Review Article

Periodontitis: a Risk Factor for "Lifestyle" Diseases

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Abstract

Periodontitis is an inflammatory disease induced by bacterial insult and host immune response. Epidemiological and clinical studies over the past decade have suggested its association with development of atherogenesis, which may lead to cardiovascular disease and its complications. Lifestyle diseases are non-communicable chronic diseases of longevity that are increasing in frequency as countries become more industrialized and people live longer. The lifestyle diseases, including for example atherosclerosis, cardiovascular diseases, stroke, type 2 diabetes mellitus, obesity and osteoporosis, are at present increasing at an alarming rate worldwide, and are related largely to diet and the way a person lives. The long office hour and the type of activities we encounter daily in our office make us in the dental professions are at risk for developing lifestyle diseases. Healthy lifestyle factors include good nutrition, regular exercise, non-smoking and body mass index of less than 25 kg/m^2, etc. Because the oral cavity is generally considered the window of systemic health and disease, the lifestyle behaviors that promote oral health also decrease risks for developing lifestyle diseases. Both periodontitis and all of the lifestyle diseases mentioned above are associated with chronic low-grade inflammation. When bacteria in the oral cavity are dysregulated, periodontal diseases will develop, particularly obvious in those suffering systemic diseases like diabetes and other metabolic disorders. Different lines of evidence point to a causal link between periodontitis and some lifestyle diseases. Current proposal regarding the microbial agent for periodontitis is based not on a single species of bacteria like *Porphyromonas gingivalis*, but on alteration of microbial community at the diseased sites. With this new proposal, periodontitis is therefore considered to be a polymicrobial origin resulting from imbalanced oral microbiota. When microbes in this unhealthy oral microbiota (known as dysbiosis) are dislodged, aspirated or swallowed, they can disturb the balance of microbiota and homeostasis at distant extra-oral sites and can influence systemic health status. Therefore, by carefully controlling the microbial balance, for example, with probiotics by health professionals, may help alleviating both oral and systemic diseases and restoring homeostatic balance of the host. Research to advance the knowledge regarding molecular pathogenesis of periodontitis and "lifestyle" diseases should provide us with ways and means to develop new approaches in patient management or identify new drug targets that will improve the quality of life of our patients.

Key words: Dental profession; Inflammation; Lifestyle disease; Metabolic syndrome; Periodontitis.

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During the last few decades, the global prevalence of diseases has shifted from communicable diseases to non-communicable diseases (NCD) and this is particularly true for people living in developing countries.[1] This is not entirely unexpected as during this period, there is a considerable improvement in public health status in all third-world countries, including nutrition, sanitation, antibiotics and vaccines which are the prime moving force in reducing the occurrence and severity of infectious diseases. This has significantly improved the fatality rate of infectious diseases in these countries, particularly in newborns and young children. World Health Organization reports the NCDs to be the leading cause of death in the world in 2008, representing over 60 % of all deaths.[1] The NCDs include, for example, breast and colorectal cancers, osteoporosis, Alzheimer's disease (AD), and a group of diseases commonly referred to as "lifestyle" diseases which encompasses the various metabolic disorders: cardiovascular diseases (CVD), stroke, atherosclerosis, obesity, insulin resistance and type 2 diabetes mellitus (T2DM). In some developed countries, as much as one-third and two-third of the population are respectively obese and overweight. A rapid increase in the incidence and prevalence of these "lifestyle" diseases creates a serious medical and public health problem in the countries in transition to become developed countries.[1] For instance, India is now probably the country with the highest increasing rate of obesity, T2DM and CVD.[2] Although the figure for obesity in Thailand is still much lower than India, the NCDs account for more than 70 % of total deaths.[3] In addition to these NCDs, there is a rapid increase of allergic diseases like asthma but this is not surprising or unexpected, as now there is an increase in air pollution in a large number of developing countries and Thailand is no exception to this pollution problem. In recent years, there is also a rapid increase of mental disorders like depression and schizophrenia as people tend to live in isolation.[4] These stress-related illnesses including loneliness can readily activate the stress-center in the brain and induce a "fight or flight" response. The latter, known to be a risk factor for CVD, is associated with increase circulating levels of proinflammatory cytokines and other mediators. In this review, I will discuss the pathogenesis of "lifestyle" diseases and point out how it might be related to periodontitis and have impact on our profession and *vice versa*.

Different people define "lifestyle" diseases differently, but it is generally referred to as preventable diseases that appear to increase in frequency as countries become more industrialized and people live longer. These diseases progress slowly and are potentially preventable by changes in diet, environment and other lifestyle behaviors.[5] The latter includes smoking, heavy alcohol consumption, sedentary living and lack of exercise. It will become more obvious later that these factors almost always pave way to obesity which often precede the development of other more severe metabolic diseases.[6,7] Worldwide increased popularity of "Western" diet leads to the occurrence of "obesity" epidemic among the present young generation.[7] In fact, obesity and overweight are increasing very rapidly in developing countries like India and several ASEAN countries, particularly in Thailand, Malaysia and Indonesia.[3] The present generation also relies on electronic communication as their primary source of contact and tends to have solitary lives and lives in isolation. This lifestyle behavior can affect their mental health, bringing the magnitude of loneliness for example to approaching an epidemic level. Moreover, a rapid advance and progress in information technology and availability of a variety of social media networking have without doubt created another epidemic, which I would like to refer to as "social media" epidemic. All of these behaviors are associated with sedentary life, which eventually leads to development of lifestyle diseases.

Lifestyle diseases are sometimes referred to as diseases of longevity as the diseases occur largely in ageing populations.[1,3] One of the most important epidemiological changes noted in the 20th century is the increase in the mean age of a population in all continents. World Health Organization recently reported

that the proportion of people aged 60 or over is growing faster than any other age groups, particularly in Asia, and it is in this ageing population that there is a parallel increase in the prevalence of periodontitis and lifestyle diseases, mostly notable for CVD and T2DM.[1,3] Therefore, how to obtain healthy ageing is a great challenge for populations and health authorities throughout the world.[1] Ageing is generally characterized by a progressive, time-dependent loss of functions, resulting from accumulation of damage to all the cell macromolecules (e.g., DNA and membrane phospholipids).[8] These molecular damages are caused for example by inflammation, metabolic stress, oxidative stress and redox change. There are many different parameters that can be used to determine the ageing process, but the common ones are telomere attrition and mitochondrial dysfunction.[8] There is increasing evidence showing associations of mitochondrial dysfunction and telomere shortening with chronic inflammatory diseases like obesity, diabetes, atherosclerosis and rheumatoid arthritis.[8,9] In fact, telomere length and telomerase activity are said to be good predictors for cellular ageing and lifespan of an individual.[8-10] It was shown recently that, compared to control, individuals with chronic periodontitis, but not in those with aggressive periodontitis, have shorter telomere length.[11] There is increase evidence suggesting that healthy lifestyle behaviors as moderate level of exercise and healthy diet can slow down ageing process, or even increasing the health span of an individual.[7,9,10] It was shown recently that greater adherence to healthy foods like the Mediterranean diet is associated with longer telomeres, thus supporting the benefits of healthy diet in promoting health and longevity.[12] Overwhelming evidence from several recent studies also suggests that healthy lifestyle phenotype depends not only on what you eat, but also on what you do and what you host (Figure 1).[13-17] Over the last decade, there is a relatively large amount of funding allocated for research in lifestyle diseases and, as a result of this increase in financial support, a considerable progress and advance have emerged from research on “lifestyle disease”, as evidenced from a large annual increase in the number of research publications during the last decade (Figure 2). It is quite obvious from the figure that the increase in the number of publications in lifestyle diseases is far greater than those for common oral diseases shown for comparison. During the last 30 years, the number of publications on lifestyle diseases increases more than 10 times, from 249 in 1985 to more than 3,000 in 2014. During the same period, the publications of popular research topics in oral diseases like dental caries and periodontitis showed respectively much lower increase, only 2 and 4 times respectively. It should be noted that although the number of publications in oral cancer in the year 2014 was over 5,000, the proportion of the annual increase was still considerably lower than that in the “lifestyle” disease.

It is generally agreed that individuals who follow healthy lifestyle practice are less likely to develop chronic diseases. A preliminary conclusion from a recent large-scale epidemiological study showed a favorable outcome of lifestyle intervention in reducing the prevalence of these diseases. In this joint research project between CDC and the German Institute of Human Nutrition, more than 20,000 adults participated and they were followed up for almost 8 years.[5] Data obtained by comparing the baseline values at the beginning of the study with those at the end of the study 8 years later clearly suggested that by following just 4 healthy lifestyle factors: non-smoking, healthy diet, moderate physical activity and body mass index (BMI) less than 30, there was 78 percent less likely to develop chronic diseases such as, CVD, type 2 DM, cancer and stroke. Although in this study, dental assessment was not made, the findings should still be considered highly appropriated for oral health researchers and professionals, as 3 of the 4 unhealthy behaviors under consideration, i.e., smoking, poor dietary habits and excess body weight, also correlate with poor oral health. It can be concluded from this study that practicing healthy lifestyle behavior is associated with noticeable reductions in chronic disease

risk, suggesting that adopting a few healthy lifestyle factors can have a major impact on the risk of morbidity and mortality of the population. It can be extrapolated from the data that oral health professionals cannot only help optimizing oral health, but can also help improving systemic health by educating their patients on the significance of these factors and can suggest to them appropriate intervention strategies or can consult medical specialty for additional methods to improve health index.

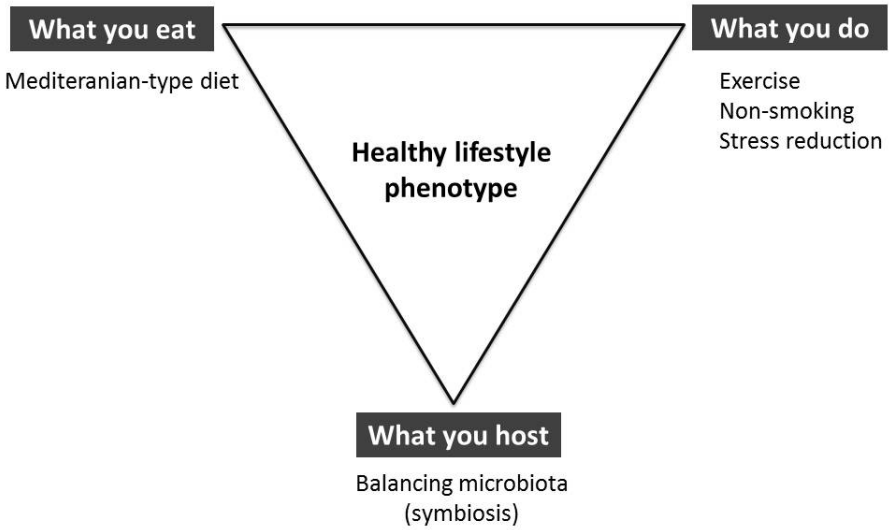

Figure 1 *Healthy lifestyle phenotype. Human health status is influenced by diet, lifestyle behaviors and microbiota. Mediteranian-type diet generally consists of fish-based, olive oil, low fat and carbohydrate, high-fiber diet, together with nuts, fruits and vegetables. Healthy lifestyle behaviors include regular exercise, non-smoking, and minimal stress. Balanced microbiota in intestine is predominantly made up of bacteria in the phylum Firmicutes and Bacteroidetes.*

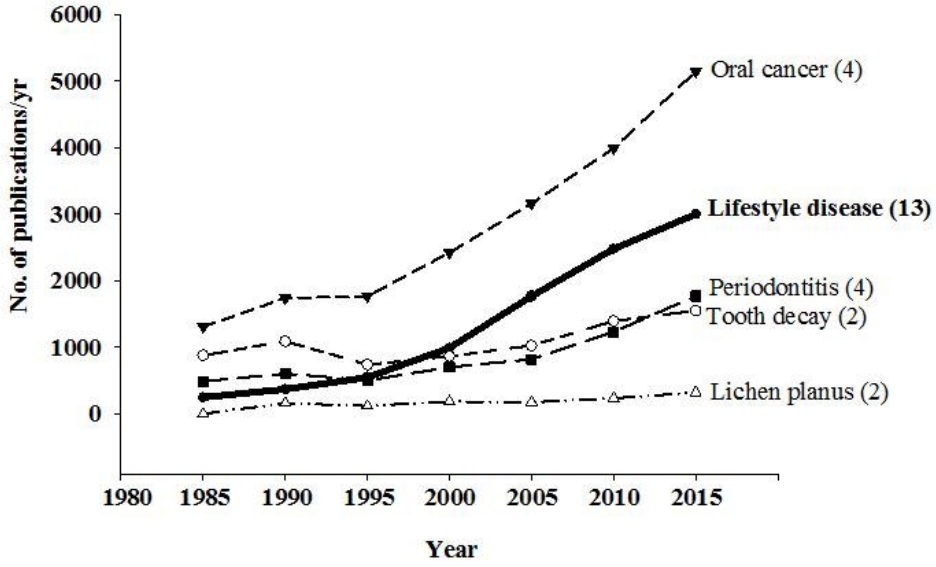

Figure 2 *Comparison of the number of publications on "lifestyle" diseases with oral diseases. Searching was performed using MEDLINE databases from 1985 to 2014 for the terms lifestyle disease, periodontitis, tooth decay, lichen planus and oral cancer. The number in parenthesis indicated the fold increased in publication number.*

Pathogenesis of lifestyle diseases

It is now well established that "lifestyle" diseases are associated with chronic low-grade inflammation (Figure 3). Modern lifestyle behaviors of the present generation including, for example, consuming unhealthy high-fat diet, sedentary habits, smoking with or without high alcohol consumption and overweighting with BMI of over 30, are detrimental to our health. These factors and activities often lead to altered immune reactivity, resulting in low-grade inflammation which after several years becomes chronic and may end up with diseases commonly referred to as "lifestyle" diseases. The latter encompasses several diseases other than those associated with metabolic disorders, and the oral diseases like periodontitis, which is being considered a risk factor for CVD in this review, also possess characteristics that are compatible with being classified a lifestyle disease.

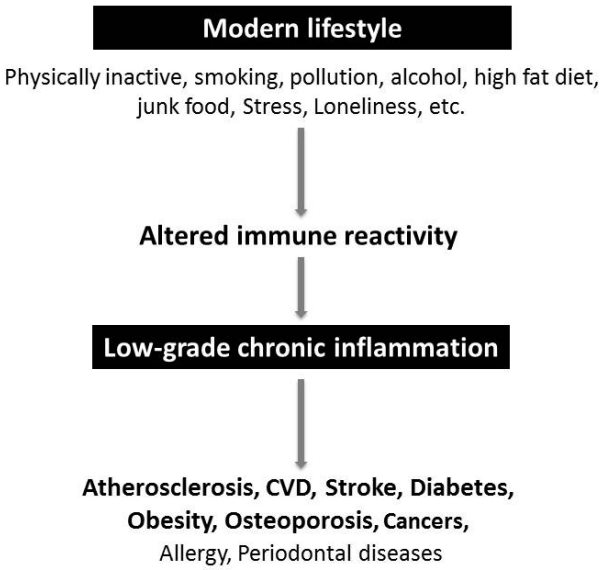

Figure 3 *Linking of unhealthy lifestyle behaviors of "Modern lifestyle" to lifestyle diseases via low-grade chronic inflammation. It should be noted that although currently both allergy and periodontal diseases are not yet classified in this group, they have some characteristics that are compatible with being a "lifestyle" disease.*

Our health status can be influenced by a number of factors, many of which can readily disturb homeostatic balance of the host (Figure 4). All of us are familiar with the impact of microbial infections which tip the balance toward disease status, but this is opposed by our immune response which tend to bring back the balance to restore homeostasis.[18] Host immune system possesses several recognition and signaling receptors to distinguish between homeostasis and threats (Figure 5) and, following activation, respond appropriately, e.g., inflammation and/or production of antimicrobial polypeptides.[18] Microbes possess a large number of molecular structures known as Pathogen-Associated Molecular Patterns (PAMPs) and antigenic (functional) molecules that respectively stimulate innate and adaptive immunity. The former recognizes Pattern Recognition Receptors (PRRs) present on or inside innate host cells and activate these cells to mount appropriate responses including production of inflammatory cytokines and other bioactive mediators, phagocytosis and intracellular killing of microbes. The latter, i.e., the antigenic molecules, activates and induces differentiation of T and B lymphocytes

of the adaptive system. These effect or cells and the mediators released, in addition to providing specific protective immunity, facilitate restoration of tissue damage to reestablish health and homeostasis. In addition to these exogenous stimuli, host-derived (endogenous) signals can be generated and released from tissue damages following microbial or non-microbial insults (e.g., physicochemical injuries, ageing and apoptotic cells). These endogenous altered "self" molecules, now referred to as Danger/Damage-Associated Molecular Pattern, (DAMPs), can also signal the immune cells via the same PRRs used by the microbes or via other signaling and scavenging receptors (e.g., RAGE, receptor for Advanced Glycation End-products; oxLDL receptor, receptor for Oxidized Low Density Lipoprotein). In addition to these physicochemical and biological insults, other form of stimuli like stress and mental disorders like depression and loneliness or even unfavorable perceptions can stimulate these host cell receptors resulting in low-grade chronic inflammation.[4,17-20] In addition to these membrane-associated receptors (Figure 5), there exist another important group of cytosolic receptors that can recognize a diverse set of inflammatory-inducing stimuli, not only from exogenous microbes and endogenous molecules, but also from environment stress (including, for example, nutritional stress from cholesterol and uric acid crystals, fatty acids, and asbestos particles). These receptors, known as inflammasomes, consist of a complex protein platform that are currently a center of biomedical research which will eventually provide significant insights into the pathogenesis of not only these lifestyle diseases, but also of several others diseases including inflammatory bowel diseases and autoimmune diseases.[18,21-23] The inflammasomes when activated initiate the synthesis of active proteases like caspases which are required for the final step in the synthesis of inflammatory mediators, e.g., IL-1 and IL-18. These mediators activate macrophages and other immune cells to produce more inflammatory mediators and induce surface alterations that facilitate atheroma formation. The plaque produced initiates a chain of reaction ending up with metabolic disorders and diseases if not properly managed. Understanding molecular pathogenesis of diseases is a way to improve or optimize current treatment of these systemic diseases. Moreover, it may not be too far-fetched to have available effective vaccines for dental caries or periodontal diseases in the near future, provided one has a better understanding in vaccine design and ways and means to identify and enhance its immunogenicity, e.g., improving activation of inflammasome NLRP3 with more effective adjuvants.

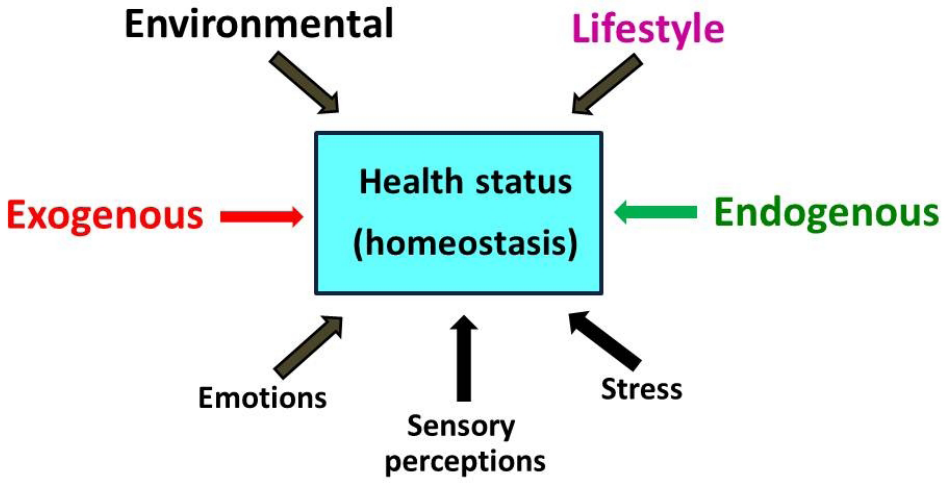

Figure 4 *Regulation of immune homeostasis. Host is constantly exposed to different insults, from exogenous microbes to endogenous damaging/altered "self" molecules to environmental stress and psychosocial insults. Following stimulation, host needs to counteract to restore the homeostatic balance.*

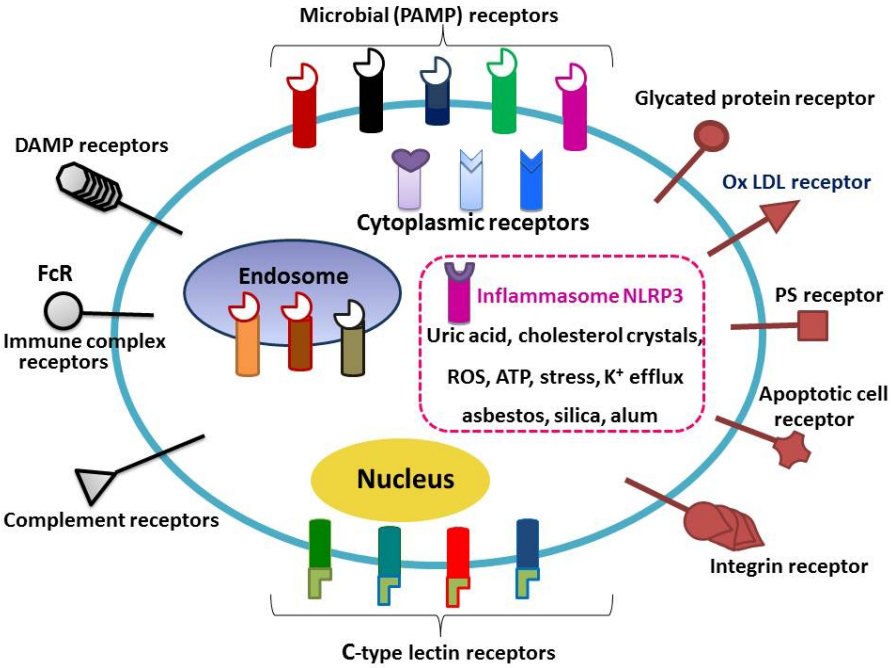

Figure 5 *Recognition and signaling receptors. There is a large number of cellular receptors that the host uses to respond and counteract the different insults, e.g., PAMPs, DAMPs and environmental stress. An example of cytosolic receptor inflammasome NLRP3 and some of its activators are shown inside the dash red rectangular box. (modified from reference 18).*

Ameliorating the progress of lifestyle diseases with lifestyle interventions

Epidemiological data mentioned earlier suggested that modulation of lifestyle behaviors can have favorable outcome in people with these diseases.[5] This preliminary observation has now been confirmed by Ornish and associates who used molecular approaches to study the effects of lifestyle changes in men with biopsy-proven low risk prostate cancer.[24,25] The studies were carried out to last for 5 years; the experimental group was asked to undertake the following lifestyle intervention measures consisting of taking high fiber, plant-based protein with low fat and refined carbohydrate diet, regular moderate aerobic exercise, appropriate stress management and social support. Leukocyte telomere length and telomerase activity, the two parameters commonly used to represent hallmarks of ageing process, in the pre- and post-intervention specimens from the experimental and control groups showed changes consistent with their prediction. The data showed a noticeable increase in both the telomere length and telomerase activity in the group undertaking this combined lifestyle intervention. Their results are in line with those of other groups showing shortening of telomere length in patients with chronic inflammatory diseases and in ageing individuals.[9,10] In summary, unhealthy lifestyle factors including smoking, consumption of processed meat, sedentary life and high BMI correlate with short telomere length and poor telomerase activity known to be associated with accelerating cellular ageing. Obese people on the other hand are known to have shorter telomeres. In consistent with expectation, healthy lifestyle factors like meditation[26] and exercise[27,28] have been reported to enhance telomerase activity and promote telomere lengthening.

Much is known about the beneficial effect of healthy diet like “Mediterranean-type” food, now said to be associated with good health and longer lifespan.[12] Unhealthy foods, e.g., high contents of saturated fat, oxidized low density lipoprotein (oxLDL) and cholesterol can directly impact health status by interacting with

appropriate receptors that signal inflammatory response (Figure 5). For example, cholesterol crystals are known to activate the inflammasome NLRP3 in immune cells and signal the production of proinflammatory cytokines IL-1 and IL-18.[6,29,30] High fat diet e.g., fatty acids, ceramides, modified LDL, and glucose, can also activate the NLRP3 inflammasome and other intracellular receptors that together tip immunological balance in favor of low-grade inflammatory response known to be associated with a number of metabolic disorders.

Epidemiological observations in those who participate in regular physical activity suggest a longer lifespan than in those with sedentary lifestyles. Although it is often said that exercise induces strong resistance against infections and is associated with good health, exact molecular mechanism(s) remains to be defined.[27,28] Exercise is known to be a strong modifier of immune response and can reverse immunosenescence in ageing populations, particularly more obvious with the adaptive arm of the immune system.[28] There are data suggesting an increase of antiinflammatory cytokines which can revert inflammatory status of an individual. This is consistent with the notion that the number of anti-inflammatory genes is linked to longer lives. On the other hand, exercise can have indirect effect through neuroendocrine axis. It is known to reduce the risk of depression and development of dementia and possibly also of the Alzheimer's disease as well. It has been suggested that exercise can also strengthen our health by mitigating cytomegalovirus infection, which is not uncommonly associated with immunosenescence. On the contrary, excessive degree of exercise may be detrimental and has opposite outcome, particularly in those with respiratory tract problems. In addition to the diet and exercise that are commonly used as behavioral interventions to alleviate lifestyle diseases, other practices known to give favorable outcome include meditation and stress reduction, refraining from smoking or excessive alcohol consumption.

Your health is influenced also by what you host

Although it is well established for decades that healthy diet and lifestyle behaviors can favorably promote healthy status, more recent data provide evidence that your health does not depend only on what you eat or what you do, but also on what you host (Figure 1).[13] On the body surfaces, particularly the gastrointestinal tract, there are trillions of friendly bacteria (commensals) which can readily promote good health via a number of mechanisms. This normal flora is now referred to as "**Microbiota**" (Figure 1). These friendly bacteria facilitate proper development of systemic and mucosal immune system and inhibit colonization of pathogens.[14-16,31,32] They also metabolize some dietary components to metabolites like short-chain fatty acids (SCFAs) and aryl hydrocarbon ligands that are beneficial to the host, e.g., promoting microenvironment that facilitates the development of immune system necessary to maintain tolerance and protect mucosal surface. Under steady state, the interaction of these bacteria with their host provides healthy environment that is referred to as "symbiosis". The beneficial outcome of this interaction depends on the number, diversity and composition of gut flora that is unique for an individual (Figure 6). However, the composition of microbiota can be influenced not only by the host immune phenotype, but also by the types of diet the host consumes, including healthy foods and supplements like probiotics and prebiotics. Changing the profile or elimination of normal flora, by, for example, taking broad-spectrum antibiotics and some noncaloric artificial sweeteners (NCSs) may interfere with the balance, resulting in a condition known as "dysbiosis".[16,33,34] Some of the NCSs are known to induce glucose intolerance in mice and in certain human subsets by indirectly acting through changing the host microbiota.[32,33] On the other hand, it has been demonstrated recently that, depending on the type of diet, gut microbiota from some individuals contain microbes that can effectively metabolize phosphotidylcholine and L-carnitine present in, for example red meat and egg

yolk, to a form that promote atherosclerosis and serve as cardiovascular risk for humans and experimental animals.[35-37] The existence of unhealthy microbiota environment for prolonged period can influence homeostasis at distant sites and may favor a development of inflammatory diseases and metabolic disorders which may eventually lead to metabolic diseases and lifestyle diseases like obesity, CVD and stroke.[35-37] Reestablishing homeostatic balance can be accomplished by taking probiotics and changing food habits. In the worst scenario when the balance is not restored, the intestine may now be colonized by a species of deadly bacteria known as *Clostridium difficile* and the disease can be fatal if not eliminated. If the conventional management to reestablishing homeostasis does not work, more drastic treatment must be taken. A new and exciting therapeutic approach, at least to me, is to reestablish a balance by a technique now known as "fecal microbiota transplantation" and it has been reported to give a complete cure in a large number of patients who resist to other methods of treatment.[31]

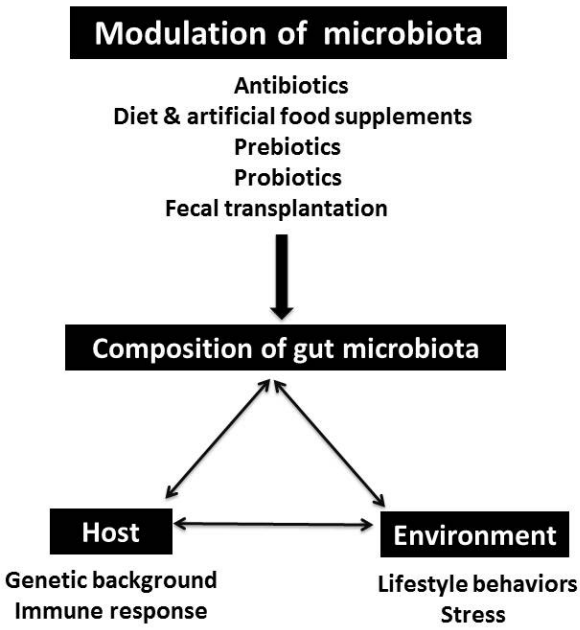

Figure 6 *Regulation of gut microbiota. Composition, diversity and density of microbiota in the gastrointestinal tract are important in maintaining health and disease of an individual. Manipulation of microbiota is a novel and exciting new approach to maintain tolerance and restoring homeostasis.*

Manipulation of microbiota to alleviate inflammatory and autoimmune diseases is a new approach of treatment that has received considerable attention in recent years. Manipulation of microbes genetically to benefit human population is an exciting new field of medical research now referred to as "**Microbial engineering**". Because of its therapeutic potential not only in the treatment of lifestyle and inflammatory diseases, but also in disease like cancers, a considerably large amount of funding is now available for research on microbiota and microbiota engineering. Within the last few years, the number of publications on microbiota has climbed logarithmically comparing with those in other areas (Figure 7). It is of special interest to note that, during this same period, there is a parallel increase of the publications on lifestyle diseases and metabolic syndrome, suggesting close interrelationship between these disciplines. This association is not surprising or unexpected, as different lines evidence from epidemiological, clinical and experimental animal studies all agree that appropriate manipulation of microbiota can definitely improve health status of the host.

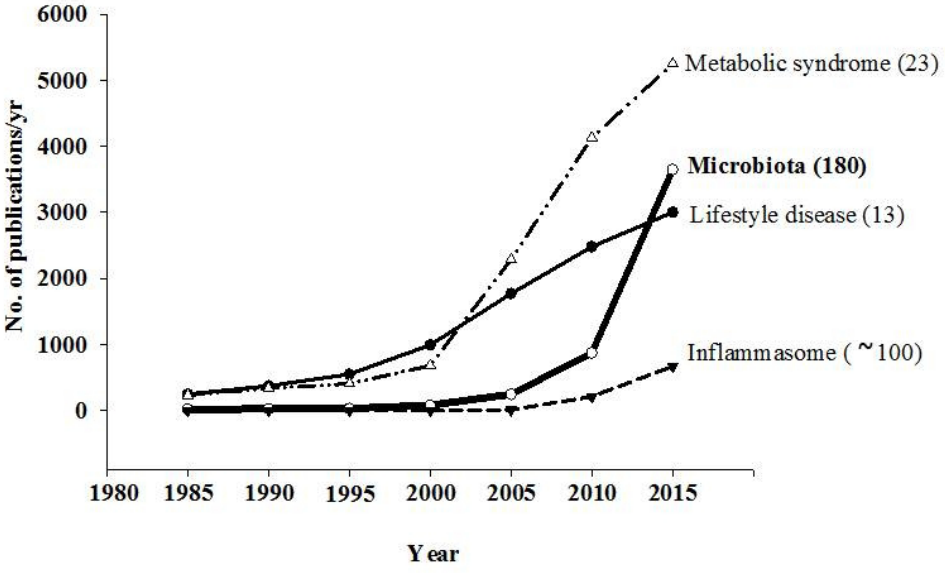

Figure 7 *Rapid progress of research on microbiota and microbiota engineering. The number of publications on microbiota is increasing logarithmically during the last 5 years. The research on metabolic syndrome and lifestyle diseases during the same period shows similar profiles, suggesting their close interrelationship with the microbiota research. The data (from 1985 to 2014) were performed using MEDLINE databases for the terms microbiota, metabolic syndrome, lifestyle disease and inflammasomes (showing for comparison purpose only).*

Periodontitis: a unique oral disease with impact on lifestyle diseases

To maintain healthy state, the periodontium requires a well-regulated immunehomeostatic microenvironment---balanced interaction between host immune responses and oral microbiota.[38-41] It was once believed that periodontitis starts when there is an increase in the frequency of the main causative agent *Porphyromonas gingivalis* at the diseased sites. This species, together with the other two anaerobic bacteria in the so-called "red complex", *Treponema denticola* and *Tannerella forsythia,* induce changes that finally end up with inflammatory destruction of periodontium. Moreover, the "self" molecules released from damaged cell and diseased tissue (DAMPs) can act as danger signals that further aggravate inflammatory destructive process.[18,21,23] However, with the more recent data, an alternative model for the pathogenesis of periodontal disease has been proposed (Figure 8).[38,39-41] In this proposal, the disease is said not to be the results from the action of any one species of bacteria, but is from the alteration of microbial community from healthy symbiotic microbiota to unhealthy and unbalanced dysbiotic microbiota. In other words, the disease periodontitis is now believed to be the result of a more complicated polymicrobial infection. When the balanced microbiota in healthy periodontal tissue is perturbed by danger stimuli, there is a shift in the composition of local microbiota to a destructive microbial community.[38-41] However, other factors can also influence the balance, and these include, for example, genetic predisposition and environmental modifiers, e.g., dietary habit, smoking, alcohol consumption, stress and lifestyle behaviors. If allowed to persist, the pathological damage will become chronic, as these microbes possess a number of tissue-destructive virulent factors that can subvert host defense and tip the balance infavor of survival and proliferation of unfriendly microbes in the inflammatory niche. Moreover, the pathogens and opportunistic microbes in the dysbiotic community in the diseased periodontium

can be dislodged, swallowed or aspirated and induce alteration of microbiota at extra-oral sites and induce inflammation and pathology at distant locations. Therefore, when the periodontium is chronically exposed to potentially pathogenic microbes in the dysbiotic community, it can exert adverse effects on general systemic health.

Overwhelming data from epidemiological, clinical and experimental animal studies over the last two decades have suggested a causal link between oral and systemic diseases, particularly between periodontitis and heart disease.[42] Although the initial observations were limited to only between periodontitis and heart disease, current studies have expanded such a relationship to include other systemic diseases, particularly with those now referred to as metabolic syndrome which encompasses the lifestyle diseases in the present review.[38] Both the periodontitis and all of these systemic diseases have at least one factor in common, i.e., the presence of low-grade chronic inflammation (Figures 3 and 8).There are several plausible mechanisms that can explain the causal link between periodontitis and these systemic lifestyle diseases (Figure 8). The two most logical explanations are translocation of periodontitis-associated bacteria into systemic circulation resulting in bacteremia or toxemia that can stimulate and activate distant tissues like heart, lungs, placenta and joints. In fact, it has been shown that *P.gingivalis* can invade aortic endothelial cells.[38] Another mechanism commonly mentioned in a number of studies is the entering of the inflammatory mediators produced locally in the periodontium into systemic circulation. Those that have been implicated are tumor necrosis factor (TNF), interleukin-1 (IL-1) and IL-6. These mediators can induce an acute phase response in the liver and other organs and promote pathology at distant sites. Some of these include atherogenesis in coronary and aortic vessels, death of ß-cells in pancreas, insulin resistance, pregnancy complications and inflammation-induced joint pathology. In addition to these mechanisms, there is recent evidence suggesting that periodontitis-associated bacteria, particularly *P. gingivalis,* can alter the composition of microbiota at distant sites.[38] There is a large body of information suggesting further that alteration in the composition of the gut microbiota can alter health status of its host in favor of obesity phenotype which facilitates initiation of systemic inflammation and metabolic syndrome. There is also a report indicating that, in the presence of *Pseudomonas aeruginosa, P. gingivalis* when aspirated by the patients, can inhibit epithelial cell apoptosis in the lung resulting in chronic obstructive pulmonary disease (COPD). The periodontitis-associated microbes are also a ble to cross placenta and initiate a microbial community in fetal tissues which subsequently leads to inflammation and pregnancy complications. Inflammatory mediators that enter systemic circulation and together with some autoantibody produced by the periodontal patients can also cross the placenta into fetal circulation and put more strain on the patient (Figure 8). Clinical observations from interventional studies by several groups of investigators clearly demonstrated that treatment of periodontal diseases can reduce systemic inflammation, judging from decrease of biomarkers like inflammatory cytokines and C-reactive proteins and improve of overall health index.[38-42] This is consistent with the limited data in humans showing some improvement of periodontal health with decreasing progression of carotid atherosclerosis and its complications.[38]

It is clearly shown from the above discussion that chronic periodontitis can have impact on the progression of lifestyle diseases and *vice versa*. Both *P. gingivalis* and other periodontitis-associated microbes, together with inflammatory mediators produced in the diseased oral tissues, can spread systemically, affecting endothelial cells in the heart, immune and secretory cells in pancreas or placenta and fetus. Periodontists recognized years ago the fact that periodontal diseases are more severe and more difficult to manage in patients with uncontrolled diabetes and *vice versa.* Clinical interventions of either one can have beneficial effect on the other. Early detection of lifestyle diseases by

oral health professionals can also help alleviation and treatment of the lifestyle diseases, and, similarly, early detection and control the lifestyle diseases by physicians can reduce complications and enhance the success the treatment of periodontal disease. We in the dental profession should be aware that hypertension for example is an important risk factor for developing lifestyle diseases, therefore, it would be best for the patients if we can recognize it at its earliest stage. Drugs given for hypertension by physicians can cause xerostomia, gingival hyperplasia and some lichenoid reactions which may complicate our treatment planning. Because both periodontitis and diseases in the lifestyle group have at least one common factor i.e., inflammation, it should be theoretically possible to design potential new approaches or drugs that can be beneficial for both diseases. Blockade of inflammasome activation, new inhibitors of inflammatory cytokines or caspase enzymes should be worthwhile research problems. In fact, some of these ideas have been put into testing clinically in small scale studies. However, the results have been inconsistent and varied from one study to another. However, this should not come as a surprise as, to begin with, inflammation itself is a complex phenomenon that is needed to be carefully dissected first.[43] Periodontitis is also a complex oral disease now considered to have a polymicrobial origin and its impact on the host depends on genetic predisposition as well as on a number of environmental modifiers like smoking and stress.[38,42] One should not be discouraging with the negative or inconsistent results that have emerged. Instead, researchers from various disciplines should work together in harmony to provide further insights into molecular link between oral disease like periodontitis and the increased incidence of lifestyle diseases.

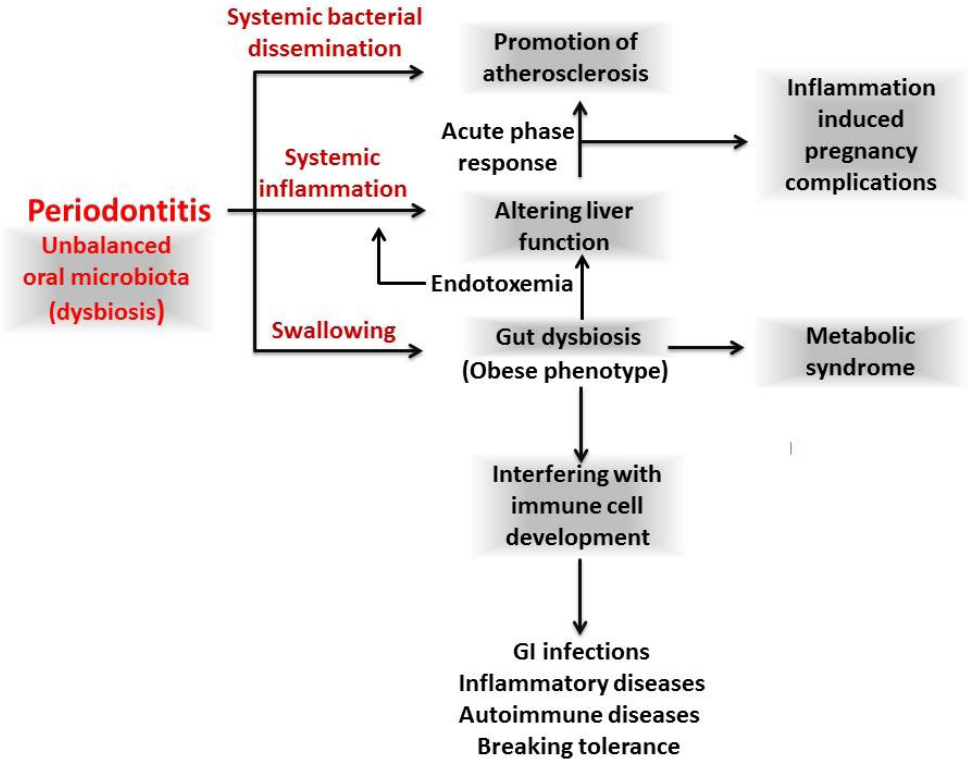

Figure 8 *Representative diagram showing potential mechanisms linking periodontitis to systemic diseases.*

Conclusion

This review is a personal perspective based on a current paradigm on oral-systemic diseases interaction. Periodontitis and "lifestyle" diseases were used as representative example for the discussion. Epidemiological studies have clearly established that modern living is an important factor contributing to a steady increase in the prevalence of lifestyle diseases worldwide. We, in the dental profession with sedentary lives, are not exceptional to this change. Both lifestyle diseases and periodontitis are characterized by low-grade chronic inflammation and current evidence point to the fact that a causal link exits between oral and systemic diseases. Both diseases are influenced by diet, lifestyle behaviors and microbiota. Periodontitis-associated microbes and inflammatory mediators generated in the diseased periodontium are able to enter systemic circulation and induce inflammatory changes and diseases at distant extra-oral sites. Exciting emerging new information is the fact that alteration in the composition of microbiota can influence health status of the host, biasing toward obesity phenotype, which makes the host more susceptible to developing lifestyle diseases. Manipulating the microbiota by various means may represent a future direction for managing some of these diseases. Knowledge on the molecular nature of the diseases together with ways and means to intervene them will in the future benefit not only us in the oral health profession but also our patients. Additional insight into the molecular basic on the mechanism of the disease process will lead to potential future therapeutic approaches and options to increase the quality of life of our patients.

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