

BRUSH YOUR TEETH—IT COULD SAVE YOUR LIFE!

A healthy human mouth harbours small amounts of dental plaque on the teeth and gums. The bacteria of that plaque do not cause disease and can, in fact, be beneficial—due to their unique relationship with the host, by which they can stimulate and help develop the immune system and help keep pathogens from colonising tooth surfaces. But if dental plaque is left to accumulate, then under certain conditions it can become anaerobic and start to change in composition, allowing opportunistic pathogens to emerge that cause an imbalance with the host (dysbiosis). This results in early periodontal disease (gingivitis). In susceptible people, this chronic inflammation of the gingival tissue and dysbiosis can cause the dental plaque to change further, allowing highly pathogenic species to emerge at the base of a periodontal pocket, which can result in an infection (a collapse in species diversity, with a substantial increase in certain pathogenic species). This can lead to the destruction of the tooth-supporting tissue, including the alveolar bone, and weaken the attachment of the tooth. Called moderate to severe periodontitis, this can lead to tooth loss when the immune system attempts to eliminate the infection.

Periodontal diseases are extremely common. One in three adults, and more than one in two Australians over the age of 65, have moderate to severe periodontitis. Epidemiological surveys have linked periodontitis to an increased risk of cardiovascular diseases, certain cancers, pre-term birth, rheumatoid arthritis, and dementia—all related to the regular bacteremia and chronic inflammation associated with the disease. The global prevalence of severe periodontitis has been estimated from 2010 epidemiological data at between 10.5 and 12.0 per cent, while the global economic burden of dental diseases, of which periodontitis is a major component, has been estimated at US\$442 billion per year.

The conventional therapy for periodontitis involves scaling and root-planing to remove dental plaque micro-organisms. Treatment can sometimes involve surgery to improve access or reduce pocket depth, and can also include use of antibiotics or antimicrobials. However, the results are variable and heavily dependent on patient compliance. Even in patients on a periodontal maintenance program involving regular professional intervention, periodontal attachment loss continues to progress at some sites, and teeth are lost.

Although periodontitis is associated with a polymicrobial biofilm in the form of dental plaque (subgingival plaque), specific bacterial species of the biofilm, such as *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* as a complex or consortium have been closely associated with severe disease, and are now considered periodontal pathogens. In a recent prospective clinical trial of patients with moderate to severe periodontitis on a

clinical maintenance program, a high level of *P. gingivalis* in subgingival plaque predicted imminent clinical attachment loss (more than 2 millimetres of loss in three months). These results are consistent with previous studies showing high levels of *P. gingivalis* at unresponsive sites, that is, periodontal sites where disease continued to progress after conventional scaling and root-planing therapy.

P. gingivalis is found at the base of deep, infected periodontal pockets as micro-colony blooms in the superficial layers of subgingival plaque next to the periodontal pocket epithelium, which helps explain the strong association with underlying tissue inflammation and bone resorption at relatively low proportions (10–15 per cent) of the total bacterial cell load in the pocket. Furthermore, mouse studies have shown that *P. gingivalis* is a keystone pathogen, which dysregulates the host immune response to favour the polymicrobial biofilm disrupting homeostasis with the host to cause dysbiosis (imbalance between the host and the bacterial community) and disease progression. The mouse periodontitis model has also been used to show that inflammation is essential to allow establishment of *P. gingivalis* at the levels in plaque (10–15 per cent or greater of total bacterial cell load) necessary to produce dysbiosis and alveolar bone resorption, which makes the mouse a good model for human disease.

The extracellular toxins or proteinases of *P. gingivalis* (called ‘gingipains’) are major virulence factors that are critical for colonisation, invasion of host tissue, dysregulation of the immune response, dysbiosis and disease. The gingipains are essential for *P. gingivalis* to induce alveolar bone resorption in the mouse model. The gingipains have also been found in human gingival tissue at sites of severe periodontitis: at high concentrations next to the subgingival dental plaque, and at lower concentrations at sites deeper into the gingival tissue. This helps explain the role played by *P. gingivalis* in the progression of severe periodontitis. In response, targeting the major virulence factors of the bacterium (the gingipains) by vaccination may help prevent *P. gingivalis*-induced periodontitis. Indeed, studies using the gingipains as a prophylactic vaccine before infection with *P. gingivalis* have shown protection against periodontal bone resorption. Recently it has been shown at the Melbourne Dental School that therapeutic vaccination with a specifically designed recombinant vaccine (called a chimera) targeting the *P. gingivalis* gingipains protects against periodontal bone resorption in those mice where *P. gingivalis* has already established an infection. This protection was mediated by resolution of inflammation and by the production of protective (gingipain-neutralising) antibodies that block the invasion

of *P. gingivalis* into the tissue and bloodstream. This is the first evidence of a specific *P. gingivalis*-associated therapy stopping disease progression and invasion of the pathogen.

The invasion of the host by *P. gingivalis* has been linked with an increased risk of developing Alzheimer's disease, rheumatoid arthritis and other diseases. Recently it was shown that *P. gingivalis* gingipains are present in 96 per cent of human brains affected by Alzheimer's disease, and that chronic oral infection of animals with *P. gingivalis* resulted in gingipains in the animals' brains, which induced the symptoms of dementia. Furthermore, *P. gingivalis* releases another specific enzyme related to the gingipains that can change the structure of (citrullinate) host proteins so that the host then makes antibodies against the citrullinated proteins. Antibodies to these citrullinated proteins have been closely linked with the development of rheumatoid arthritis. Hence the evidence is building for a role for *P. gingivalis* as a major human pathogen associated with chronic infection, inflammation and a number of diseases, including periodontitis. As periodontitis is preventable by good oral hygiene (tooth brushing and subgingival flossing), these recent results suggest that cleaning your teeth effectively and preventing the development of periodontitis may also help prevent the onset of life-threatening systemic diseases—hence brushing your teeth could indeed save your life!

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