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Effect of Hypertensive drugs in Periodontitis

(Literature Review)

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Abstract

Hypertension is one of the major risk factors for cardiovascular diseases. Oxidative stress and endothelial dysfunction are among the critical components in the development of hypertension. Inflammation has received much attention recently and may contribute to a pivotal role in hypertension. Periodontitis, a chronic low-grade inflammation of gingival tissue, has been linked to endothelial dysfunction, with blood pressure elevation and increased mortality risk in hypertensive patients. Inflammatory biomarkers are increased in hypertensive patients with periodontitis. Over the years, various researches have been performed to evaluate the involvement of periodontitis in the initiation and progression of hypertension and its medications. Many cross-sectional studies documented an association between hypertension medication and periodontitis. However, more well-designed prospective population trials need to be carried out to ascertain the role of periodontitis in hypertension. High blood pressure (BP) and periodontitis are two highly prevalent conditions worldwide with a significant impact on cardiovascular disease (CVD) complications. Poor periodontal health is associated with increased prevalence of hypertension and may have an influence on BP control. Risk factors such as older age, male gender, non-Caucasian ethnicity, smoking, overweight/obesity, diabetes, low socioeconomic status, and poor education have been considered the common denominators underpinning this relationship. However, recent evidence indicates that the association between periodontitis and hypertension is independent of common risk factors and may in fact be causal in nature. Low-grade systemic inflammation and redox imbalance, in particular, represent the major underlying mechanisms in this relationship. Neutrophil dysfunction, imbalance in T cell subtypes, oral-gut dysbiosis, hyperexpression of proinflammatory genes, and increased sympathetic outflow are some of the pathogenetic events involved. In addition, novel findings indicate that common genetic bases might shape the immune

profile towards this clinical phenotype, offering a rationale for potential therapeutic and prevention strategies of public health interest. This review summarizes recent advances, knowledge gaps and possible future directions in the field.

The aim of this review is to examine the current literatures on the relationship between periodontitis and hypertension medications as well as to explore the possible biological pathways underlying the linkage between these health conditions.

Keywords: Periodontitis diseases, hypertension, vascular diseases, periodontal, hypertension, blood pressure

1. Introduction

1-1. Periodontitis

Periodontitis, or gum disease, is a common infection that damages the soft tissue and bone supporting the tooth. Without treatment, the alveolar bone around the teeth is slowly and progressively lost[1]. Current evidence indicates that chronic periodontitis occurs in predisposed individuals who have an abnormal inflammatory/immune response to the sub gingival plaque biofilm at the gingival margin[2]. Bacteria in the mouth infect tissue surrounding the tooth, causing inflammation around the tooth leading to periodontal disease. When bacteria stay on the teeth long enough, they form a film called plaque, which eventually hardens to tartar, also called calculus. Tartar build-up can spread below the gum line, which makes the teeth harder to clean. Then, only a dental health professional can remove the tartar and stop the periodontal disease process[3]. Pain is usually absent unless an acute infection forms in one or more periodontal pockets

or if HIV-associated periodontitis is present. Impaction of food in the pockets can cause pain at meals. Abundant plaque along with redness, swelling, and exudate are characteristic. Gums may be tender and bleed easily, and breath may be foul. As teeth loosen, particularly when only one third of the root is in the bone, chewing becomes painful[4]. The primary causative agent resulting in periodontal disease is the mixed bacterial colonization in the oral tissue. While there are other factors which act as secondary etiologic factors accelerating the propagation and development of periodontal diseases like developmental grooves, calculus, dental plaque, overhanging restorations, anatomical features like the short trunk, cervical enamel projections, systemic factors, genetic factors, smoking, and stress[5]. To understand the pathophysiology of periodontal disease, it is essential to know about the complex dental biofilm as well as the Immune response associated with the disease.

Dental plaque is a complex biofilm, which is the colonization of bacteria enclosed by a protective matrix. This matrix is composed of extracellular polysaccharide and glycoproteins providing a protective environment for microbes in the dental biofilm. [This component of the dental biofilm makes it 1000 to 1500 times more resistant to antimicrobial agents. The various circulatory channels present in the biofilm aid in the distribution of many nutrients and excretion of the generated metabolic wastes. "Quorum sensing" is a mode of communication between the micro colonies of bacteria within the dental biofilm. “auto inducers" are molecules secreted by microbes; the concentration of these molecules helps in regulating bacterial gene expression. The biofilm, by different pH concentrations and metabolites, has various microenvironments within the biofilm. These microenvironments make the ecosystem suitable for a

variety of microbes inhabiting in the same dental plaque[6]. Smoking is one of the most important risk factors for periodontitis, and the reduction in periodontal disease prevalence is related to the drop in smoking rates.11 Negative effects of smoking cigarette, cigar, cannabis, and pipe on periodontal tissues are similar.12 The smokers are 3 times more likely to have a severe form of periodontal disease than non-smokers.13 The smokers also present significantly increased the loss of alveolar bone and higher prevalence of tooth loss compared with non-smokers, and they have poor outcomes of all forms of periodontal treatments.10,12,14,15 Evidence suggests that smoking changes oral microbial flora increases the level of certain periodontal microorganisms or affects host response.11 The nicotine has been shown to cause periodontal tissue breakdown, directly or indirectly through interaction with other factors[7]. Poor oral hygiene is linked with periodontal disease, and lack of proper tooth brushing and other measures of oral hygiene can encourage bacterial deposition and build-up of dental plaque on teeth and gums which can set a stage for inflammatory changes in periodontal tissues. There is pronounced relationship between poor oral hygiene and increased accumulation of dental plaque, high prevalence and increased severity of periodontal disease. Axels son et al. conducted a prospective study of 15 years duration and found no further deterioration of periodontal structure among the subjects who maintained proper oral hygiene and took routine professional dental care[8]. Vulnerability to infections and periodontal diseases intensifies when there is diminished salivary flow due to certain medications. The most common medications which can minimize the flow of saliva and produce dryness of mouth include tricyclic antidepressants, atropine, antihistamine, and beta blockers. Some drugs (phenytoin,

cyclosporine, and nifedipine) can induce the abnormal growth of gingival tissues which frequently complicates the appropriate removal of dental plaque underneath the enlarged gingival mass, and thus, can further aggravate the existing periodontal disease[9]. In a recent report of the Joint EFP/AAP workshop on periodontitis and systemic diseases, it was concluded that there is a consistent and strong epidemiologic evidence that periodontitis imparts increased risk for future cardiovascular disease. It was also concluded that although in vitro, animal and clinical studies do support interaction and biological mechanisms, still, well-design intervention trials to investigate the impact of periodontal treatment on prevention of atherosclerotic cardiovascular disease, are a needed.

Vascular diseases are nowadays recognized to have a strong local and systemic inflammatory pathogenic contribution. In atherosclerosis, along with the accumulation of cholesterol debris on the artery wall, it is well established that immune reactions and the participation cells and mediators such as cytokines are implicated in the immunopathogenesis of vascular diseases. Among several factors, inflammatory cytokines such as TNF-α, IL-1, and IL-6, have been shown to be secreted by infiltrating leukocytes or by foam cells. Parallels, several investigations have demonstrated the importance of chronic infections in the atherosclerotic process, namely by inducing a systemic inflammatory state and of autoimmunity. Some microbes can cause persistent infection in the vessel wall and promote a pro-inflammatory environment. Alternatively, the infection may also induce autoimmunity against vascular cells and lead to atherosclerotic process. In this context, chronic periodontitis and its chronic inflammatory nature are associated with an increased risk for cardiovascular disease. Bacteremia and an inflammatory systemic state

associated with chronic periodontitis are important factors in the initiation of the endothelial lesion as well as in the potentiation of the vascular wall inflammatory process. The inflammatory process is also modulated by pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 both in chronic periodontitis and in cardiovascular diseases. Finally, some studies demonstrate a decrease on systemic inflammatory biomarkers following periodontal treatment and consequent possible benefit in the reduction of cardiovascular risk. However, while there is evidence suggesting that periodontal therapy reduces systemic inflammation and improves endothelial function, evidence on its effects on cardiovascular events in long term is still limited and further studies are needed. Accordingly, a recent publication of American Heart Association (AHA) stated that although periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction in short-term studies, there is no evidence that they prevent atherosclerotic vascular disease or modify its outcomes[10].

1-2. Hypertension

High blood pressure is a common condition in the US that increases the risk of stroke and heart disease. Blood pushing against the walls of arteries in the body creates pressure, which generally varies throughout the day. High blood pressure, also known as hypertension, is blood pressure that is consistently higher than what is considered normal. There are 2 types of blood pressure measures: systolic and diastolic. Systolic blood pressure is the pressure in the arteries when the heart beats, while diastolic pressure is the pressure in the arteries when the heart rests. Normal systolic blood pressure is less than 120 millimeters of mercury (mm Hg), and

normal diastolic blood pressure is less than 80 mm Hg, together described as 120/80 mm Hg. High blood pressure may be defined slightly differently by clinicians because some guidelines suggest that high blood pressure is that which is consistently higher than 130/80 mm Hg, while other guidelines suggest higher than 140/90 mm Hg[11]. Hypertension is the most common preventable risk factor for cardiovascular disease (CVD; including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation and peripheral artery disease), chronic kidney disease (CKD) and cognitive impairment, and is the leading single contributor to all-cause death and disability worldwide10. The relationship between BP and the increased risk of CVD is graded and continuous, starting as low as 115/75 mmHg, well within what is considered to be the normotensive range. Successful prevention and treatment of hypertension are key in reducing disease burden and promoting longevity in the world's population. In treating hypertension, it is important to consider a person's predicted atherosclerotic CVD (ASCVD) risk more than the level of BP alone, as persons with high CVD risk derive the greatest benefit from BP lowering treatment[12].

1-3. Association between periodontitis and hypertension

Periodontitis is associated with approximately cardiovascular diseases, Over the years, various researches have been performed to evaluate the involvement of periodontitis in the initiation and progression of hypertension. Many cross-sectional studies documented an association between hypertension and periodontitis. However, more well-designed prospective population trials need to be carried out to ascertain the role of periodontitis in hypertension. Xin-Fang Leong et. and Rita Del Pinto Al. reported in two separated cross-sectional study, that there is an association

between hypertension and periodontitis. However, there is no strong proof to indicate that a causal relationship exists[13, 14]. Linda L. Humphrey conformed that periodontal disease is a risk factor or marker for CHD that is independent of traditional CHD risk factors, including socioeconomic status in a study done at the United State of America[15]. The frequency of potential oral manifestations in patients with hypertension was significantly high, thus showing an association of gingival and periodontal pathology in hypertensive patients[16]. Observational data from National Health and Nutrition Examination Survey (NHANES) 2009 to 2014 cohorts indicate that a good periodontal status is associated with a better SBP profile during antihypertensive therapy by a magnitude of about 2.3–3 mm Hg. Low-grade systemic inflammation that is typical of periodontitis might explain this finding because it has been regarded as the mechanism underlying the association of periodontitis with several cardiovascular risk factors and diseases. However, because a causal relationship cannot be inferred from observational data, future studies should focus on the direction of the reported association and the long-term impact of periodontal therapy on cardiovascular risk factors and outcomes in populations with different racial/ethnic background[17]. Ching Wang et. al. provides indirect evidence for the possible relationship between systemic diseases and periodontitis. There was a significantly higher frequency of medication intake related to cardiovascular disease and diabetes in patients with periodontitis. A disease severity-dependence with medication intake frequency was also noted[18]. There is a class of drugs called calcium channel blockers (CCBs), which are commonly used to treat high blood pressure (hypertension) and certain other heart conditions. Some people who take these medications experience a condition called

gingival hyperplasia, or an overgrowth of gum tissue. This effect has also been seen in some epileptics who take an anti-seizure medication called phenytoin[19]. An important class of drugs used for treating high blood pressure can sometimes cause an overgrowth of gum tissue. This in turn can affect your appearance, and your ability to clean your teeth[20]. Periodontal disease widened the gap even farther, up to 7 mmHg, among people with untreated hypertension, the study found. Blood-pressure medication narrowed the gap, down to 3 mmHg, but did not completely eliminate it, suggesting that periodontal disease may interfere with the effectiveness of blood pressure therapy[21]. Periodontitis has also been associated with insulin resistance and a higher risk for the metabolic syndrome, which is characterized by oxidative stress. This seems to act as a common link to explain the relationship between each component of the metabolic syndrome (including hypertension) and periodontitis[22]. There are significant reductions in CRP and improvement of endothelial function following IPT at all analyzed time points[23]. A causal relationship between periodontitis and BP was observed providing proof of concept for development of clinical trial in a large cohort of hypertensive patients. ClinicalTrials.gov: NCT02131922[24].

2. Results and Discussions

In reviewing the most recent study to investigate the relationship between periodontitis disease and hypertension medication. we found a significant and strong association between periodontal disease and blood pressure and no significant association between clinically measured severe periodontal disease and self-reported hypertension diagnosis. The association periodontitis and blood pressure was even stronger among participants with a known hypertension diagnosis or those taking anti-hypertensive medications.

The association between periodontitis and hypertension is of paramount importance as the progression of cardiovascular disease is highly affected by the degree of blood pressure control achieved among people with hypertension. The identification of modifiable risk factors for the progression of damage caused by hypertension is of high priority at a global level as it continues to be a major cause of morbidity, mortality, and a significant contributor to health care expense[25]. Recent scientific evidence suggests a possible connection between periodontal disease and systemic inflammation, which in turn is associated with an increased risk of hypertension[26-29]. Only a handful of studies have previously evaluated the association between periodontal disease and hypertension, but so far little is known about the natural history of this association[30]. Existing studies report a variety of measures of periodontal disease, and use different definitions of hypertension outcomes.

In a cross-sectional study of 3,352 periodontal patients and 902 population controls in Sweden, Holmlund et al.[31] reported a significant linear trend between periodontal disease severity and self-reported treatment for hypertension (OR for trend=1.32, 95% CI: 1.13–1.54, adjusting for age, gender, number of teeth and current smoking). In a recent prospective cohort of Japanese manufacturing company employees,[32] Morita and colleagues demonstrated an increase (RR=1.5, 95% CI: 1.0–2.3) in incident hypertension risk (having ≥130 mmHg systolic or ≥85 mmHg diastolic blood pressure during the follow-up visit) associated with presence of periodontal pockets of at least 4 mm at baseline (a clinical measure of moderate-to-severe periodontal disease), after adjusting for age, gender, and binary measures for cigarette smoking, regular exercise, eating between meals and healthy body weight). One of the strengths of these reports was clinical assessment of periodontal

disease status, similar to our current study; however, summary periodontal measures used in these publications were different, which makes comparisons across studies more difficult. In the recent analysis of 11,029 U.S. adults (17 and older)[33] _ENREF_33 there was no significant association between periodontal disease severity and high blood pressure (OR for severe periodontitis=1.29, 95 % CI: 0.85–1.98, adjusted for age, gender, years of education, poverty ratio, ethnicity, smoking, chronic heart diseases, cancer, diabetes, stroke, emphysema, asthma, arthritis, lupus, thyroid disease, and goiter). Similarly, there was no association among adults older than 44 years of age (OR=1.36, 95% CI: 0.80–2.33). This study used the same periodontal measures as in our current study. However, periodontal data was collected only in randomly assigned half-mouths of each participant, rather than in the whole mouth. This may have resulted in non-differential misclassification (under-diagnosis) of periodontal disease and, therefore, underestimation of the magnitude of the association between periodontitis and blood pressure.
Other study was in accord with the first two reports, with the magnitude of the association being much larger in our study. PREDHS participants with severe periodontal disease an almost 3-fold increase in odds of having high blood pressure, compared with those without severe periodontal disease (multivariate OR=2.93, 95% CI: 1.25–6.84). This association remained strong and statistically significant even after adjusting for anti-hypertensive medication use and number of teeth. Our study population was older compared to previous publications, which suggests that local and perhaps consequent systemic inflammation might play a greater role in blood pressure control among elderly.

The analysis on stages of hypertension suggested a threshold relation between periodontal disease and blood pressure, rather than a linear trend.

However, we had limited power among participants with stage 2 hypertension (SBP ≥160 and DBP ≥100 mmHg). The relation between severe periodontitis and blood pressure appeared to be stronger among participants with a known diagnosis of hypertension and those taking anti-hypertensive medications, suggesting that elderly with severe periodontitis may have poorer response to anti-hypertensive treatment compared to those who have a healthier periodontium. Since the majority of PREDHS hypertensive presented with ISH (N=76) or SDH (N=26), results from the stratified analysis limited to ISH and SDH were similar to those obtained from the overall population.

Smoking and diabetes have previously been shown to be effect modifiers of the relations between periodontal disease and cardiovascular outcomes;26 however, we did not observe any effect modification by these variables. In age- and gender analysis among never-smokers, periodontal disease was associated with an OR of 3.09 (95% CI: 1.12–8.57); however, we were unable to adjust for binge drinking in model 2, due to small power and instability of the model. The association between periodontitis and blood pressure was somewhat weaker and not significant among non-diabetics (model 2 OR=2.00, 95% CI: 0.75–5.35), compared to the estimates from the overall population, which might be explained by limited sample size in this stratum. At the same time, a weaker association among non-diabetics suggests potential residual confounding of our main results by severity of undetected diabetes and pre-diabetes.

Studies over the years had several strengths, including collection of high-quality clinical data on periodontal disease and blood pressure. We conducted a full-mouth oral examination on all participants; all our dental examiners were trained according to NHANES criteria and showed excellent agreement with the reference examiner. We also collected detailed

information on potential confounders, including variables reflecting health behavior, such as utilization of preventive dental services, fruit and vegetable intake, and flossing. Our study participants were not requested to refrain from their medications prior to the examination; hence, the blood pressure measurements obtained from participants on anti-hypertensive treatment reflect the true level of blood pressure control usually achieved among them. Hypertension is not likely to cause periodontal disease. Since our blood pressure measurements were taken on only one occasion, day-to-day variations in blood pressure may have resulted in random misclassification of our outcome measure of high blood pressure. However, we expect that this misclassification was non-differential with regards to periodontal disease status, which would result in underestimation of the true odds ratio between periodontal disease and high blood pressure. Also, due to a relatively small sample size, we did not have enough statistical power for some of our subgroup analysis (e.g., analysis limited to diabetics, never, past and current smokers). Our information on diabetes, one of major potential confounders of this relation, was self-reported, which does not exclude possible residual confounding; hence our results should be interpreted with caution. In addition, our study was limited to Hispanic elderly of Puerto Rican descent, which may limit the generalizability of our findings to other populations. Despite these limitations, our study demonstrates a possible strong relation between periodontal health and blood pressure control, which may have a major public health impact among elderly. Given the limitations of our study, further studies are needed to confirm this association in other populations.

3. Conclusion

In summary, the current epidemiological data, mainly from cross-sectional studies, show an association between hypertension and periodontitis.

However, there is no strong proof to indicate that a causal relationship exists. In order to connect the relationships between dentistry and medicine, additional issue needs to be addressed for the improvement in managing the overall health of patients. Future studies should be conducted to yield better understanding of the mechanisms and interactions between hypertension and periodontitis, which will further strengthen the involvement between dental and medical communities. Since previous studies demonstrated an elevation in BP which is associated with periodontitis, preventive approaches targeted at reducing BP should also be included in the management of periodontitis. Periodontal health is achievable in both individual level as well as the population level. These preventive measures should be emphasized in oral health promotion programme, in order to enhance overall health outcomes. Severe periodontitis is independently associated with increased Oxidative Stress and reduced anti-oxidant capacity. Angiotensin-converting enzyme inhibitors may increase the prevalence and extent of chronic periodontitis in Brazilian patient.

4. References

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