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PERIODENTAL DISEASE EFFECT ON CARDIOVASCULAR SYSTEM

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ABSTRACT

Over the years, advancement made in the field of scientific research has opened up new horizons in understanding the intricate aspects involved in the pathogenesis of various inflammatory human diseases including periodontitis. In recent times, there has been an increasing interest evinced in the areas relating to the impact of oral infection models have emerged as useful tools to study the hypothesis that infection isa cardiovascular disease (CVD) risk factor. Periodontal infections are a leading culprit, with studies reporting associations between periodontal disease and CVD. The results, however, have varied, and it often is unclear what conclusions canbe drawn from these data health especially periodontal infection on the cardiovascular system.

Keywords: Inflammation, Periodentities, Atherosclerosis, Cardiovascular disease, Epidemiology.

INTRODUCTION

Inflammation referring to a protective tissue response to injury has been implicated in the pathogenesis of manyhuman diseases. It plays a central role in complex multifactorial chronic inflammatory diseases including periodontitis and cardiovascular disease (CVD). Periodontitis over the years, advancement made in the field of scientific research has opened up new horizons in understanding the intricate aspects involved in the pathogenesis of various inflammatory human diseases including periodontitis. In recent times, there has been an increasing interest evinced in the areas relating to the impact of oral health especially periodontal infection on the cardiovascular system. With the advent of inflammation paradigm being considered in the coronary artery disease pathogenesis, research has focused on the role of chronic infections caused by oral pathogens on the endothelial is a chronic 'infectious/inflammatory' disease of multifactorial etiology [1]. Though it is initiated by dental plaque associated microorganisms, the inflammatory process is sustained by the host.

Periodontal pathogens have been detected in atherosclerotic plaques in humans and animal models, Suggesting that periodontal infections may result in bacteremias and enhance atherosclerotic plaque formation [2-4]. A number of inflammatory cytokines, which have been reported to be associated with periodontitis, are also involved in atherothrombogenesis [5,6]. Furthermore, patients with periodontal disease share many of the same risk factors as patients with CVD including age, gender (predominantly male), lower socioeconomic status, stress, and smoking [7].

PATHOBIOLOGY OF PERIODONTITIS

The inflammation begins in the gingiva initially and remains confined to it. Most of the time the condition is reversible. When allowed to progress, periodontal inflammation sets in with gradual destruction of the supporting tissues over time and the condition is characterized by irreversible loss of the supporting tissues of the teeth. Though periodontitis is initiated by microbes, the progression and destruction of the tissues is predominantly due to the reactive host response to microbial attack ('by stander damage'). Page and Kornman showed a new dimension depicting the central role of

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inflammation in the pathogenesis of periodontal disease[8]. All these processes can disrupt the homeostasis when toxins gain entry into the systemic circulation. The pro inflammatory cytokines TNF-á (tumour necrosis factor alpha), IL-1â (interleukin-1 beta), gamma interferon and PGE2 (prostaglandin E2) reach a high tissue concentration in periodontitis. The periodontium thus serves as a renewing reservoir for these mediators, that is spilled over into systemic circulation thereby inducing and perpetuating the systemic effects (Fig 1). IL-1â favors coagulation, thrombosis and retards fibrinolysis. Chemical mediators IL-1, TNF-á, and thromboxane can cause platelet aggregation and adhesion, formation of lipid-laden foam cells and deposition of cholesterol in the arteries.

The reason being the enormous bacterial load in diseased periodontium, a source for infection for continuous release into systemic circulation. The total surface area of the diseased pocket epithelium in contact with sub-gingival bacteria and their products in a patient with generalized moderate periodontitis has been estimated to be approximately the size of the palm of an adult hand with even larger areas of exposure in cases of more advanced periodontal destruction [9].

Unique features of periodontal infection

Periodontal infection is considered unique for various reasons cited below [10, 11]

1. Periodontitis is a polymicrobial infection.
2. It is a longstanding chronic infection that is asymptomatic most of the times.
3. Normal daily activities like chewing, brushing and flossing can cause a transient bacteremia (in the process, cytokines and mediators are also pumped out into systemic circulation).
4. Unusual anatomic feature – the tooth is partially exposed to the external environment and partially embedded within the periodontal connective tissue.
5. The teeth are non-shedding surfaces unlike skin and provide a continuous microbial colonization that comes in contact with the supporting tissues of the teeth.
6. The microorganisms that initiate periodontal disease reside within a protective environment (i. e) the biofilm.
7. Presence of teeth enhances the complexity of the host parasite relationship.

ATHEROSCLEROSIS

Atherosclerosis, an inflammatory disease of the lining of blood vessels associated with local accumulation of lipids in the form of cholesterol, especially LDL, along with coronary thrombosis, is the main reason of morbidity and mortality in the developed and developing countries. During the last decade, some studies evaluated the relation between inflammation and cardiovascular disease. Based on the results of these studies it was concluded that inflammation plays a key role in the development of atherosclerosis. Atherosclerosis can result in the narrowing of arteries because of sub endothelial deposition of cholesterols, and calcium forming a plaque within the vessel walls.

Infection and Atherosclerosis

It has been established that the development of atherosclerotic plaques throughout the body, and in particular the cardiac vessels, is associated with a number of potential risk factors. Generally, it has been assumed that atherosclerotic plaques form as a result of the accumulation of low-density lipoprotein (LDL) cholesterol in the arterial wall. However, it has been noted that the formation of the lesion is due to a complex series of events, reminiscent of an inflammatory reaction. The origin of this inflammatory reaction has lead to the consideration that infection may be a component of the mechanism that results in the development of this lesion.

An elevated level of c-reactive protein, a non-specific marker of inflammation, has been associated with an increased risk of cardiovascular disease. Elevated levels of pathogens, either individually or as a cumulative "pathogen burden" have correlated with elevated c-reactive protein levels [12]. Pathogens that have been investigated include Chlamydia pneumoniae, Helicobacter pylori, herpes simplex virus (HSV), hepatitis A virus (HAV), cytomegalovirus (CMV), as well as more recent investigation into the effects of putative periodontal pathogens on the development of cardiovascular disease. A number of studies have looked at the effect of Chlamydia pneumonia and the incidence of cardiovascular disease. Since the late 1980s, it has been suggested that elevated antibody levels and immune complexes containing C. pneumonia were detected in acute MI patients [13]. More recent studies have suggested a 2 to 4-fold increased prevalence of cardiovascular disease when anti- C. pneumonia antibodies were detected. Other lines of evidence implicating *C.pneumoniae* include the identification and culture of viable C. pneumonia organisms from atheroma, animal models with C. pneumonia induced atherogenesis as well as the growth of C. pneumoniae in vascular cells *in vitro*. However, not all investigations point to this conclusion. Nieto suggested that data from the Atherosclerosis Risk in Communities Study indicated that IgG antibody titers to C. pneumonia were elevated in both cardiovascular disease and non cardiovascular disease participants. Based on samples following carotid endarterectomy, it was demonstrated that C. pneumonia did not play a causal role in the progression of disease in an advanced carotid atherosclerosis population.

OVERVIEW OF THE STAGES IN THE DEVELOPMENT OF ATHEROSCLEROSIS

The stages in the development of atherosclerosis involves a series of events that include development of fatty streak, progression to complex plaque and plaque

rupture [12]. During the stage of fatty streak – initially there is an accumulation of monocytes in the vessel intima which is an initial event in the development of early atherosclerotic lesion. There is adherence of monocytes to endothelium through the expression of MCP-1(Monocyte chemoattractantprotein-1). They migrate across the endothelial cells in to the intima. They mature in to macrophages that express scavenger receptors and engulf modified lipoproteins. Foam cells' (i. e) lipid-laden macrophages are formed in the vessel intima. Macrophages multiply, release growth factors, cytokines that amplify and sustain the pro-inflammatory signals.

Next step features progression to complex plaque fixation with accumulation of fibrous tissue in vessel. Certain growth factors like platelet derived growth factor and cytokines like IL-1, transforming growth factor-beta from endothelial cells and monocytes stimulate smooth muscle cells to produce interstitial collagen.

One of the sequelae that occurs following complex plaque formation is plaque rupture. Thrombus formation results from the physical disruption of the plaque. In case of non-ruptured plaque, the fibrous cap protects blood from the lipid core of the plaque. When there is a fracture of fibrous cap, blood comes in contact with the lipid core and a thrombus gets formed. It is viewed that inflammation interferes with the integrity of the fibrous cap through blocking the creation of new collagen fibers and stimulating the destruction of existing collagen by the action of matrix metalloproteinases (MMPs).

Cardiovascular Diseases (CVD)

Cardiovascular Diseases (CVD) make up the most prevalent category of systemic diseases in developed as well developing countries and are increasing with age.[13] World Health Organization statistics in 1995 indicated that CVD were responsible for 20% of deaths worldwide and in some developing countries accounted for 50% of deaths.[14] CVD has contributed to a third of global deaths. The low and middle-income countries were responsible for 78% of CVD deaths in 1999. By 2010 CVD is estimated to be the leading cause of death in developing countries.

Periodontal disease and Cerebrovascular Disease-Stroke

The relationship of periodontal disease to ischemic stroke has been evaluated in a number of studies. The outcome is different across the reported studies, ranging from total stroke to fatal stroke, nonfatal stroke and ischemic stroke [13-15] The study of Beck and colleagues compared men who had any type of stroke with men who did not develop CVD during the follow up. They found a significant association between periodontal disease and total stroke: relative risk (RR) of 2.80.Wu and colleagues found a possible association between periodontal disease and ischemic stroke (RR=2.11); the risk was even higher when limited to fatal stroke [15]. Although studies have shown an association between tooth loss or periodontal disease and stroke, no two studies are consistent in defining the outcome and exposure. Hence, no association has been truly replicated. It is difficult to rule out residual confounding variables, as there are several common risk factors [16].

Periodontal disease and Coronary Heart Disease(CHD)

Periodontal disease is a chronic infection and may be associated with inflammatory systemic conditions. A number of studies provided a significant data and statistics to suggest and support the relationship of periodontal disease to cardiovascular diseases. Most of the risk factors for cardiovascular disease are also regarded as risk factors for periodontal disease [17].

Mattila suggested a statistical association between severity of coronary stenosis and dental infections. Data are compatible with hypothesis that oral infections might play a role in the development of adverse cardiovascular outcomes. Studies conducted by Beck et al and Arbes et al also provided some support to the hypothesis that periodontal disease and tooth loss might play a role in the development of CHD [17,18]. However likelihood of considerable residual confound in confounding remains there in all these studies. Hujoel presented a negative association between periodontal disease and subsequent CHD in first National Health And Nutrition Examination Surveys (NHANES-I) longitudinal study with a 21 years follow-up [19].

Other Common Aspects of Periodontitis and Cardiovascular Disease

One of the most intriguing notions with respect to the putative relationships between periodontitis and cardiovascular disease may related to some of the similarities in their underlying pathophysiological and physiological regulatory systems. For instance, as has already been discussed, smoking is a significant risk factor for both diseases. Current data in our laboratories suggest that an important component of cigarette smoke, aryl hydrocarbons, have the ability to inhibit bone formation, particularly in the presence of periodontal disease causing bacterial co-factors. As such, these data could help to explain, in part, how cigarette smoking might lead to periodontal bone loss.

Interestingly, we now also have data to suggest that these same aryl hydrocarbons may promote vascular disease, as measured by vascular calcification. Thus, a common risk factor, smoking/aryl hydrocarbons, mitigates negative effects in two disparate systems: the periodontium and vascular tissues.

Along similar lines, it is also well-known that matrix metalloproteases (MMPs), including the collagenases, likely play an important role in periodontal

tissue break down. Similarly, it is known that matrix metal loproteasesalsoplay a role in cardiovascular disease ranging from destabilization of a theromastoregulation of the development of heart failure and the deleterious changes in extracellular matrix in the myocardium. Again, one see sparallelisms between periodontal tissue destruction and cardiovascular disease both mediated and/or regulated by a similar pathway, in this case one associated with MMPs. In fact, there is increasing evidence that inhibition of MMPs, already shown to be effective for inhibition of periodontal attachment loss, can also inhibit the development of cardiac failure.

In light of these common aspects, it is also conceivable that any relationships observed between cardiovascular disease and periodontitis could be related to the possibility that pathological or biological factors that adversely affect one system also adversely affect the other.

Potential mechanisms of the association between periodontitis and CVD

Some studies have suggested that potential links between periodontitis and CVD include direct effects from bacteria and indirect effects through host inflammatory responses as well as autoimmune responses. Since the DNA of P. gingivalis has been detected in atherosclerotic plaques [22,23] and periodontal infections can result in bacteremias and endo-toxemias in the patients[24-26], systemic effects on the cardiovascular system through these exposures seem biologically reasonable. Three potential mechanisms of the association between periodontitis and CVD include:

- direct bacterial effects on platelets and host cells,
- systemically or locally induced inflammatory mediators,
- autoimmune responses.

Platelets play a critical role in hemostasis and thrombosis. In vitro studies on the interaction of platelets with two bacteria found in the oral cavity, Staphylococcus aureus and Streptococcus sanguis, have shown that the bacteria can induce platelet aggregation [27-29] . Recent studies have demonstrated that P. gingivalis can also activate plate- lets, induce platelet aggregation and increase protease activity [30-32]. An ultrastructural study of P. gingivalis induced platelet aggregation was conducted using electron microscopy [33]. A sharp and rapid increase of small-sized platelet aggregates was observed immediately after the addition of P. gingivalis to human platelet rich plasma (PRP), followed by the formation of medium- and large-sized aggregates in 2-3 min. Furthermore, P. gingivalis was mostly present between the adherent platelets and some were

Periodontal disease and Peripheral Arterial Disease (PAD)

PAD shares a common underlying pathological change, atherosclerosis, with coronary heart diseases and stroke. Very few studies have been reported on the relationship of period ontal disease to PAD.

In a cohort study of 51529 health professionals aged 40-75 including 29683 dentists conducted between 1986- 1998, tooth loss and periodontal disease experience was recorded through self reported biennial questionnaires [20]. A total of 342 cases of PAD (255 definite and 87 probable) were recorded. In this multivariate model age, smoking, alcohol, family history of myocardial infarction, multivitamin supplement use, vitamin E intake, history of hypertension, diabetes, hypercholestrolemia and the profession (dentist/nondentist) were adjusted and updated on the basis of biennial questionnaires. Periodontal disease was also taken as a causative factor for tooth loss. From the study it was concluded that men with a history of periodontal diseases or any tooth loss during follow-up HADA significantly higher risk of PAD than men without any periodontitis or without any tooth loss. Incident tooth loss was significantly associated with PAD, especially among men with periodontal diseases. In a follow up study on 1030subjects of 25-30 years, Mendez et al reported that subjects with clinically significant periodontal disease at baseline had a relative risk of 2.27 of having PAD [21].

REPORT ON META ANALYSIS

Of all the epidemiological study designs, meta-analysis reports carry the highest weightage to draw conclusions about the research question. The findings of these meta analysis with respect to the link between CAD and periodontitis have concluded the following:

1. Periodontal disease is a risk factor or marker independent of traditional CAD risk factors with relative risk estimates ranging from 1.24 to 1.35 [34]
2. Significantly increased prevalence and incidence of CAD in patients with periodontitis raising the possibility that periodontitis independently predicts CAD [35]
3. Prospective and retrospective follow-up studies have shown that periodontal disease may only slightly increase the risk of CVD [36, 37].

CONCLUSION

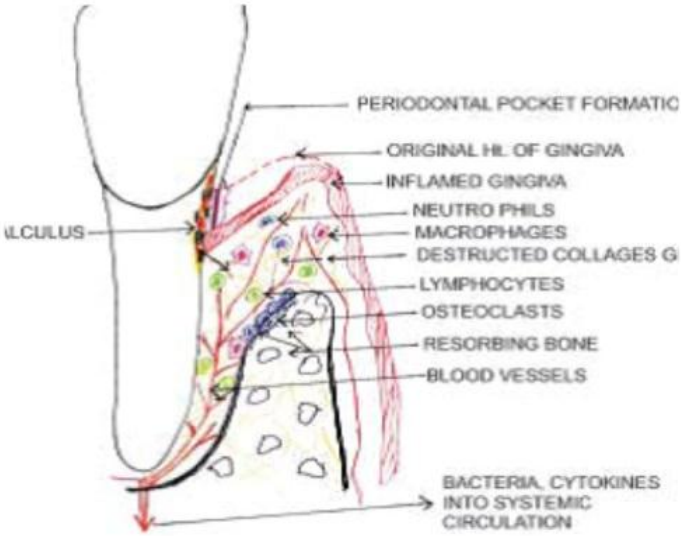
At a minimum, periodontal infections are epidemiologically associated with CVD; that is, periodontal infections seem to be found more frequently in patients with CVD. However, the critical question of whether periodontal infections area risk factor for or contribute causally to CVD and cerebrovascular disease remains un answered. The possibility that periodontal disease and CVD share common risk factors or are manifestations of a similar underlying pathology remains, as several analyses were conducted post hoc and statistical adjustment for confounders can be imperfect. However, the mounting evidence points to an association of periodontal disease at the biological, clinical, radiographic and microbiological levels

in relation to clinical and subclinical vascular disease. Because periodontal infections are so prevalent, the potential attributable risk of such an association would be substantial at the population level. There is, however, no direct peer-reviewed evidence to suggest that treating or preventing periodontal infections leads to fewer clinical cardiovascular events. Some insurance company studies, however, find fewer medical care needs in patients who maintain their periodontal health. If the relationship holds, one of the remaining issues will be to determine whether the possible contribution of periodontal disease to CVD risk can be addressed better via treatment of existing disease or through prevention before a threshold of irreversible subclinical CVD is reached.

ACKNOWLEDGEMENT
Nil

CONFLICT OF INTEREST
None.

Fig 1



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