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"From Gums To Arteries: The Role Of Periodontitis In Cardiovascular Disease"

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Abstract
"The study aims to assess literature examining the connection between cardiovascular diseases (CVDs), such as myocardial infarction (MI), hypertension (HTN), coronary atherosclerosis (CAS), infective endocarditis (IE), heart failure (HF), arterial fibrillation (AF), peripheral artery disease (PAD), and periodontitis. Periodontitis ranks as the sixth most prevalent human disease, and there appears to be a significant overlap in risk factors between these conditions, suggesting potential implications for their prevalence and treatment."
Cardiovascular diseases (CVDs) are inflammatory conditions affecting the coronary arteries, characterized by the development of atherosclerosis that can lead to impairment and, in severe cases, mortality. CVDs represent the foremost cause of death globally. In recent decades, researchers have increasingly examined the impact of periodontal disease (PD) on CVD. PD serves as a risk factor capable of triggering the formation, progression, and destabilization of atherosclerotic plaques in arteries. Two mechanisms have been proposed to explain this association: direct invasion of periodontal pathogens into the bloodstream and indirect elevation of systemic inflammatory mediators. Evidence suggests that improving one condition may positively influence the other. This review synthesizes findings from epidemiological studies and research focusing on potential causal pathways, aiming to provide a comprehensive understanding of the relationship between PD and CVD

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I. Introduction

Periodontitis is a chronic inflammatory disease influenced by multiple factors, triggered by the buildup of bacterial biofilm and marked by gradual deterioration of the structures supporting the teeth. It represents a significant public health concern [1]
Periodontitis ranks sixth among prevalent human diseases, impacting 740 million individuals globally.

It is characterized by chronic, bacteria-induced inflammation that leads to tissue destruction around the teeth. The microbiota associated with periodontitis releases proinflammatory mediators locally and systemically. Given its status as a chronic infectious condition in dental health, periodontal disease (PD) shares several pathogenic pathways with cardiovascular diseases (CVDs). The persistent low-grade systemic inflammation attributed to periodontitis establishes a strong association with CVDs. [2]

In periodontal tissues, the inflammatory response is marked by the local synthesis of several pro-inflammatory mediators and enzymes, including C-reactive protein (CRP), interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and matrix metalloproteinases (MMPs).[3]

Periodontal medicine

The phrase "periodontal medicine" refers to the group of practices that discuss the potential effects of periodontal infection and inflammation on extraoral health.

Research on systemic inflammation in medicine began to shed light on possible connections between periodontitis and cardiovascular disease, which are both now recognized as inflammatory disorders, in the early 1990s. According to Ridker et al. (1998), people with persistently high Creactive protein had a much higher chance of incident cardiovascular events.Around the same period, dentist Russell Ross proposed that atheroma lesions were not just a build-up of lipids in the walls of major arteries, but rather an inflammatory process (Ross 1999).Furthermore, Ridker discovered that in women in good health, CRP levels were excellent predictors of cardiovascular events. As a result, CRP is now frequently used as a diagnostic tool.

The initial theory regarding the connection between cardiovascular disease and periodontitis originate from a longitudinal research conducted on veterans by Beck et al. in 1996. According to the mechanism, those who have oral infections and a hyperinflammatory characteristic are more likely to get cardiovascular disease. Moreover, focusing on inflammation clarified how oral infections may affect a number of inflammation-related diseases.

Major clinical trials investigating the potential of treating periodontal disease to lower cardiovascular events have not been conducted. Nonetheless, periodontal therapy has been shown to modify cardiovascular disease risk variables in interventional studies conducted in the 2000s.

More recently, systemic levels of CRP, fibrinogen, and white blood cells have been demonstrated to be dramatically reduced by nonsurgical periodontal therapy; these factors have all been linked to an increased risk of CHD (Bokhari et al. 2012). According to these researchers, following periodontitis treatment, the proportion of individuals with elevated CRP (>3 mg/L) dropped by 38% in the intervention group and increased by 4% in the control group, translating into a 12.5% absolute risk reduction. Moreover, a 2017 randomized controlled trial (RCT) showed that patients with prehypertension and periodontitis may see a reduction in blood pressure and endothelium microparticles when receiving comprehensive periodontal care without the use of antihypertensive medication.Improvements in probing depth were associated with a decrease in endothelium microparticles and blood pressure.(4)

II. Focal Infection Theory

A historical idea known as the "focal infection theory" postulates that focal infections could be the root cause of numerous chronic illnesses, including common and systemic conditions. This would account for almost all diseases, including mental illnesses, cancer, atherosclerosis, arthritis, and other conditions. (5)

W. Miller proposed his idea of localized infection in 1891, suggesting that bacteria and/or their byproducts can enter bodily areas close to or far from the mouth. Dr. F. Billings then conjectured that a variety of localized infections, including endocarditis, rheumatism, nephritis, arthritis, and other inexplicable disorders, could be attributed to infected teeth and tonsils.

The link between internal medicine and dentistry, particularly the so-called focal infection theory, has been a topic of discussion for many years. Dental pulp disorders and periapical infections have traditionally been implicated in the etiology of localized illnesses. However, their significance has been downplayed in recent years as more attention has been focused on the potential links between systemic illnesses and periodontal infections. In actuality, systemic disorders may be exacerbated by periodontal infections and their byproducts, as well as inflammatory mediators generated in periodontal tissues, if they penetrate the bloodstream.

This mechanism has led to the suggestion that chronic periodontitis is a risk factor for a number of conditions, including bacterial endocarditis, diabetes mellitus, respiratory disorders, preterm birth, rheumatoid arthritis, osteoporosis, pancreatic cancer, metabolic syndrome, renal diseases, and neurodegenerative disorders like Alzheimer's disease. A number of theories have been put out to explain these associations, including common vulnerability, systemic inflammation, direct bacterial infection, and cross-reactivity, sometimes known as molecular mimicry, between bacterial antigens and se-lf antigens. The introduction of periodontal medicine has been made possible in this scenario by the correlation between periodontal disease and systemic(6)

Periodontal systemic connection

Inflammation of the tissues supporting teeth is a hallmark of periodontal diseases, which are disorders of the mouth.Periodontitis typically results in a gradually damaging loss of periodontal ligament and bone (loss of the teeth's attachment apparatus). There are known risk factors for periodontitis, such as certain types of plaq ue bacteria, smoking, and diabetes mellitus. The relationship between periodontal disorders and systemic diseas es was initially believed to be unidirectional. There is growing evidence at this time to suggest that these entities may have a reciprocal interaction. Current case-control and cross-
sectional research suggests that the risk of cardiovascular disease is increased by two times and the risk of preter m low birth weight infants is increased by seven times, respectively, in individuals with periodontitis. These firs t findings suggest a possible link between oral and systemic health.These investigations also provide credence to the main theory that periodontal disease entails a systemic and local host inflammatory response. Understanding how diseases are related to one another may be essential for developing intervention techniques that lower patient risks and stop systemic illness consequences. In light of the available data linking periodontal disease to systemic illness, this report aims to lay the foundation for improved communication between medical professionals and periodontists in the context of military health care.(7)

Cardiovascular diseases brief

Heart failure, stroke, and coronary artery disease are among the conditions collectively referred to as cardiovascular disease (CVD), which affects the heart and blood arteries. With 17.9 million deaths a year, or 32% of all deaths globally, it continues to be the largest cause of mortality worldwide. Heart failure, hypertension, coronary artery disease (CAD), and cerebrovascular illnesses like stroke are all included in the category of cardiovascular disease (CVD). (8)

Types

1 CoronaryArtery Disease (CAD): CAD is characterized by the accumulation of plaque in the coronary arteries, narrowing them and increasing the risk of heart attacks. It is a major cause of death and one of the most prevalent types of CVD.

2 Cerebrovascular Disease: This category comprises conditions affecting the blood vessels in the brain, such as stroke, which can result in death or long-term neurological impairment.

3 Heart Failure: Breathlessness and fluid retention are signs of heart failure, which happens when the heart is unable to pump blood efficiently. It frequently comes from long-term illnesses like hypertension and CAD.

4 Hypertension: Because it puts more strain on the heart and arteries, high blood pressure, or hypertension, is a major risk factor for heart attacks and strokes.(9)

Hazard Contributors

There are two groups of CVD risk factors: modifiable and non-modifiable.

Modifiable Factors: The most modifiable risk factors are lifestyle decisions including smoking, binge drinking, eating poorly, and not exercising. Obesity, diabetes, and high cholesterol are among the conditions that raise the risk of CVD.

Non-Modifiable Factors: Gender, age, and family history all have an impact; men and older people are typically more vulnerable.(10)

Avoidance and Control

The mainstay of prevention is changing one's lifestyle to include eating a balanced diet full of fruits, vegetables, and whole grains, getting regular exercise, and abstaining from tobacco and excessive alcohol usage. Reducing the risk of CVD requires careful monitoring and drug management of blood pressure, cholesterol, and diabetes. Medical procedures like angioplasty or bypass surgery might be required in more serious situations. (11)

Worldwide Effect

75% of deaths from CVD occur in low- and middle-income nations, where the illness is disproportionately prevalent. The growing prevalence of CVD in these areas is attributed to urbanization, changes in lifestyle, and aging populations. The effects on the economy and healthcare system are as profound, as CVD raises healthcare expenses and reduces productivity.(12)

Epidemiology

With a global frequency of 20–50%, periodontitis is a prevalent chronic inflammatory disease that damages the supporting structures of teeth. Periodontitis and cardiovascular disease (CVD), the world's leading cause of mortality, are associated with a number of risk factors, including age, smoking, diabetes, and socioeconomic level. Epidemiological research has repeatedly demonstrated a link between periodontitis and a higher risk of cardiovascular disease (CVD), which includes heart failure, stroke, and coronary artery disease (CAD). (13)

One of the main causes of CVD is atherosclerosis, which is thought to be accelerated by the systemic inflammation brought on by periodontitis. Elevations in inflammation indicators such as C-reactive protein (CRP), which are linked to periodontitis, are also linked to a higher risk of cardiovascular disease. Moreover, periodontopathogens like Porphyromonas gingivalis have the ability to reach the bloodstream and may play a role in the development of atherosclerotic plaque and vascular inflammation.

According to study, people with periodontitis are 25% more likely than people without the condition to have cardiovascular disease (CVD). Likewise, the Atherosclerosis Risk in Communities (ARIC) study found a correlation between increased rates of myocardial infarction and stroke and severe periodontitis. The significance of periodontal care in public health initiatives targeted at lowering the worldwide burden of CVD is highlighted by this association, which implies that enhancing oral health may potentially reduce the incidence of cardiovascular events.(14)

III. Mechanism

Two proposed mechanisms outline this phenomenon.

The first mechanism involves periodontopathic bacteria directly adhering to endothelial cells through a direct process .9 Polymerase chain reaction assays conducted on atherosclerotic plaques support this hypothesis. Streptococcus mutans was identified as the most prevalent bacterium in cardiovascular samples containing thrombus tissues (78%), followed by Aggregatibacter actinomycetemcomitans 10 Other bacteria found in atherosclerotic lesions within coronary arteries include Tannerella forsythia, Prevotella intermedia, and notably Porphyromonas gingivalis. However, the specific intracellular impacts of periodontopathogenic organisms on

atherosclerosis remain unclear, though some pathogens like P. gingivalis may induce the formation of foam cells or persist within cells, leading to localized inflammation and endothelial dysfunction .(15,16)

The second proposed mechanism operates indirectly through periodontal disease (PD) triggering increased levels of inflammatory cytokines. PD initiates an inflammatory cascade, resulting in elevated levels of various inflammatory mediators such as interleukin 8, interleukin 6, interleukin 1, and tumor necrosis factor, all of which are associated with atherosclerotic vascular disease. Some of these mediators accelerate fibrinogen and CRP production and release. Furthermore, bacterial lipopolysaccharides decrease flow and provoke a robust immune response. These elements contribute to atherosclerosis by affecting endothelial cells, enhancing oxidative stress, and altering lipid metabolism. This is supported by previous research demonstrating endothelial dysfunction in patients with periodontitis.(17)

Artherosclerotic cardiovascular disease

Atherosclerotic illness is an immune response-related localised thickening of the vascular intima between the smooth muscle cell (SMC) layers and endothelial lining of blood vessels. (18)

It is unknown what causes atherosclerosis mostly

In young adults, there is an increase in lipid deposition at certain locations, and a smooth muscle and fibrous tissue cap covers a core of lipid and necrotic debris. Fibrous plaques, which are raised lesions caused by these alterations, protrude into the lumen and start to obstruct blood flow.(19)

The term peripheral arterial disease (PAD) refers to the condition whereby atherosclerosis and its sequelae in the femoral, iliac, and abdominal aortas cause ischemic necrosis (gangrene) or transient arterial insufficiency in the lower extremities during exertion. An aneurysm in the abdominal aorta might burst into the abdominal cavity or fill with a thrombus due to weakening of the media underneath the atherosclerotic plaque.(16)

IV. Staging

The Early Fatty Streak Phase

An important component of the inflammatory cascade, nuclear factor-kappaB (NF-kB) is upregulated in regions that are prone to atherosclerosis. Uniform laminar flow areas cause the endothelium to overexpress Kruppel-like factor (KLF)-2 and 4, which produces athero-protective endothelium with an anti-inflammatory and anti-thrombotic profile. Once the LDL particles exit the circulation and reach the artery intima, they become caught by proteoglycans and undergo modifications. Although the exact nature of LDL's alterations is unknown, oxidative modification—which produces oxidised LDL—seems like a promising possibility. Since cellular cholesterol content does not influence scavenger receptors (SRs) like SRA and CD36, modified LDL is taken up by these SRs, leading to the development of foam cells. prostacyclin and NO levels are low, but plasminogen activator inhibitor type 1 (PAI-1) and cell adhesion molecules (CAMs) levels are up.

Early Fibro Atheroma Phase

After the development of foam cells, smooth muscle cells migrate from the media into the intima, regulated by many factors such as insulin-like growth factor (IGF), PDGF, and angiotensin II. The collagen-enriched fibrous plaque, which forms beneath the endothelium and is thought to shield the vessel wall against plaque rupture, is largely produced by these cells. Additionally, lymphocyte responses through type-1 T-helper (TH1) and type-2 T-helper (TH2) cells are involved.

Advancing Atheroma: Thin-Cap Fibroatheroma and Its Rupture

The necrotic core that surrounds the thin-cap atheroma is highly populated by T cells, cholesterol crystals, and macrophages that are abundant in cholesterol and are prone to rupture. Uncontrolled proteolytic enzyme activity, such as matrix metalloproteinases (MMPs), weakens the fibrous cap by exposing the intima and causing a thrombus to form by platelet aggregation and tissue-factor activation that spreads into the artery lumen. The most common name for this lesion is "vulnerable plaque" due to the possibility of rupture and potentially fatal thrombosis.

Plaque rupture

The causes of plaque rupture are not well studied, but main factors include expression of enzymes like MMPs, Myeloperoxidase produced by inflammatory cells that weaken the fibrous cap, high-shear arterial regions, macrophage calcification, and iron deposition..

Growth and Development of the Necrotic Core

Intraplaque haemorrhage has a role in the formation of the necrotic core because red blood cells are a rich supply of free cholesterol and lipids, which are crucial components of ruptured plaques.

Intraplaque haemorrhage, macrophage mortality, and insufficient phagocytic clearance are the main causes of necrotic core growth in the advanced stage. Microscopically, healed plaque ruptures are easily identified by looking for breaks in the fibrous cap of healed lesions that comprise collagen and/or proteoglycans.(16)

V. Summary

Heart failure, stroke, and coronary artery disease (CAD) are among the cardiovascular disorders (CVD) that are associated with a higher risk of developing periodontitis, a chronic inflammatory disease of the gums and the tissues that support the teeth. There may be a link between the two disorders because they both have similar risk factors such age, socioeconomic position, diabetes, and smoking. Systemic inflammation, a major contributor to atherosclerosis, the main cause of cardiovascular events, is believed to be triggered by periodontitis.It is crucial to incorporate periodontal care into methods for preventing cardiovascular disease because of the possible connection between both disorders. Enhancing dental hygiene and treating periodontitis in a timely manner can potentially minimize systemic inflammation and lower the risk of cardiovascular events, providing a comprehensive strategy to lessen the worldwide burden of both diseases.

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