercise contribute to the genesis and course of depression (Jacka and Berk, 2012) and are associated with a higher periodontitis prevalence (Nishida et al., 2000; Moynihan and Petersen, 2004; Al-Zahrani et al., 2005). Furthermore, animal models and clinical studies have highlighted causal relationships between sleep deprivation and severity of periodontitis on the one hand (Grover et al., 2015; Nakada et al., 2015) and between sleep deprivation and mood changes on the other hand (Costae Silva, 2006; Turek, 2007; Kronfeld-Schor and Einat, 2012). Moreover, stress, distress, and psychological resistance (personality, coping and social support) were connected with periodontal disease (Genco et al., 1999; Dumitrescu, 2006; Peruzzo et al., 2007; Warren et al., 2014) and depression (Hammen, 2005; Klein et al., 2011; Rosenquist et al., 2011; Luca et al., 2013).

Common genetic contributing factors have been also identified for the two diseases. Involvement of genetic polymorphism of brain-derived neurotropic factor (*BDNF*) and serotonin (5-hydroxytryptamine *5-HT*) has been reported

in depression studies (Roy et al., 2014). In the same time, BDNF genotype GG was correlated with higher levels of BDNF, TNF-α, and the chemokine CXCL10 in patients with chronic periodontitis (Corrêa et al., 2014), while 5-HTTLPR polymorphism was associated with aggressive periodontitis (Costa et al., 2008; Mendes et al., 2013). A recent large sized *in silico* data analysis performed by Kao et al. (2011) has prioritized 169 genes out of 5055 candidate genes for depression. Besides BDNF and 5-HTTLPR, among top prioritized gene products related also to alveolar bone resorption and periodontal involvement being Tumour necrosis factor (TNF) polymorphism (Khosravi et al., 2013; Ding et al., 2014).

An examination of the research investigating the relationships between oral health and general health (Petersen, 2006; Kandelman et al., 2008) revealed a strong relationship between periodontal health or disease and various medical conditions (e.g., metabolic syndrome, cardiovascular disease, adverse pregnancy outcomes, respiratory disease, rheumatoid arthritis, cancer, inflammatory bowel disease, and Alzheimer disease; Williams and Offenbacher, 2000; Aarabi et al., 2015; Bascones-Martínez et al., 2015; Hatipoglu et al., 2015; Leech and Bartold, 2015; Nagpal et al., 2015; Payne et al., 2015; Javed and Warnakulasuriya, 2016). In the same time, an emerging body of evidence demonstrates a co-morbidity of depression with severe physical disorders with high mortality rates, such as cancer, stroke, and acute coronary syndrome (Kang et al., 2015) and particularly among patients with multiple physical disorders (Sobel et al., 2005; Maes et al., 2011a; Smith et al., 2014; Wu et al., 2014; Kang et al., 2015). Among them, several systemic medical conditions [Human immunodeficiency (HIV) infection, diabetes mellitus, obesity] are considered well documented risk factors for periodontal disease (Grossi et al., 1994; Ritchie, 2007; Kinane et al., 2008; Genco and Borgnakke, 2013) and depression (Pratt and Brody, 2014; Semenkovich et al., 2015; Serafini et al., 2015).

DEPRESSION AS A CAUSE OF PERIODONTAL DISEASE

Several mechanisms have been proposed to explain the mechanism by which depression plays a causal role in the in the $aetiology of inflammatory periodontal disease:

- Depression supports a chronic **dysregulated hypothalamic-pituitary-adrenal (HPA) axis** and further determines cortisol and adrenal disturbances, as well as immune dysfunction and excessive secretion of proinflammatory cytokines (Heim et al., 2008; Miller et al., 2009; Guerry and Hastings, 2011; Belvederi Murri et al., 2014; Moylan et al., 2014). Through these processes, depression might affect progression of periodontal infections in patients susceptible to periodontitis (Saletu et al., 2005) and might be associated with a worse treatment outcome through a delay of wound healing (Bosch et al., 2007). Moreover, animal studies have demonstrated that various classes of antidepressants can reduce levels of oxidative stress markers (Eren et al., 2007a,b; Maes et al., 2011a; Leonard and Maes, 2012), increase several endogenous antioxidants (Maes et al., 2011a) and also decrease the periodontal disease severity (Branco-de-Almeida et al., 2012; Aguiar et al., 2013; Galli et al., 2013). Captivatingly, these biological processes have been revealed to participate to the aetiology of depression and periodontal disease co-morbidities, as well, and thus may represent a bridge between these pathologies (Maes et al., 2011b; Bullon et al., 2014; Rossetti et al., 2014; Jani et al., 2015; Kang et al., 2015).
- **Changes in health-related behaviors**, such as oral hygiene, smoking, diet, alcohol consumption that occurs in depressed patients can also be related to the occurrence of periodontal disease (Kurer et al., 1995; D'Alessandro et al., 2014; Peltzer and Pengpid, 2014; Yuen et al., 2014; Alkan et al., 2015). However, one study failed to find a relationship between depression and dental plaque levels (Marques-Vidal and Milagre, 2006).
- Moreover, the **antidepressive medication may also lead to xerostomia** (Friedlander and Norman, 2002; Thomson et al., 2006; Macedo et al., 2014), alterations in gingival circulation and changes in saliva composition that might result in an exacerbation of periodontitis. However, further research is required in this area as some studies have found a causal relationship between reduced salivary flow and periodontal disease (Farsi et al., 2008; Márton et al., 2008; Samnieng et al., 2012), whereas not in others (Hirotomi et al., 2006; Syrjälä et al., 2011).

PERIODONTAL DISEASE AS A CAUSE OF DEPRESSION

Finally, periodontal disease may contribute to the onset of depression through different pathways:

- Depression is associated with a chronic, low-grade inflammatory response, activation of cell-mediated immunity, and compensatory anti-inflammatory reflex system, as well as an augmentation of oxidative and nitrosative stress, which contribute to neuroprogression in the disorder (Berk et al., 2013; Slavich and Irwin, 2014). Recent meta-analyses revealed that depressive patients have higher serum levels of pro-inflammatory cytokines such interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNFα; Howren et al., 2009; Dowlati et al., 2010; Maes, 2011; Hiles et al., 2012; Valkanova et al., 2013; Sarkar and Schaefer, 2014; Black and Miller, 2015) as wells increased levels of acute phase proteins (e.g., C-reactive protein, complement factors, chemokines; Berk et al., 1997; Pasco et al., 2010; Cekici et al., 2014). Moreover, the administration of pro-inflammatory cytokines and lipopolysaccharide has been able to induce depressive-like behaviors in rodent studies (Manosso et al., 2013; Mello et al., 2013; Kurosawa et al., 2015; Zhu et al., 2015). Critically, periodontal disease is also associated with high levels of systemic inflammation, in particularly, interleukin-6 (IL-6), TNF-α, and C-reactive protein (CRP; Pussinen et al., 2007; Bansal et al., 2014) that may potentiate inflammatory and oxidative and nitrosative stress processes and thus may lead to a vulnerability to depression (Battino et al., 1999; Chapple and Matthews, 2007; Berk et al., 2013; Bullon et al., 2014).

- Furthermore, periodontal disease may increase the risk for depression through the psychosocial effects (e.g., shame, isolation, embarrassment, loneliness) of poor oral hygiene and halitosis, frequent characteristics of patients with periodontal disease (Morita and Wang, 2001; Tsai et al., 2008; Pham et al., 2012; Silveira et al., 2012; Durham et al., 2013; Guentsch et al., 2014).
- Periodontal disease is also one of the leading causes of edentulousness due to the inflammatory destruction of the tooth supporting tissues: the periodontal ligament and the alveolar bone (Kassebaum et al., 2014b). As the contour and aesthetics of the face are maintained by natural teeth and alveolar bone, tooth loss may affect the patients' quality of life, not only due to dental loss of chewing functionality, but also when it impairs their body-image, diminishes self-esteem, and social status (Gerritsen et al., 2010; Saintrain and de Souza, 2012; Al-Harthi et al., 2013). This is supported by the positive correlations between tooth loss and depression that have been revealed by a high number of studies (Anttila et al., 2001; Davis et al., 2001; Persson et al., 2003; Rosania et al., 2009; Coles et al., 2011; Matthews et al., 2011; Okoro et al., 2012; Urzua et al., 2012; Yamamoto et al., 2012; Luo et al., 2015; Roohafza et al., 2015), psychological counseling being necessary to be provided along with periodontal and prosthetic treatment (Priyadarshini et al., 2014).

CONCLUSION

An interdisciplinary approach in psychoimmunology and periodontology has been used to highlight the biological and psychosocial mechanism and mediators of the depression and periodontitis connection, in order to call attention to potential new therapeutic strategies for both depressed individuals and periodontal disease patients.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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