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The relationship of inflammation to systemic diseases and chronic periodontitis

We all know that periodontal diseases are the result of bacterial imbalance and the immune response of the host to infection. It is this inflammatory host response and proinflammatory mediators that are produced that cause the tissue changes that occur as a result of periodontal diseases. Several epidemiological studies have suggested the association between chronic periodontitis and some systemic diseases. Some studies propose that proinflammatory mediators in periodontal disease are the same mediators involved in diseases such as heart attack, stroke, diabetes, rheumatoid arthritis, pregnancy complications, Alzheimer's disease and others. Inflammation is recognized as the key contributor to a number of chronic diseases, and among them are periodontitis and cardiovascular diseases. There are those that think that correct terminology is the perio-systemic link, versus the oral-systemic link. Kao's opinion is that the oral-systemic link is a misnomer and that the connection is more correctly called the 'perio-systemic link'. Whatever you choose to call it, we know that there is a link (1).

Studies to date discuss three possible justifications for the proposed epidemiological associations. One study theorizes that bacteria migrating to the bloodstream from the periodontal pocket can attach to injured vascular endothelium and initiate or exacerbate the atherosclerotic disease process (2). This hypothesis is supported by the demonstration of periodontal pathogens in atheromas taken from coronary and carotid arteries. Other studies connect inflammatory mediators from periodontal diseases to the increased risk for cardiovascular disease (3). Other researchers propose that risk factors common between the two diseases may be acting as a confounder in the analysis of association (4).

We now have sufficient studies to conduct meta-analyses, which are analyses to determine whether the volume of evidence supports an association between the two diseases. The meta-analyses to date conclude that periodontitis is a significant and independent risk factor for atherosclerotic cardiovascular disease (5, 6). At the same time, impressive evidence emerged from the cardiovascular profession to suggest that the most reasonable explanation for this association with any chronic inflammatory disease, such as periodontitis, appears to involve the role of systemic inflammatory mediators that have been strongly implicated in atherosclerotic cardiovascular disease events.

In spite of their intrinsic limitations, observational epidemiological studies can provide insight into credible causal pathways and to inform the design of intervention studies. An example by Garcia stated that the finding that tooth loss associated with an increased risk of ischemic heart disease (IHD) and periodontitis in middle-aged and elderly women does not necessarily plausibly imply that replacement of missing teeth will result in IHD risk reduction (7). According to Garcia, it may be more reasonable to hypothesize that risk factors may contribute to both tooth loss and to IHD and are the more appropriate points of intervention. Mechanisms involving various inflammatory pathways have been proposed as the most successful pathways for targeting interventions aimed at improving oral health for the overall objective of improving cardiovascular outcomes (8).

Most inflammation is principally protective. Acute inflammation usually resolves if the irritant is removed and if the resolution is not interrupted. The inflammatory response can become destructive, such as when an acute infection becomes chronic. The inflammatory response may not be allowed to resolve and complete the repair phase (9). The same outcome may result in some people if the inflammatory response is exaggerated when it's activated. Such exaggerated inflammatory responses may result from genetic differences among individuals or may result from other inflammatory diseases throughout the body. Inflammation may also be destructive if the normal repair processes are disrupted, for example as a result of smoking. Dr. Kornman suggests using risk factors to help identify patients who are more likely to have future destructive periodontal disease. The most well-documented risk factors for future progression of periodontitis are smoking, diabetes and certain genetic variations (9).

There are many clinical challenges in diagnosing and monitoring periodontal inflammation. Clinically, we often use bleeding as an indication of the level of inflammation that exists in the periodontal tissue. Bleeding on probing (BOP) does not necessarily predict future disease activity. We have long known that BOP has a low positive predictive value for the progression of periodontitis (10). Lang found that the consistent absence of bleeding over several visits was an excellent predictor of periodontal stability. Several indices are used to clinically assess gingival inflammation, such as the Gingival Index (GI), but they are seldom used in clinical practice. Periodontal pocket measurements and attachment loss are used to assess periodontal disease, but cannot accurately measure inflammation or predict future outcomes. According to Kao *et al.*, much of the focus of dentists and dental hygienists is on periodontal pocket depth. They caution that we should also measure clinical attachment level CAL), the presence and prevalence of gingival inflammation and radiographic evidence of alveolar bone loss (11). If we believe that decreasing the oral inflammatory load can support oral and systemic health, we must be able to accurately assess risk and disease and be able to detect changes in the inflammatory process.

Currently, our therapy consists of eliminating pathogenic bacteria that incite the inflammatory response through mechanical or chemical means, to achieve a balance of bacteria that supports health. What will the role be of the dental hygienist, the dentist, the physician, the nurse and others that treat patients in the future? Promising future approaches will rely more on modifying the inflammatory response itself, by limiting the activity of proinflammatory pathways and by amplifying pathways that resolve inflammation (12). Mechanisms being studied attempt to limit tissue destruction by directly blocking proinflammatory pathways without affecting bacterial accumulations, although we are advised to continue to reduce the bacterial burden to the point of a healthy balance. Future therapy may function by modulating the inflammatory response earlier in the process of disease, interrupting the initial cascade of mediators that increase inflammation and bone resorption, or by enhancing the resolution of inflammation (13). The intricate proinflammatory pathways present many places at which potentially therapeutic interventions could occur, by either inactivating effector cells or molecules themselves, or by limiting their activation or production.

A possible new intervention may be the drug Protelos (strontium ranelate, Servier Laboratories) used currently to treat osteoporosis (14). Strontium ranelate has been shown to stimulate osteoblasts to secrete osteoprotegerin (OPG), thus preventing the activation of osteoclasts. Studies also show that it upregulates the differentiation of osteoblasts from stromal cells in bone, preventing bone resorption and enhancing bone deposition. Strontium ranelate is available as a treatment for osteopenia and osteoporosis in Europe, but it has not been approved by the FDA for use in the United States (15, 16).

New research shows that the resolution of inflammation relies not only on the reduction in proinflammatory pathways, but also is an active process mediated by specific resolution pathways (17). Molecules that appear to be important in the resolution of inflammation are lipids made from fatty acids, such as lipoxins and resolvins. These anti-inflammatory lipids are made from omega-3 polyunsaturated fatty acids in addition to those made from omega-6 fatty acids such as arachidonic acid (AA), which is also the precursor of some proinflammatory lipids (12). Lipoxins can encourage the resolution of inflammation by limiting the migration of additional polymorphonuclear leucocytes (PMNs) into the site of inflammation, activating non-inflammatory monocytes and stimulating the removal of dead PMNs by macrophages. For a visual image, go to: A Novel Approach to Resolving Inflammation at: http://www.dentalcare.com/media/es-MX/products/owbh_11.pdf.

Diabetes

Using guidelines established by the American Diabetes Association, a recent study determined that 93% of subjects who had periodontal disease (compared with 63% percent of those without the disease) were considered to be at high risk for diabetes and should be screened for the disease (18). The guidelines recommend that diabetes screening should be carried out in people who are 45 years old or older who have a body mass index of 25 and at least one additional risk factor. In Dr. Strauss's study, additional risk factors such as high blood pressure and a first-degree sibling with diabetes were reported in a significantly greater number of subjects with periodontal disease than in subjects without the disease. Dental hygienists and dentists can screen patients for diabetes by evaluating them for risk factors such as: being overweight; belonging to a high-risk ethnic group (African-American, Latino, Native American, Asian-American, or Pacific Islander); having high cholesterol; having high blood pressure; having a first-degree relative with diabetes; having had gestational diabetes mellitus; or having given birth to a baby weighing more than nine pounds. As well, use of a glucometer in the dental office or clinic to evaluate blood samples is suggested.

Diabetes mellitus accelerates atheromas increasing the risk of a stroke. Compared with the 5 percent atheroma rate reported among healthy people, rates were significantly higher in diabetes mellitus patients. Clinicians treating diabetes mellitus patients may encounter atheromatous lesions on panoramic radiographs and refer them for treatment (19).

Pregnancy

Oral Health During Pregnancy and Early Childhood: Evidence-based guidelines for health professionals are a document that substantiates the relationship between health and oral health status and promote the importance and safety of dental care during pregnancy. In February 2009, an expert panel of medical and dental professionals presented a review of scientific literature and recent research to derive practice guidelines based on evidence and professional consensus. Wherever possible, the material was adapted, supplemented, updated and rewritten based on the 2006 New York State Department of Health publication, *Oral Health Care During Pregnancy and Early Childhood Practice Guidelines*. Best practice suggests that periodontal care should be provided during pregnancy. The expert panel and advisory committee developed the following consensus statement: 'Prevention, diagnosis and treatment of oral diseases, including needed dental radiographs and use of local anaesthesia, is highly beneficial and can be undertaken during pregnancy with no additional foetal or maternal risk when compared to the risk of not providing care. Good oral health and control of oral disease protects a woman's health and quality of life and has the potential to reduce the transmission of pathogenic bacteria from mothers to their children.' The complete guidelines – for medical, dental, early childhood and public health providers – and evidence-based information can be downloaded from CDA Foundation's Web site (20).

Conclusions

Epidemiological data indicate that periodontal disease is an independent risk factor for myocardial infarction, coronary

heart disease, diabetes and other diseases and conditions (21). Evidence supporting a causative role of chronic infection in coronary heart disease and other diseases is mostly circumstantial. The evidence supports the hypothesis that periodontitis leads to systemic exposure to oral bacteria and that a potential source of systemic inflammatory mediators, capable of initiating or worsening conditions associated with atherosclerosis and coronary heart disease, are cytokines and lipopolysaccharide (LPS) produced in the infected periodontal tissues, which enter into the blood stream. Cytokines produce their effects directly, while the LPS activates a systemic cascade of inflammatory cytokines, capable of inducing effects associated with atherosclerosis and coronary heart disease. The continued systemic exposure to Gram negative bacteria and LPS results in a release of cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and prostaglandin E2 (PGE2), which may be a significant factor in the pathogenesis of coronary heart disease and stroke.

The suggestion that periodontal disease is a significant risk factor for coronary and other systemic diseases begs a new outlook on oral health and should prompt us to view this as we do other areas of preventive medicine. It is likely that in the future, periodontal disease may be added to the list of factors that are used to assess patients' risk profiles for coronary heart disease, stroke, diabetes and other diseases. In addition, treatment of periodontal disease should become a standard part of the therapy for patients with the above diseases.

The American Academy of Periodontology (AAP) hosted a workshop in January 2008 in Boston titled, 'Inflammation and Periodontal Diseases: A Reappraisal.' The workshop brought together over eighty leading experts in the fields of dentistry, clinical medicine and basic science. Workshop proceedings were published in a special supplement in the August issue of the Journal of Periodontology (22).

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Maria Perno Goldie
President Elect IFDH
Seminars for Women's Health
E-mail: mgoldie@sbcglobal.net