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RESEARCH ARTICLE

TRACING THE LINK BETWEEN ANTICARDIOLIPIN ANTIBODIES AND PERIODONTITIS

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ABSTRACT

Periodontal disease is a chronic infection affecting the tissues surrounding and supporting the teeth, primarily caused by the bacteria of dental plaque. It begins as gingivitis, an inflammation of the soft tissues, and can progress to periodontitis, where destruction of connective tissue attachment and alveolar bone can eventually lead to tooth loss. Periodontitis is associated with cardiovascular disease and, also with measures of atherosclerosis and endothelial dysfunction. Anticardiolipin may explain some of the observed associations between periodontitis and systemic conditions such as cardiovascular disease and adverse pregnancy outcomes.

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INTRODUCTION

Periodontitis is considered to be a multifactorial disease with no clear cut etiology with varied clinical features. Since the past few decades, studies have proved that periodontal disease negatively impacts systemic health and have proposed diverse mechanisms of this association. It is suggested that association between systemic conditions and periodontitis results from the effect of periodontal pathogens especially gram negative bacteria, which induce the production of systemic inflammatory mediators (Kornman, 1997). Endotoxins of plaque microorganisms are capable of penetrating gingival tissues and entering the blood stream to bring about a systemic lipopolysaccharide-specific antibody response (World Health Organization, 2003). Periodontitis is also suggested as a risk factor for the coronary heart disease, atherosclerosis, preterm births and chronic kidney diseases. Cardiolipin is found to play a pivotal role in mitochondrial protein import, cell wall biogenesis, ageing, apoptosis, ceramide synthesis and translation of electron transport chain components.

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Cardiolipin can start an early antibody response in diseases with mitochondrial damage. Anti-cardiolipin antibodies are antibodies directed against cardiolipin and are found in 1% to 5% of systemically healthy individuals. Most of the chronic inflammatory diseases are diagnosed by evaluating the levels of anticardiolipin antibodies which are produced in response to cardiolipin which happens to be a phospholipid (diphosphatidylglycerol) found in mammalian tissues, eukaryote organisms and also produced by some prokaryotic bacteria (Miyakis, 2006). Various mechanisms linking periodontal infections and cardiovascular diseases have been put forth. One of them being studied in detail is the role of anticardiolipin antibodies since patients with periodontitis have demonstrated elevated anticardiolipin antibody levels. This review encompasses the knowledge and significance of these antibodies and their correlation to periodontal diseases.

Antiphospholoipid Antibodies

Substances in the blood, called phospholipids, are required for the normal coagulation process. Sometimes though, the body mistakenly recognizes phospholipids, as foreign substances and forms antibodies against them, thus creating an

autoimmune reaction. These antibodies are called anti-phospholipid antibodies. There are 3 groups of antibodies classified as antiphospholipids: β-2-glycoprotein I-dependent anticardiolipin (anticardiolipin), anti-β-2-glycoprotein I (anti-b2GPI), and lupus anticoagulant (LA). Thus laboratory investigations to detect these antibodies usually involve multiple assays for autoimmune anticardiolipin, anti-b2GPI, and LA (Miyakis, 2006).

Anti-cardiolipin antibodies

Anti-cardiolipin antibodies (anticardiolipin) are antibodies belonging to the family of antiphospholipid antibodies often directed against cardiolipin and found in several diseases, including syphilis, Antiphospholipid syndrome, livedoid vasculitis, vertebrobasilar insufficiency, Behçet's syndrome, idiopathic spontaneous abortion, and systemic lupus erythematosus(SLE). They are a form of anti-mitochondrial antibody. Anticardiolipin antibodies are immunoglobulins of the IgG or IgM class, which can either be β2GP1 dependent or independent. β2GPI is a plasma protein that binds to negatively charged phospholipids and is thought to provide a protective homeostatic mechanism preventing pathological prothrombotic reactions initiated by platelets or endothelial cells. β2GPI-dependent anticardiolipin are frequently pathogenic, and such antibodies may be induced by certain bacterial and viral pathogens ().[4] Patients with anticardiolipin antibody usually exhibit a tendency toward thrombosis. It has been suggested that antiphospholipid antibodies, the family of autoantibodies to which anticardiolipin antibodies belong, prevent prostacyclin production. Prostacyclin, which is a potent vasodilator and inhibitor of platelet aggregation. is produced by vascular tissues. It is a natural antagonist to thromboxane, a potent vasoconstrictor and platelet aggregation-inducing prostaglandin that is released by aggregating platelets. Production of prostacyclin by the endothelial cells is considered an important mechanism in protecting the vascular wall from the deposition of platelet aggregates and subsequent thrombosis. Thus the inhibition of prostacyclin would favor thrombosis. Anticardiolipin antibodies also bind to phospholipid antigens of the placental vessels, inducing placental infarction.[5] It is the platelet aggregation and increased coagulation that are surmised to contribute to fetal death.

Association of anticardiolipin with periodontitis

Studies have previously shown that a greater proportion of patients with chronic periodontitis or aggressive periodontitis have elevated serum anticardiolipin levels than systemically and periodontally healthy individuals (Chaston, 2014). Patients with antiphospholipid syndrome are prone to develop arterial and venous thrombi and women with antiphospholipid syndrome frequently experience recurrent spontaneous abortion. In addition, there is some evidence for early atherosclerosis in these patients. Such patients usually have serum anticardiolipin levels in the very high range. On the other hand, periodontal infections are associated with preterm labor, low birth weight, atherosclerosis, endothelial dysfunction, and myocardial infarction, though cause and effect relationships are yet to be proven. The concentrations of anticardiolipin in sera from these patients, though clinically elevated (i.e. greater than levels found in 95 % of the general population), are largely in the moderate range. Thus, there are similarities between the sequelae of antiphospholipid syndrome and conditions with increased risk in periodontitis patients but the severity of the associated clinical manifestations are quite different, as are the serum concentrations of these antibodies (Schenkein, 2013). Furthermore, antiphospholipid syndrome appears to involve additional functional thrombotic defects and is frequently characterized by the appearance of additional autoantibodies that contribute to the onset of prothrombotic events. Nevertheless, it is difficult to ignore the similarities between these conditions, especially in view of data indicating that the antibodies found in periodontitis patients appear to have some proinflammatory effects on endothelial cells. The results from studies are consistent with an interpretation that anticardiolipin in periodontitis patients could contribute to systemic disease in a manner consistent with the concentrations of antibodies found in these patients in comparison to those with true autoimmune disease.

It is very likely that anticardiolipin antibodies in periodontitis patients can be induced by oral microbial pathogens, and researchers have preliminarily observed in the laboratory that *P. gingivalis*, a pathogen in periodontitis, can induce production of antibodies reactive with cardiolipin/β2GP1 complexes in both mice and rabbits. It is known that anticardiolipin and Antiphospholipid syndrome-like symptoms can be induced by a variety of microbial pathogens. This can occur by molecular mimicry due to the presence of microbial peptide sequences homologous to the target antigenic peptide for pathogenic anticardiolipin present on β2GP1 (Schenkein, 2013). It has in fact been demonstrated that some periodontal microbial pathogens, including *P. gingivalis, A. actinomycetemcomitans, and T. Denticola* have peptide sequences with sufficient homology to a key hexapeptide in β2GP1 to induce mutually cross-reactive antibodies with the potential to be pathogenic. There are additional studies showing that infections may trigger antiphospholipid syndrome in other rheumatic diseases, suggesting a microbial origin for both pathogenic and non-pathogenic anticardiolipin. In periodontitis, this type of antibacterial immune response could be in part responsible for associations of periodontal infections with adverse cardiovascular and pregnancy outcomes in some patients, or they merely may be markers of events that co-occur with these conditions. Common risk factors like smoking, associated with periodontitis as well as systemic disorders also result in elevated anticardiolipin levels (Yadalam, 2016).

Effect of periodontal therapy on anticardiolipin levels

Various researchers have studied the association of periodontitis with elevated serum anticardiolipin levels. In a study by Pradeep et al it was stated that severe periodontitis subjects exhibited marked increase in anticardiolipin IgG and IgM compared to control group (Pradeep Kumar, 2011). Chaston et al studied the effect of periodontal therapy and concluded that the oral microflora is a likely source of antigen inducing Anti-CL in patients with chronic periodontitis , since IgM anti-CL levels can be reduced by scaling and root planing in the short term (Pradeep Kumar, 2014).

Conclusion

Till date it is not known definitively whether anticardiolipin contributes to the associations that have been found among periodontitis and systemic conditions such as atherosclerosis,

stroke, and detrimental pregnancy outcomes. In addition, the persistence of anticardiolipin in patients with periodontitis has not yet been studied. Thus, the possible impact of periodontal therapy on systemic health due to reduction in anticardiolipin titers is highly speculative. Data from recent studies reveal the feasibility of short-term reduction of IgM anticardiolipin in patients with moderately elevated levels of these antibodies. Also, these results further implicate the oral flora as a nidus of biologically active and potentially pathogenic antibodies by molecular mimicry. Long-term clinical trials incorporating assessment of anticardiolipin as one of many possible markers of disease, can determine the biologic significance of elevated anticardiolipin in periodontal disease populations, and the impact of periodontal therapy on systemic health.

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