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Chronic Periodontal Disease and Its Correlation with Carotid Intima-Media Thickness

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Abstract: Chronic periodontal disease (periodontal disease, PD) is considered the sixth most prevalent disease affecting human health, with approximately 740 million people impacted globally. Over the past few decades, numerous studies have focused on the relationship between PD and cardiovascular diseases. Clinically, prior to the clear formation of atherosclerotic plaques, a subclinical indicator of increased carotid intima-media thickness (CIMT) is often observed. CIMT refers to the distance between the inner boundary of the carotid artery lumen and the outer boundary of the media layer, and it has been confirmed as an independent risk factor and predictive marker for coronary artery disease. As a potential risk factor, PD may lead to CIMT thickening through various mechanisms. This paper aims to explore the relationship between PD and CIMT, as well as the potential underlying mechanisms.

Keywords: Chronic Periodontal Disease; Carotid Intima-media Thickness; Epidemiological Studies; Atherosclerosis.

1. Introduction

Chronic periodontal disease, as a chronic inflammatory disease, is primarily characterized by the destruction of the supporting structures around the teeth [1]. The main cause of periodontal support tissue destruction is periodontal pathogens. Studies have shown significant differences in the composition of the periodontal microbiota between healthy individuals and those suffering from periodontal disease [2, 3]. When periodontal disease occurs, the levels of Gram-negative bacteria (including *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, etc.) increase in the subgingival biofilm [4]. Numerous studies on periodontal bacteria suggest that these bacteria can induce chronic inflammation, which compromises the integrity of the epithelial barrier, allowing periodontal pathogens to enter the underlying connective tissue and bloodstream [5-7]. The entry of bacteria and their virulence factors into the bloodstream may trigger a systemic inflammatory response [8].

2. Pathogenesis of Atherosclerosis

Atherosclerosis (AS) is one of the most common causes of cardiovascular diseases. AS can lead to vessel narrowing, blockage, or rupture, resulting in myocardial infarction, stroke, and limb ischemia [9]. AS is considered a chronic inflammatory disease of the arterial wall, caused by multiple stimulating factors. The development of AS is a slow, long-term accumulation process. Initially, endothelial barrier damage occurs, followed by the accumulation of cholesterol-rich lipoproteins in the subendothelium. Vascular smooth muscle cells (VSMCs) migrate from the vascular media to the subendothelium, proliferate, and synthesize extracellular matrix (ECM), leading to intimal thickening, termed diffuse intimal thickening (DIT). Subsequently, resident VSMCs and monocyte-derived macrophages accumulate beneath the endothelium and transform into foam cells after ingesting modified lipoproteins, ultimately leading to the formation and expansion of atherosclerotic plaques [10]. Traditional risk factors for AS include smoking, dyslipidemia, hypertension, and diabetes [11]. In recent decades, research has found that infections play an important role in regulating AS, such as infections caused by *Porphyromonas gingivalis* [12], *Helicobacter pylori* [13], and others.

3. Carotid Intima-Media Thickness (CIMT) and Cardiovascular Risk

Atherosclerotic cardiovascular disease is a major global public health issue. It is the leading cause of death and disability, accounting for one-third of global deaths [14]. Despite the high prevalence of the disease, clinical outcomes have significantly improved with advances in cardiovascular treatments. Recent research on cardiovascular diseases has shifted towards disease prevention. Current diagnostic methods for AS (e.g., exercise electrocardiograms, stress echocardiography, thallium scanning, and coronary angiography) can only detect AS when it reaches the later stages or when occlusion occurs [15]. However, CIMT measurement is safe, economical, non-invasive, and simple. Unlike traditional methods used for symptomatic patients to detect significant carotid stenosis through duplex scanning, CIMT is typically measured using B-mode ultrasonography, making it more suitable for screening asymptomatic populations [16]. CIMT is defined as the combined thickness of the intima and media layers of the carotid artery. This measurement has been validated both visually and microscopically in vivo and in vitro [17, 18]. CIMT reflects the pathological processes affecting both layers of the arterial wall and may indicate early arterial thickening due to AS or vascular hypertrophy in the context of hypertension [19]. Thus, CIMT is considered a marker reflecting changes in vascular structure over time, with systemic atherosclerosis and its associated risk factors being the main drivers. CIMT is often used as a surrogate endpoint and an intermediate

marker in clinical trials. Numerous studies have shown that CIMT measurement is a powerful tool for detecting AS at pre-obstructive stages [16, 20]. Additionally, some studies suggest that increased CIMT is associated with increased cardiovascular risk. A meta-analysis indicated that after adjusting for age and gender, for every 0.10 mm increase in CIMT, the relative risk of myocardial infarction and stroke increased by 15% and 18%, respectively. Further analysis showed that patients with CIMT greater than 0.79 mm had a 1.6-fold higher risk of heart failure compared to those with CIMT below 0.62 mm. Infection plays a key role in the development of AS, and chronic periodontal disease is a chronic infectious disease; therefore, chronic periodontal disease may be associated with the development of AS. CIMT, as a subclinical symptom of AS, can serve as a surrogate marker for AS, and its measurement is more convenient for epidemiological studies. This review explores the correlation between CIMT and PD and provides evidence for AS prevention.

4. Correlation between Periodontal Disease and CIMT

4.1. Inflammatory Factors Associated with Periodontal Disease and CIMT

Currently, there are different explanations regarding the relationship between periodontal disease and the increased risk of CIMT. The main viewpoints can be summarized into three perspectives: first, the increase in CIMT associated with periodontal disease is linked to periodontal bacterial infection [12]; second, the upregulation of inflammatory mediators during the inflammatory response plays a key role; and third, it is the combined effect of the first two factors. Periodontal bacteria have been detected in atherosclerotic plaques and the intima of the human aorta and coronary arteries. Figuero et al. used nested polymerase chain reaction (PCR) to detect periodontal bacteria in atherosclerotic plaques, with *Porphyromonas gingivalis* (Pg) being the most commonly found, followed by *Actinobacillus actinomycetemcomitans* (Aa), *Tannerella forsythia* (Tf), and *Campylobacter rectus* [22].

The initial inflammatory response in the body is mainly triggered by plaque and its toxic products, which further activate the host's defense cells (such as T cells, B cells, macrophages, fibroblasts, endothelial cells, keratinocytes, etc.). These cells produce and release multiple cytokines, and the large release of endogenous factors may lead to secondary damage to target tissues or organs. Cytokines play a crucial role in various stages of atherosclerosis, from disease initiation to plaque rupture, and they are core components of the inflammatory response system [23-25]. The interaction between microbes and host cells, through the activation of pattern recognition receptors and their downstream signaling pathways, induces the secretion of cytokines such as the interleukin-1 (IL-1) family, IL-6 family, and C-reactive protein (CRP) [26]. CRP, as a prototype marker of inflammation, has been shown to be elevated in chronic periodontitis (CP) and also serves as a predictor of cardiovascular events. Increased CIMT is an alternative marker of atherosclerosis. In this context, studies have found that elevated CRP levels in periodontal disease patients are associated with CIMT thickening. A study on the predictive value of CRP for CIMT in CP patients showed that the CRP level in the CP group (19.58 ± 17.03) was significantly higher than in the non-CP group (5.54 ± 1.63, $P < 0.004$), and the CIMT value in the CP group (1.09 ± 0.45) was significantly higher than in the non-CP group (0.57 ± 0.06, $P < 0.001$). Additionally, a significant positive correlation ($r = 0.863$, $P < 0.001$) was found between CIMT and CRP levels in the CP group, suggesting that CRP may be a potential mediator in the association between periodontal disease and CIMT [27]. Some researchers have pointed out that periodontal treatment can moderately reduce CRP concentrations in the short term [28]. However, Fábio et al. [29] conducted a stratified analysis and found that when high-sensitivity CRP levels were above 3 mg/L, a significant correlation between periodontal disease and CIMT was observed, whereas no significant correlation was found in subjects with CRP levels below 3 mg/L. Therefore, further evidence is needed to clarify the role of inflammatory mediators in the process by which periodontal disease induces CIMT increase.

4.2. Clinical Studies on Periodontal Disease and CIMT

Several clinical studies have demonstrated a correlation between periodontal disease and CIMT. A study of elderly hypertensive patients found that, compared to those without periodontal disease, those with periodontal disease had a significantly higher risk of CIMT thickening (OR = 4.10; 95% CI: 1.61-10.48, p = 0.003) [30]. Research by Pinho et al. also found a significant association between the severity of periodontal disease and CIMT thickness. Specifically, a cross-sectional study involving 6017 participants aged 52 to 75 years found that compared to individuals without periodontal disease, severe periodontal disease patients (OR = 2.09, 95% CI: 1.73-2.53) and moderate periodontal disease patients (OR = 1.40, 95% CI: 1.17-1.67) were significantly more likely to have CIMT $\geq$ 1 mm [31]. These findings suggest that chronic periodontal disease may play a role in CIMT thickening.

4.3. Effects of Periodontal Treatment on CIMT

As a chronic inflammatory disease, conventional periodontal treatments such as supragingival scaling and subgingival curettage can effectively alleviate the progression of periodontal inflammation. Studies have investigated the impact of periodontal treatment on CIMT and AS. A study examining the effects of mechanical periodontal therapy on serum interleukin-6 (IL-6) and carotid matrix metalloproteinase (MMP)-2 and MMP-9 expressions in rats with chronic periodontal disease and AS showed that mechanical periodontal therapy induces a short-term systemic inflammatory response and alleviates vascular inflammation in the long term. When combined with local and systemic antibiotic treatments, mechanical periodontal therapy improves vascular lesions and systemic inflammation [32]. Another study involving 15 chronic periodontal disease patients with high-risk systemic diseases found that after one month of local antibiotic application and mechanical debridement, CRP and tumor necrosis factor-alpha (TNF-α) levels were significantly reduced compared to baseline, suggesting that periodontal treatment effectively reduces CRP and TNF-α levels, thereby reducing the future risk of atherosclerosis in periodontal disease patients [33].

Therefore, the link between PD and CIMT can be attributed to direct invasion by periodontal pathogens or indirectly to the inflammatory mechanisms triggered by bacteria associated with periodontal disease, which may influence the initiation or progression of atherosclerotic lesions. Some periodontal

pathogens, particularly *Porphyromonas gingivalis*, have become a focus of various studies and are associated with systemic diseases [35], such as CVD [36], DM [37], rheumatoid arthritis [38], preterm low birth weight, and myocardial infarction [39, 40]. The role of periodontal pathogens in the onset and progression of atherosclerosis has been emphasized in numerous studies, but results remain uncertain, and causal mechanisms are still lacking. As research on the correlation between CP and CIMT increases, the potential link between them is becoming clearer. However, due to the unclear mechanisms underlying this relationship, future research should further explore these mechanisms and investigate the effects of periodontal interventions. Future large-scale multi-center clinical studies should verify the correlation between CP and CIMT and ensure the universality and accuracy of the research findings through an increased sample size.

5. Conclusion

In conclusion, CP may lead to CIMT thickening through bacterial infection and immune responses, and periodontal pathogens have been found in atherosclerotic plaques. Clinical studies have also demonstrated that CP patients have thicker CIMT compared to healthy individuals. Some studies on periodontal treatment have shown that treatment can not only reduce CIMT thickness but also lower inflammatory factors influencing the development of AS. This highlights the importance of periodontal health for overall health and the positive effects of periodontal treatment on cardiovascular health.

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