In adult patients with periodontitis, how could it lead and what is its correlation to heart disease?

Abstract

Oral health has a strong connection to systemic health and thus it is important to research how periodontitis may lead to heart disease. Recent research has shown a positive correlation between periodontitis, or periodontal disease(PD), and congestive heart failure (CHF). Periodontal disease refers to the inflammation of the gingiva and the destruction of the maxillary and/or mandibular bone. Congestive heart failure occurs when blood flow towards the heart is restricted, resulting in a heart attack, and in most cases results in fatality. In an adult patient with periodontitis, there are several bacterial pathogens present in the oral cavity, such as P. gingivalis, T. forsythia, T. denticola, and A. Actinomycetemcomitans. These pathogens enter the bloodstream through the diseased area and have been known to cause a large assortment of health issues, one of which is Congestive Heart Failure. Risk factors for PD include smoking, poor oral home care, medications, and previous diagnosis of gingivitis. Risk factors for CHF include obesity, coronary artery disease (CAD)/atherosclerosis, hypertension, and diabetes. Reducing and controlling these risk factors can allow for a more comfortable and healthy quality of life. If periodontal disease is diagnosed and treated in its early stages, the risk of CHF may be reduced, and thus possibly reducing the prevalence of one of the biggest causes of hospitalization in the elderly population.

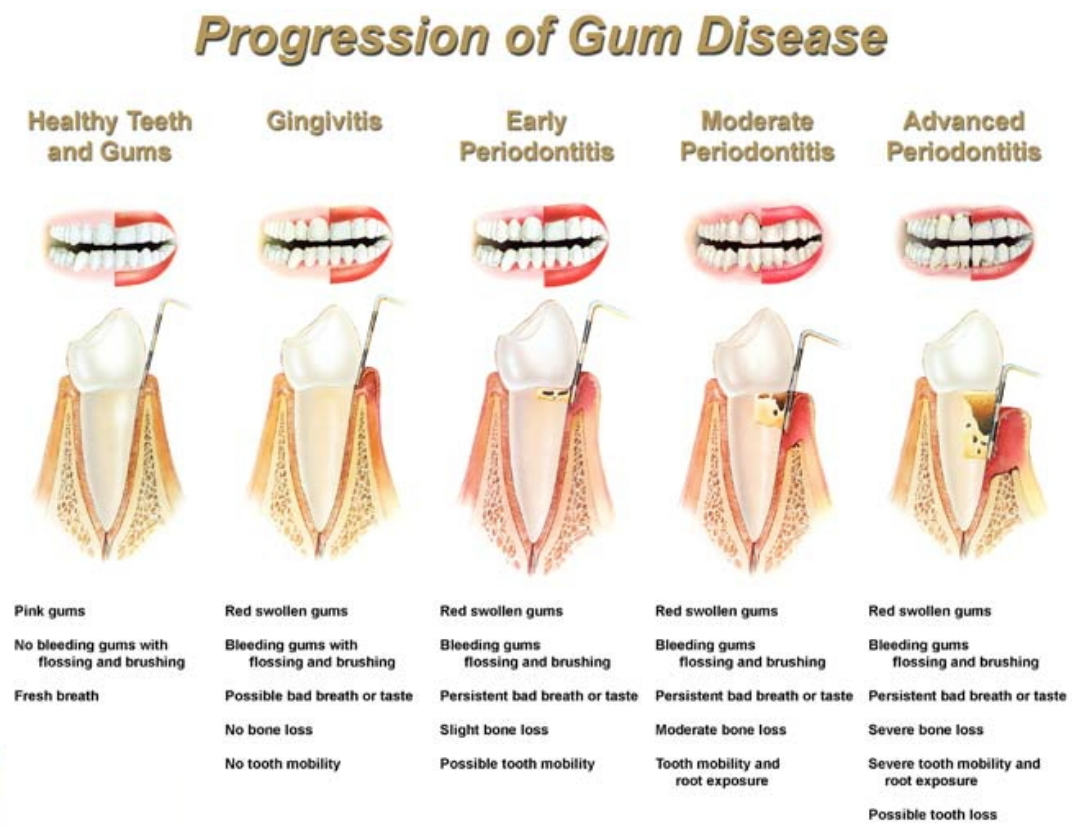
Introduction

Oral health and systemic health have been shown to have a bidirectional relationship, as the mouth is acting as a gateway to the rest of the body. Periodontal disease comprises 4 stages: healthy gingiva, gingivitis, periodontitis, and advanced periodontitis (Fig 1).[16] Periodontitis is a chronic inflammatory disease of the oral cavity and is categorized by inflammation of gingiva and loss of periodontal ligament and alveolar bone. Possible indicators of periodontitis include red and inflamed gingiva, loss of bone structure around teeth, generalized bleeding and sensitive gingiva, pain upon chewing, deep periodontal pockets, and recession. Periodontitis can lead to alveolar bone loss, the destruction of the periodontal ligament, and tooth loss. The key difference between gingivitis and periodontitis is the loss of bone. Periodontal disease begins with the buildup of dental plaque, also known as calculus, combining with the naturally occurring bacteria in the oral cavity, forming a sticky film on the surface of the tooth. If left alone, it can harden into tartar which forms when minerals naturally present in the saliva such as calcium, sodium, bicarbonates, copper, and magnesium are deposited onto the plaque's biofilm, causing the plaque to calcify and harden. This initial stage of periodontal disease is known as gingivitis - characterized by red, bleeding, and inflamed gingiva.[16]

If gingivitis is not properly treated through frequent hygiene visits, it can progress to the next stage of periodontal disease, periodontitis. The formation of a deeper pocket between the tooth and the gingiva can be observed, indicating mild bone loss. The PPD, or the Periodontal Pocket Depth, is a measurement of the depth of the pocket based off the most coronal aspect of gingiva. The Clinical Attachment Loss is used to assess the loss of periodontal tissue support around the tooth. The CAL, or the Clinical Attachment Loss, is a measurement that is the sum of the periodontal pocket depth in addition to the gingival recession measured on that tooth. According to the updated 2018 Periodontal Classification System, in Stage 1 or mild

periodontitis, the PPD measurement should be <= 4mm, and the CAL should be <= 2mm in most cases. If still left untreated, mild periodontitis will progress to moderate periodontitis or Stage 2. During Stage 2, much greater bone loss will be observed, and the PPD measurements will deepen, developing to <= 5mm, and the CAL will be between 3mm and 4mm. If still left untreated, it can worsen into Stage 3 or Stage 4 periodontitis, where tooth loss and a large amount of alveolar bone loss can be viewed.

Periodontal disease affects 47.1% of the world's adult population above age 30, and affects people around the world. Risk factors for periodontitis include smoking, diabetes mellitus, hormonal changes, obesity, malnutrition and inadequate consumption of nutrients, Vitamin C deficiency, genetic risk factors, and Crohn's disease. [18]



Heart disease is the leading cause of fatality in the world, responsible for 1 in 3 deaths worldwide. Coronary heart disease (CHD) is usually caused by a buildup of fatty deposits on the walls of arteries around the heart. Atherosclerosis, the buildup of plaque which makes the

arteries narrower, restricts flow of blood to cardiac muscles, causing coronary heart disease (CHD). Atherosclerosis is most common in the carotid, coronary, popliteal, and the abdominal aorta arteries. The buildup of plaque restricts blood flow, and can lead to a stroke, pulmonary embolism, or cardiac arrest. CHD can be characterized by sudden and sharp chest pains, shortness of breath, and rarely, indigestion. Atherosclerosis is mainly caused by a sedentary lifestyle and unhealthy eating habits, mainly diets filled with high cholesterol foods. It is also more prevalent in people with diabetes mellitus, and smoking. Food high in carbohydrates and most kinds of red meat contain high levels of low density lipoproteins, or LDL-C, also known as “bad cholesterol”. HDL-C, or “good cholesterol”, takes the LDL-C away from your arteries and to your liver for processing. LDL-C is the main cause of atherosclerosis, as it gets lodged in arterial walls, and restricts endothelial function, narrowing the arteries.[15]

The pathogenesis of atherosclerosis begins with damage to the endothelial cells. The endothelium functions as a barrier between the rest of the arterial wall and the inside of the blood vessel, restricting access to the interior. The endothelium additionally secretes anticoagulation proteins, preventing clotting and allowing the blood to flow smoothly through the vessel. Endothelial cell damage can be caused by hypertension, smoking, hyperglycemia and hypercholesterolemia, the increased number of LDL-Cs in the circulation. This increases the permeability of the arterial wall. The first step in atherosclerosis trapping LDL-C in the lesion site. The damaged arterial walls allow LDL to migrate to the tunica intima, the inner layer of the wall. Low density lipoprotein trapping results in the increased concentration of LDL in the intima, the innermost layer of the blood vessel wall. When the damaged endothelial cells are exposed to the LDL, they express adhesion molecules on their cell membranes which can capture nearby leukocytes, such as monocytes. The monocytes undergo diapedesis, which is when they change shape to be able to enter the tunica intima through the arterial wall. This process is not normal, and only occurs in situations when the cells express adhesion molecules. The white blood cells produce a molecule called a free radical. Free radicals are unstable molecules which

cause the oxidation of LDL. Oxidized LDL, or Ox-LDL, are quite effective at activating and attracting white blood cells. This causes the white blood cells which come into contact with the LDL to release more free radicals, oxidizing more LDL, which activates more white blood cells, creating a positive feedback situation.[15]

At this point, macrophages in the tunica intima begin to phagocytize the modified LDL particles. This ultimately leads to the formation of a foam cell. A foam cell is a macrophage saturated with LDL particles in the cytoplasm, giving it a foamy appearance. These foam cells ultimately die, and release their contents, which are engulfed by more macrophages.

Eventually the build up of lipids and the dead cell fragments begin to form a plaque with a lipid core. Over time, it accumulates calcium salts and more dead cells and begins to calcify and harden.

The plaque is covered by a layer of endothelial cells. If this layer of endothelial cells, known as the fibrous cap, is compromised, the plaque can rupture and a clot can form on the vessel wall.

When the plaque ruptures, it releases prothrombotic materials into the bloodstream causing a clot to form. This clot can migrate to the heart causing a myocardial infarction or heart failure. Atherosclerosis in a mild form can go unnoticed, but as it worsens it poses a great danger.[15]

Methods

This is a systematic review of the question, in adult patients with periodontitis, how could lead and what is its correlation to heart disease? During the writing of this research paper, 19 scholarly articles were reviewed.

Discussion

Recent research shows strong evidence revealing a direct relationship between periodontal disease and cardiovascular diseases. High-risk bacterial pathogens such as *Aggregatibactor actinomycetemcomitans (Aa)*, *Porphyrmonas gingivalis (Pg), Tannerella forsythia (Tf), treponema denticola (Td),* and *Fusobacterium nucleatum (Fn)*, which are prevalent in periodontitis and cardiovascular disease, also carry the ability to enter the bloodstream through the oral cavity.[10]

As the periodontopathogens travel through the bloodstream, they release endotoxins known as lipopolysaccharides (LPS). The lipopolysaccharides consist of a lipid and multiple saccharides bound together, and are excreted by many bacteria. The lipopolysaccharides bind to Toll-Like Receptor 4, a pattern recognition receptor in the cell. When the TLR4 is activated, it signals the cell to release the inflammatory cytokines discussed earlier: IL-1, IL-6, and TNF

alpha. In many inflammatory diseases, pro-inflammatory cytokines have been appertained to an important pathogenic role for promoting cell adhesion, permeability, and apoptosis as part of the inflammatory response by interacting with specific receptors on various cell types. There are 2 mechanisms in which periodontal pathogens can aggravate the pathogenesis of atherosclerosis. The first is the direct invasion of arterial walls and atherosclerotic plaques by bacteria which infiltrate the bloodstream. The second is the pro-atherogenic and inflammatory effects resulting from bacterial toxins released by oral pathogens.[14]

Porphyromonas gingivalis is a gram-negative, rod-shaped anaerobic bacterium. P. gingivalis releases a variety of endotoxins, or LPS molecules. These lipopolysaccharides are components found in the cell walls of gram negative bacteria, and bacteria are constantly shedding large proteins. The inflammatory response to a pathogen is largely due to Toll-Like Receptor 4, which recognizes exogenous molecules from extracellular pathogens, such as the endotoxins from P. Gingivalis. TLR4 is expressed on the cell surface of endothelial cells, cardiac myocytes, and the cells of the central nervous system.

The recognition of the LPS begins with a LPS binding protein, which binds to LPS monomers, and brings them to a protein known as CD14. The CD14 protein can be bound to the cells peripherally, through a glycosylphosphatidylinositol anchor. CD14 brings the LPS to the ectodomain of TLR4. This is known as CD14 dependent activation, where the CD14 brings the LPS to the TLR4. A protein known as MD2 helps the TLR4 recognize the endotoxin. Homodimerization of TLR4 ectodomains are induced when the LPS binds to the MD2, CD14, and TLR4. The dimerization of the ectodomains leads to the dimerization of the intracellular component - Toll IL1 receptors. A protein known as MyD88 recognizes the dimerization and binds to the receptor. This causes an incredibly complex transduction pathway, of which the end result is the inflammation and expansion of the blood vessel wall.[10]

The expansion of the blood vessel wall causes the enlargement of the plaque and larger protrusion into the lumen of the blood vessel. This leads to a greater risk of rupture, and

creation of a thrombus. This inflammatory process is a marker of the later stages of atherosclerosis.

So, the P. gingivalis releases endotoxins from its plasma membrane during its mitosis phase, which are recognized by the TLR4 and set off a chain reaction, leading to progression of atherosclerosis. This is the first way in which P. gingivalis and periodontal pathogens accelerate atherosclerosis.

The second way in which periodontal pathogens can accelerate atherosclerosis is direct invasion of the cardiovascular host cells. Although P. gingivalis primarily colonizes oral epithelia, daily bacteremias through tooth brushing and chewing, especially in those with weakened gums and periodontitis, facilitates the entry of this bacterium into the circulation.

P. Gingivalis invades the cells in a 5 step process, starting with adhesion, then entry, trafficking, persistence, and exit. Little is known about the exit process. P. gingivalis begins its invasion by using a number of adhesins to adhere to the cell. Once it has attached, P. gingivalis begins its entry by internalizing using lipid rafts in the host cell's membrane. Then, P. gingivalis trafficks through the autophagic pathway. But, once P. gingivalis is within the autophagosomes of a cell, it prevents the final step of the pathway, in which an autolysosome is formed, and the contents of the autophagosome are degraded. This effectively creates a replicating or persistence vesicle for the bacterium to reside in. This is ideal for the P. gingivalis strain, because the vesicle in which the bacterium resides is still tagged as an autophagosome, and the cell continues to deliver cellular proteins to the vesicle. The P. gingivalis uses these proteins to gain the peptides and amino acids necessary for its survival. P. gingivalis then begins its persistence. Different strains persist for different times. This stage has not been studied in depth. P. Gingivalis exits epithelial cells through the endocytic recycling pathway, which allows bacteria to exit from infected cells.[14]

When P. gingivalis invades the cardiovascular cells, it can have multiple effects. The first of these effects is induction of the inflammatory response in the cells it infects. The bacterium

activates toll-like receptors, which are present on the surface of immune cells and recognize bacterial pathogens. This can trigger the production of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor-alpha, leading to the chronic inflammation of the arterial walls. As previously discussed, this inflammatory process accelerates the progression of atherosclerosis. It can contribute to the development of atherosclerosis by promoting the recruitment of immune cells to the site of infection, which contribute to the formation of plaque by forming foam cells.

Another effect that P. gingivalis has is that it can directly alter lipid metabolism in the cells it infects. The bacterium upregulates the expression of scavenger receptors, like CD36, which are involved in the intake of Ox-LDL by macrophages. This increases the formation of foam cells, which also increases the progression of atherosclerosis. Foam cells accumulate in the arterial walls and contribute to the formation of the atherosclerotic plaque. When P. gingivalis infects cardiovascular cells, it can induce the expression of CD36 through several mechanisms. One mechanism involves the activation of nuclear factor-kappa B, which is a transcription factor that regulates the expression of genes involved in inflammation and immune responses. P. gingivalis also activates NF kB through the TLR2 pathway. Once activated, NF-kB can stimulate the expression of CD36, leading to a larger uptake of Ox-LDL by macrophages and formation of foam cells. Another mechanism involves the production of reactive oxygen species, which can activate the expression of CD36. P. gingivalis induces the production of ROS in cardiovascular cells, leading to the upregulation of CD36 and formation of foam cells.[1]

The final effect P. gingivalis can have is the upregulation of the expression of matrix metalloproteinases (MMPs) in the cells that it infects. MMPs are enzymes which degrade extracellular matrix proteins in the arterial walls of the cardiovascular cells in the fibrous cap. This weakens arterial walls and can contribute to plaque rupture and thrombosis, which can lead to heart attacks and stroke. Similar to the upregulation of CD36, the activation of NF-kB by P. gingivalis leads to a larger expression of MMPs. A different mechanism involves the activation of mitogen-activated protein kinase pathways, which are involved in the regulation of cell

proliferation, differentiation, and apoptosis. The bacterium activates MAPK pathways, which can upregulate the expression of MMPs and promote tissue remodeling. The production of ROS, induced by P. gingivalis in cardiovascular cells activates the expression of MMPs. ROS activates redox-sensitive transcription factors, like activator protein-1 and nuclear factor erythroid 2-related factor 2 (Nrf2, which can upregulate the expression of MMPs. It is to be noted that the upregulation of MMPs is also a contributor and accelerator of tissue destruction in periodontitis, and is observed in the severe and late stages of periodontitis.[8]

Overall, P. gingivalis can accelerate atherosclerosis through multiple mechanisms, including triggering the production of pro-inflammatory cytokines, and the upregulation of MMPs, and CD36.

Proof of P. gingivalis colonization in atherosclerotic plaques is shown in a study performed in 1998, in which Socransky et. al organized the bacteria of the subgingival plaque into two main classes of microorganisms, the “orange” and “red” complexes. The “red” complex consists of 3 tightly related species: *T. forsythia, P. gingivalis*, and *T. Denticola.* This complex is strongly related to pocket depth and bleeding on probing. The other complex, “orange” complex, included *F. Nucleatum/periodonticum* subspecies*, P. intermedia, P. nigrescens, Peptostreptococcus micros, C. rectus, C. gracilis, C. showae, Eubacterium nodatum,* and *Streptococcus constellatus,* and seemed to have preceded colonization by species of “red” complex. Species from the “red” complex bacteria (RCB), have been found in vascular lesions, which has suggested them to be involved in the pathogenesis of atherosclerosis. By sampling carotid atheromatous plaques in 52 patients, F. Cairo et al. discovered T. forsythia in 79%, P. gingivalis in 37%, and A. actinomycetancomitans in 5% of the samples taken from carotid atheroma patients.

Periodontal pathogens have also been connected to diabetes, rheumatoid arthritis, oral and colorectal cancer, gastrointestinal diseases, respiratory tract infection and pneumonia, adverse pregnancy outcomes, and Alzheimer’s disease.

Conclusion

In conclusion, this research paper has explored the connection between periodontal disease (PD) and atherosclerotic cardiovascular disease (ASCVD). Several factors such as direct invasion of the cell by periodontal pathogens and the release of endotoxins which cause an inflammatory response and the progression of atherosclerosis. The implications of this research are significant, as it shows that oral health may have broader implications in overall health and wellbeing. Dental health professionals and physicians should work together to prevent the progression of both diseases. In conclusion, the research conducted in this paper adds to the growing body of evidence suggesting that periodontal disease and ASVD may be linked. Continued research in this area is necessary to fully understand the relationship between these two conditions and to develop effective prevention and treatment strategies.

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