Department of Clinical Dentistry
faculty of Health Sciences

Periodontitis Etiology, Diagnosis, Current and Future Therapy

A Literature review

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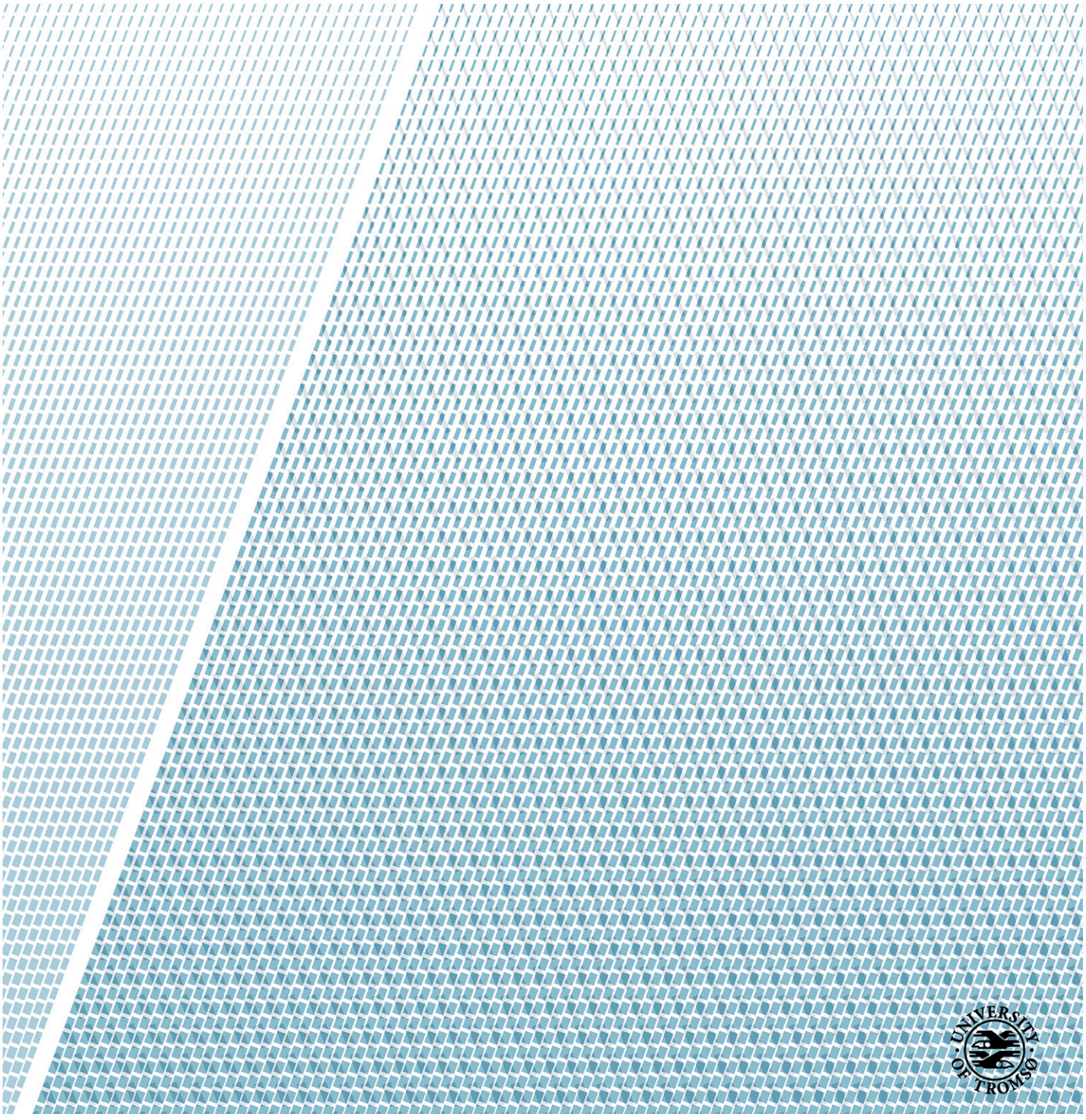

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Abstract

It is becoming clear that periodontitis is an inflammatory disease initiated by oral microbial biofilm, and likely due to poor oral hygiene and the failure of host immune system. Host response to the bacterial biofilm by the production of cytokines and subsequently inflammation response destroys the periodontium in the pathogenesis of the disease. This could lead to loosening or loss of teeth.

In this study, the implicated bacteria and identified cytokines network are addressed as well as the biofilm formation process.

The possible biomarkers in the saliva and other fluids are addressed. It is also clear that periodontitis is affected by other host diseases and vice versa. In addition to the non-surgical and surgical methods to treat periodontitis patients and possible topical treatment, more specific methods that utilize cytokine antibodies, cytokine blockers, complement inhibition by Cp40 and cysteine proteinases inhibition by KYT-41 are being developed. Recently photodynamic therapy was reported to promote bone recovery 7 days after periodontal intervention (SRP) in experimental animals. The use of induced pluripotent stem cells (iPSCs) will eventually be a very helpful and promising in periodontal tissue repair.

Keywords:

Periodontitis, stress, cytokines, *Phorphyromonas gingivalis, Aggregatibacter actinomycetemcomitans,* Cp40, Complement inhibition*,* cytokine- antagonists, cytokine antibodies, KYT-41, PDT, iPSCs.

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1. Introduction

The oral cavity is a complex biotope where it lives a huge number of bacteria of different species among the hard tissues of the teeth and soft tissues of mucosa [1]. The different aerobic and anaerobic microorganisms prefer the mild climate present in the oral cavity and together they form a complex and stable ecosystem. A high humidity, a suitable temperature and regular supply of nutrients offer perfect conditions for the microorganisms, that could help to overcome the saliva defence mechanisms outlined in Figure 2 [2]. Colonization of the bacteria occurs on favourable surfaces as the tooth surface, the dorsum of the tongue, in subgingival or endodontic localisations [3].

Colonization of pathologic periodontal bacteria in the biofilm that is attached to the tooth surface, may develop into a periodontal pocket, a pocket that is pathologically deepened into the gingival crevice (Figure 1) [4]. An infection that is characterized by destruction of the periodontal tissues, the periodontium, is called periodontitis [1].

Periodontitis is the most common disease of the oral cavity caused by bacteria [3]. It is the bacterial species of the red-complex that is strongly associated with periodontal disease, which include the bacteria *Porphyromonas gingivalis, Tannerella forsythia,*and *Treponema denticola.* Also *Aggregatibacter actinomycetemcomitans* and *Eubacterium nodatum* are pathogens that are associated with periodontal disease [5]. *Porphyromonas gingivalis*, *Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans* are regarded as the major pathogens in advancing periodontitis (see Figure 4) [6]. These gram-negative microorganisms are considered as the primary etiologic determinants of periodontal disease and are strongly associated to the clinical parameters of periodontitis [5, 7].

Recently, it has become more known that periodontitis is an inflammatory disease triggered by the host response to the biofilm [8]. This inflammatory disease affects the tooth-supporting structures and it is the major cause of tooth loss in adults [7]. Tooth loss impacting negatively upon speech, nutrition and at least quality of life and self-esteem [9]. Periodontitis doesn't only affect the teeth, as it increases the risk for diabetes, atherosclerosis and rheumatoid arthritis it can also affect systemic health [4]. Periodontitis has systemic inflammatory consequences [9].

One of the main risk factors is stress. It`s known that stress may disrupt the microbiological homeostasis (Figure 3) [4]. If we see periodontitis as a result of disruption of the host-microbe homeostasis, could we better understand this inflammatory disease? Stress induces cytokines; is higher concentration of cytokines in the saliva associated with periodontitis?

2. The periodontium

The periodontium is a functional unit that consist of 4 different types of tissue; the gingiva, the root cementum, the alveolar bone proper and the periodontal ligament [3], all of these tissue types together anchors the teeth in to the bony socket (Figure 1).

With different types of fibres that runs from the surface of the tooth, the cementum, through the gingiva and into to the alveolar bone proper, the tooth is attached to the jaw. The periodontal ligaments are cell- and fibre rich connective tissue and the majority of the fibres consist of collagen. The periodontal fibres also contain cells from the immune system and the neurovascular element. Through the gingival plexus and the desmodontal blood vessels, the periodontal ligament (PDL) is well vascularized. Also, both sensory and autonomic nerve fibre endings are found [3]. In that way, the periodontal ligaments regulate homeostasis and the functions in innate immunity [10].

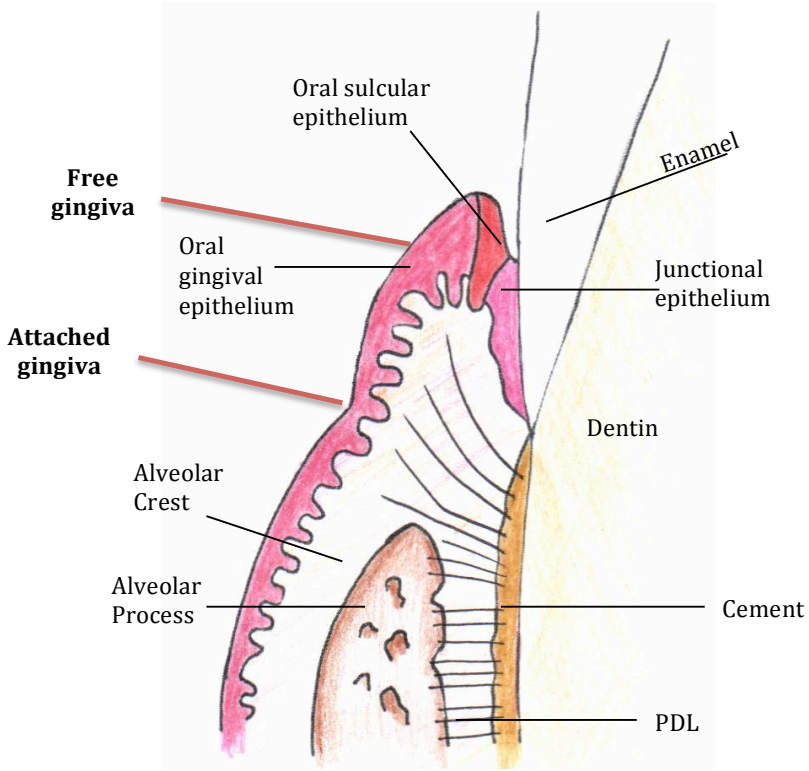

Figure 1. The anatomical structures of the periodontium. *Adopted from Periodontal regenerative therapy, by Anton Sculean, 2010 [11].*

3. Defence mechanisms in the oral cavity

The oral cavity for healthy individuals is well equipped with defence mechanisms against invading pathogens. The saliva is the first line of defence containing organic and nonorganic antibacterial barriers (Figure 2) [2].

In addition to inorganic components in the saliva that are antibacterial, some defence proteins, like salivary immunoglobulins and salivary chaperokine HSP70/HSPAs (70 kDa heat shock proteins), are involved in both innate and acquired immunity. Cationic peptides and other defence proteins like lysozyme, bactericidal/permeability increasing protein (BPI), BPI-like proteins, PLUNC (palate lung and nasal epithelial clone) proteins, salivary amylase, cystatins, proline-rich proteins, mucins, peroxidases, statherin and others are primarily responsible for innate immunity [12].

The gingival epithelial cells participate in innate immunity by producing a range of antimicrobial peptides to protect the host against oral pathogens. These epithelial antimicrobial peptides (EAPs) include the β-defensin family, cathelicidin (LL-37), calprotectin, and adrenomedullin. While some are constitutively expressed in gingival epithelial cells, others are induced upon exposure to microbial insults. It is likely that these EAPs have a role in determining the initiation and progression of oral diseases [13].

However, this early defence mechanisms of the saliva and gingival epithelial cells could be overcome by poor oral hygiene that lead to a great increase of bacterial colonization. Low quality or a small volume of saliva in addition to a lower immune response could help in the colonization of oral cavity by bacterial pathogens.

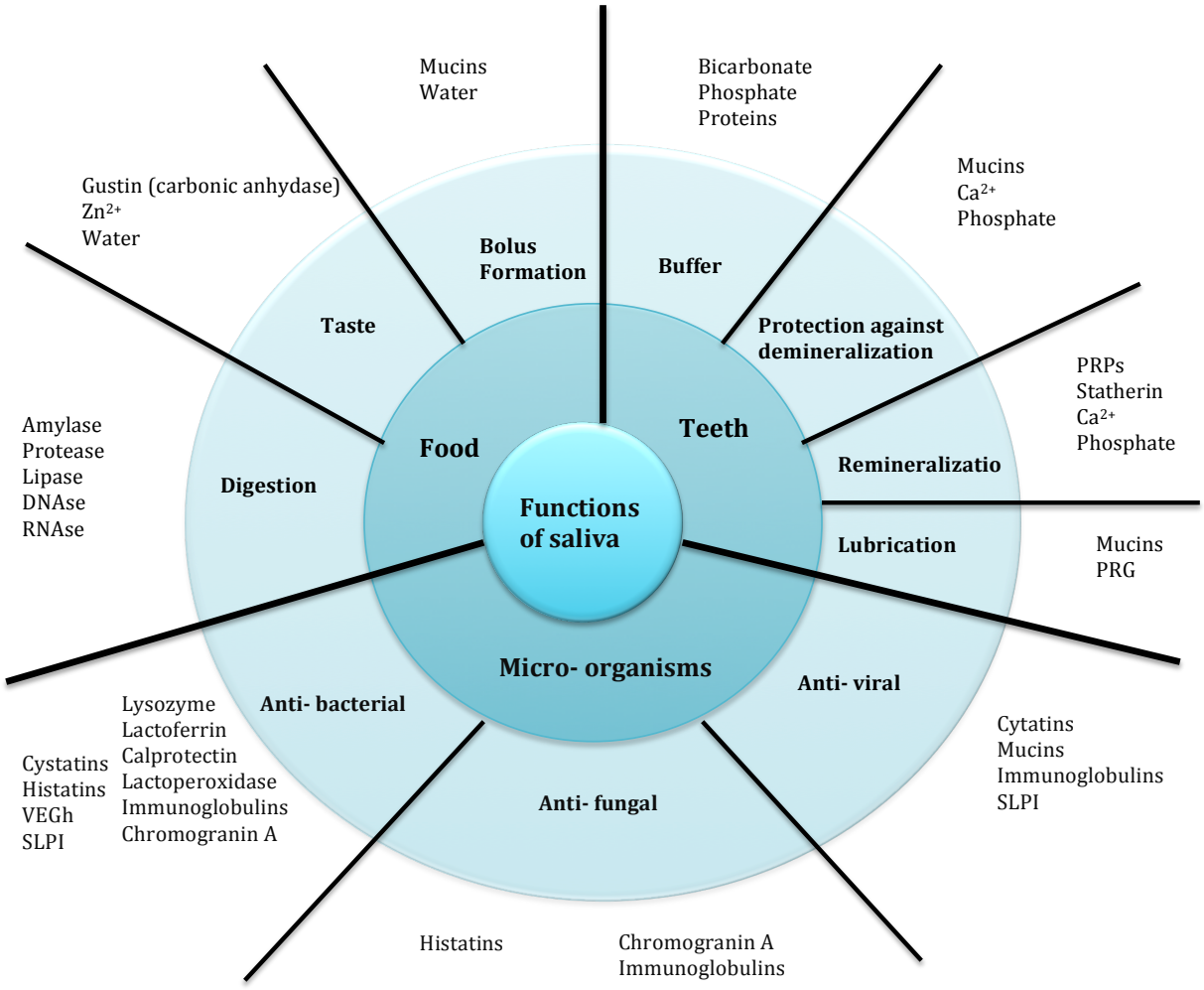

Figure 2. A schematic presentation of the main functions of saliva in relation to its constituents. *Described by Amerongen and Verman 2002[2].*

4. Periodontitis initiation

A breakdown of periodontal host microbe homeostasis by novel underlying mechanisms may in turn precipitate dysbiosis and periodontitis in a susceptible host. Periodontal tissue homeostasis could be likened to an‘armed peace’ between the host and the periodontal microbiota, with occasional microbial attacks that are readily subdued by immune defences. This controlled inflammatory state is likely represented by stable gingivitis, which would therefore reflect a protective host response. The transition to periodontitis requires both a dysbiotic microbiota and a susceptible host (Figure 3) [4].

When the complex microbial communities switch from a commensal to a pathogenic entity, uncontrolled inflammation of the periodontal area could occur. Communication between constituent species leads to polymicrobial synergy between metabolically compatible organisms. These organisms obtain functional specialization within the developing bacterial community and as a result, dysbiotic community targets specific aspects of host immunity to further debilitate the immune surveillance while promoting an overall inflammatory response [4].

Keystone pathogens such as *Porphyromonas gingivalis*, can even in low numbers elevate the virulence of the entire community [14]. Rather than being an inducer of inflammation, *Porphyromonas gingivalis* manipulate the host response. By depressing the innate immune system including the cross talk with Toll- like receptors (TLRs) and complement system, *Porphyromonas gingivalis* make the host defence weaker resulting in an unfavourable growth and development of the entire microbial community. The homeostasis is triggered and cause destructive changes in the periodontium [4]. On the other hand, in a already disrupted homeostasis, the virulence of a keystone pathogen is not necessarily depended to cause inflammatory pathology [4].

Initiation, progression and resolution of periodontitis involve over- and under-expression of cytokine genes associated to various T-helper subsets. In addition, variations in individual T-helper response subset/genes during disease progression correlated to protective/ destructive outcomes [15].

The gingival sulcus, a 0.1 to 0.5 mm deep sulcus between the tooth and gingiva, offer a perfect place for bacteria colonization and is bordered by the surface of the tooth, the gingival sulcus epithelium and is lower limited by the junction epithelium (Figure 1). The junctional

epithelium, which is placed at the inner surface of the free gingiva, is not keratinised as the oral gingival epithelium and oral sulcus epithelium are. However, as a defence mechanism against bacteria it has a very high turnover rate and presence of leukocytes. The lamina propria of gingiva contains both cellular and humoral components of the immune system [3].

Summarized, together the periodontium and the saliva, provide extensive defence mechanisms to prevent bacterial invasion of the periodontal bacteria such as *Treponema denticola, Tannerella forsythia, Porphyromonas ginigvalis and Aggregatibacter actinomycetemcomitans*.

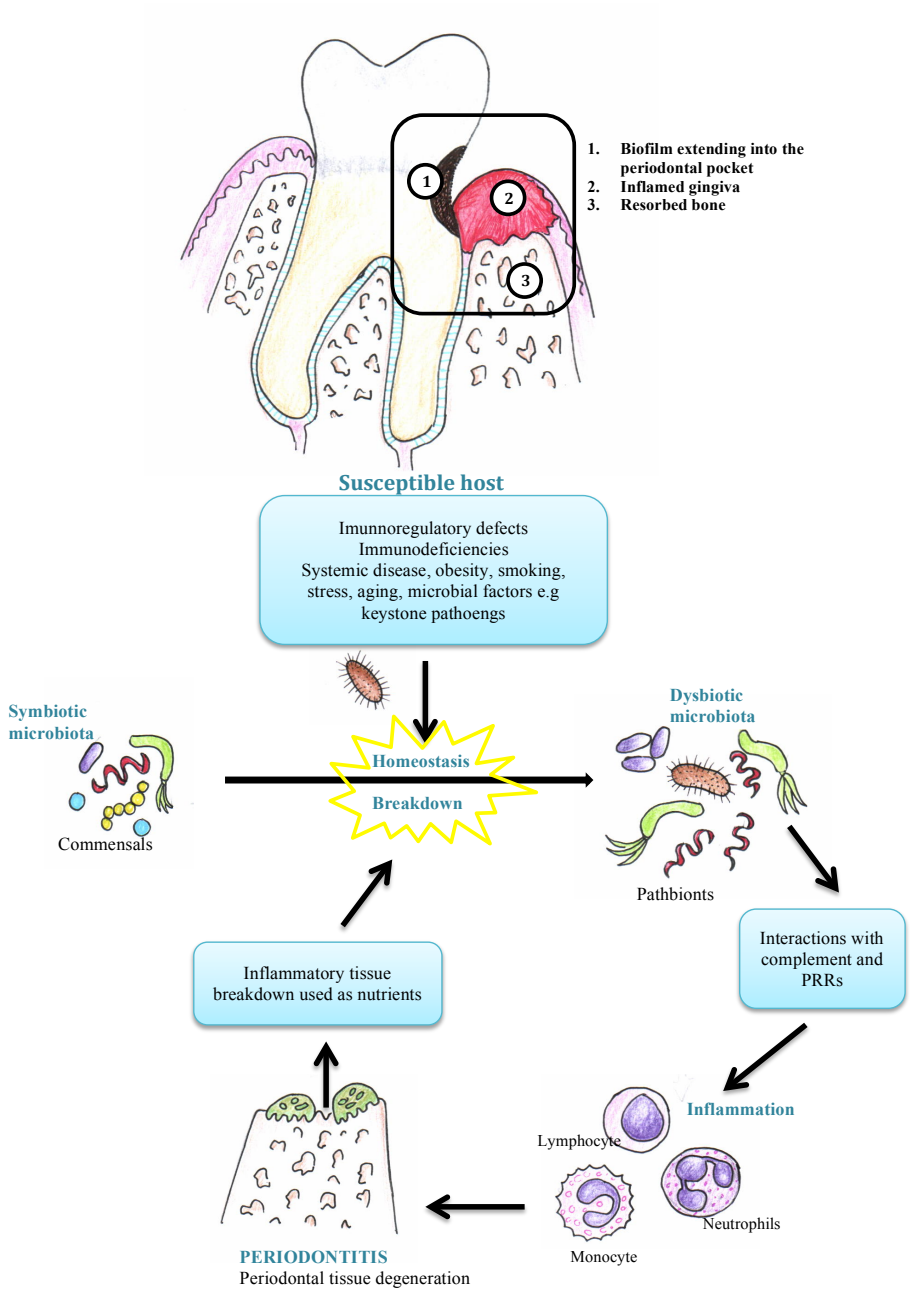

Figure 3. A self-perpetuating pathogenic cycle; Polymicrobial synergy and disbiosis in susceptible hosts cause periodontitis*. Periodontal health requires a controlled inflammatory state that can maintain host-microbe homeostasis in the periodontium. A susceptible host can shift the microbial balance towards dysbiosis, a state that former commensals behave as pro-inflammatory pathobionts. The inflammation caused by the dysbiotic microbiota depends in great part on crosstalk signalling between complement and PPRs. This has two major and interrelated effects: it causes inflammatory destruction of periodontal tissue including boneloss. This in turn provides nutrients from tissue breakdown peptides and other products that further promote dysbiosis and hence tissue destruction; thereby generation a self-perpetuating pathogenic cycle. It should be noted that host susceptibility might not simply be a determinate of the transition from a symbiotic to a dysbiotic microbiota, but there could also underlie a predisposition of the host to develop inflammation to cause irreversible tissue damage. In principle, there might be individuals who can tolerate the conversion of a symbiotic microbiota into a dysbiotic state, and will not result in periodontal bone loss. Adopted from Hajishengallis, 2014 [4].*

5. Oral pathogenesis

This multifactorial disease, periodontitis, could occur in isolated places or at different sites on the teeth in the oral cavity [3]. Diseases in the periodontium have many etiological factors; the foremost initial contributor is the formation of supragingival plaque [7].

5.1 Dental biofilm formation

The first phase of the formation of the plaque starts immediately after cleaning the solid surface of the teeth, by adsorbing of hydrophobic and macromolecules, the pellicle [16]. The conditioning film consists of different glucoproteins from the saliva (mucins) and antibodies that alter the charge and free energy of the surface and makes it easier to bacteria to adhere. Some bacteria need time to attach, while others attach by structures as fimbriae and extracellular polymeric substances [16]. The behaviour of the bacteria changes while they attach to the pellicle, which result in bacteria multiplication and growth of extracellular matrix production. If the plaque is not arrested, it will accumulate further by sequential adsorption of organisms and form a more complex and mature biofilm [3, 16].

Further, the biofilm increases in thickness by the synthesis of extracellular polymers, and makes diffusion through the biofilm hard. A completely anaerobic environment develops as a reduced oxygen gradient develops [16].

When the pocket is deepened and the biofilm is getting thicker it`s harder for the bacteria to reach nutrients in the saliva, that normally serve as an important nutrition source. In deep periodontal pockets the nutritional sources for further bacterial metabolism then comes from periodontal tissues and blood. To break down the complex macromolecules the periodontal bacteria produces hydrolytic enzymes. As a result, these enzymes cause destructive processes of periodontal tissues [16].

The accumulation of gram-negative bacteria in the dental biofilm, initiate the periodontal disease [17]. Gram-positive cocci are the primary bacteria that colonize in the biofilm, followed by Gram-positive rods. It is the receptors on these bacteria that permit the Gram-negative organisms to adhere, as the Gram-negative organisms are not able to adhere directly to the pellicle. As the plaque ages, matures and the heterogeneity increases more Gram-negative anaerobic bacteria colonize to the biofilm [16].

The biofilm is required but not sufficient to induce periodontitis [4]. It is increasingly clear that the untreated host mediated response to the biofilm would cause the destructions of tissue and bone of the periodontium [8]. The detailed connection between the spectrum of the microbial flora in the biofilm and the direct responsible to develop periodontitis has not jet been established [18]. In spite of cross-sectional studies that have pictured the correlation between determined pathogens and periodontitis, remains the cause-and effect relationship between certain pathogens in longitudinal studies [18].

Regular oral hygiene plays a major role in the prevention of colonization of bacteria on the tooth surface. It has been concluded that professionally administered plaque control significantly improves gingival inflammation and lowers plaque scores, with some evidence that reinforcement of oral hygiene provides further benefits. It is strongly recommended that all people should brush their teeth twice a day for at least 2 minutes [9].

If the biofilm remains, because of suboptimal oral hygiene, the polymorphonuclear granulocyte/complement axis, an important line of defence that prevents further penetration of the bacteria into the connective tissue can be overwhelmed. Clinically, gingivitis or mild periodontitis can then be observed. If the bacteria penetration or exposure of their metabolic products, the Th1 mediated immunity will be activated through activation of macrophages and lymphocytes. The activation of Th1 cells leads to secretion of protective, specific antibodies that may be protective in future episodes of the disease [3]. Although accumulation of dental plaque may cause gingivitis; gingivitis does not necessarily lead to periodontitis. Stable gingivitis may indicate a protective host response [4].

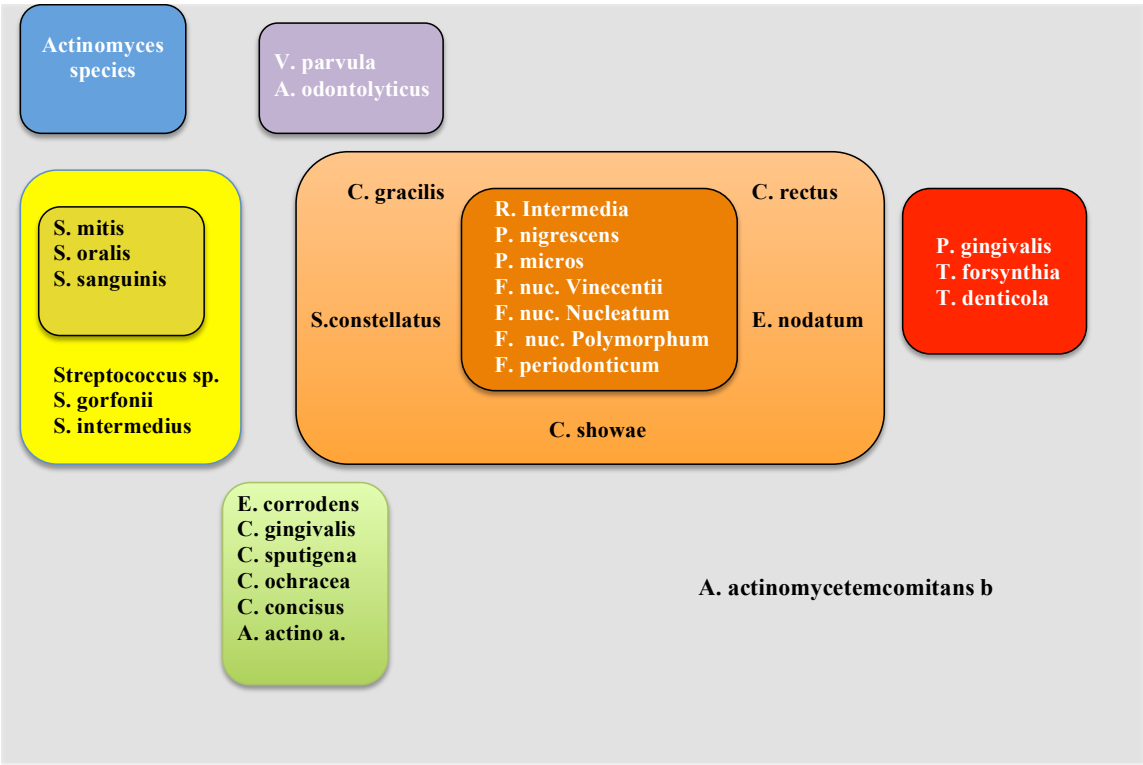

Figure 4. Bacteria of the periodontal pocket, organized in different complexes. *This figure also shows us the sequence of colonization, from left to right. The primary colonizers as Actinomyces oris and streptococci occur most frequently in the colonization. The large complex in the middle contains potential periodontal pathogens. This is bacteria as Prevotella spp., Fusobacterium spp. and Campylobacter spp, and are usually present at low concentrations in all oral cavities and only in response to changes in the ecosystem they could potentially multiply and cause pathological conditions. To the right in the figure, the red complex is placed which are strongly associated with destructive periodontal disease. In the red complex, the bacteria Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola belong. Outside the complex flora Aggregatibacter actinomycetemcomitans b is placed. Sterotype a is associated with the "green complex"[3]. Adopted from Sockransky et al. [19].*

5.2 Molecular pathways in the pathogenesis of periodontitis

There are numerous molecular pathways in the pathogenesis of periodontitis. Known pathways for the pathogenesis are apoptosis, matrix metalloproteinase (MMP)-REDOX/ nitric oxide (NO) activation, toll-like receptors, nuclear factor- κB (NF-κB) signalling, the network between cytokine and chemokines, the complement cascade and the osteoclast genesis [20].

If pathogens penetrate further into the connective tissue and thus attach to the periodontal tissue, the bacteria invasion gets a totally different and a more serve outcome (Figure 6) [7]. Mainly it is the epithelial cells and polymorphonuclear leukocytes (PMNL) are the two types of host cells that meet the periodontopathogenic bacteria during inflammation in the periodontium [20].

The gram-negative periodontal pathogens may activate the periodontal ligament fibroblast, through activation of the Toll-like receptors (TLRs) by the attachment of the lipopolysaccharides of the bacteria. The TLR activates nuclear factor κ of already activated B cells, and an expression of pro inflammatory factors occurs [10].

Moderate or aggressive periodontitis are seen if Th2 mediated polyclonal B-cell stimulation gets activated. The Th2 mediated polyclonal B-cell stimulation causes expression of pro inflammatory cytokines and mediators as IL-1 and PGE2 [3]. Under the influence of these cytokines, Th0 cells differentiate into Th17 cells [7]. Th17 cells then produce Interleukin -17 and recruit neutrophils (PMNs) and reactive oxygen species (ROS) are produced via an oxygen-dependent mechanism [7]. When the bacteria bind to the surface of the neutrophils, phagocytosis occurs and the result is production of a phagosome that further undergoes maturation by fusion with endosomes and lysosomes. The lysosomal vesicles include these reactive oxygen species (ROS) that again activate the NF-κB signalling pathway that maintain the persistence of inflammation [20]. ROS causes oxidative DNA damages to the periodontal apparatus [7], and develop gingival tissue degeneration [4].

The immune response that is supported by Interleukin -17 (IL-17) combines with the receptor activator of RANK and RANKL on the gingival fibroblast, T cells and B cells, which leads to osteoclastic bone resorption [7]. The activation of osteoclast that resorb the alveolar bone, are well established in both human and animal models and involve the activation of RANKL (Figure 5) [4].

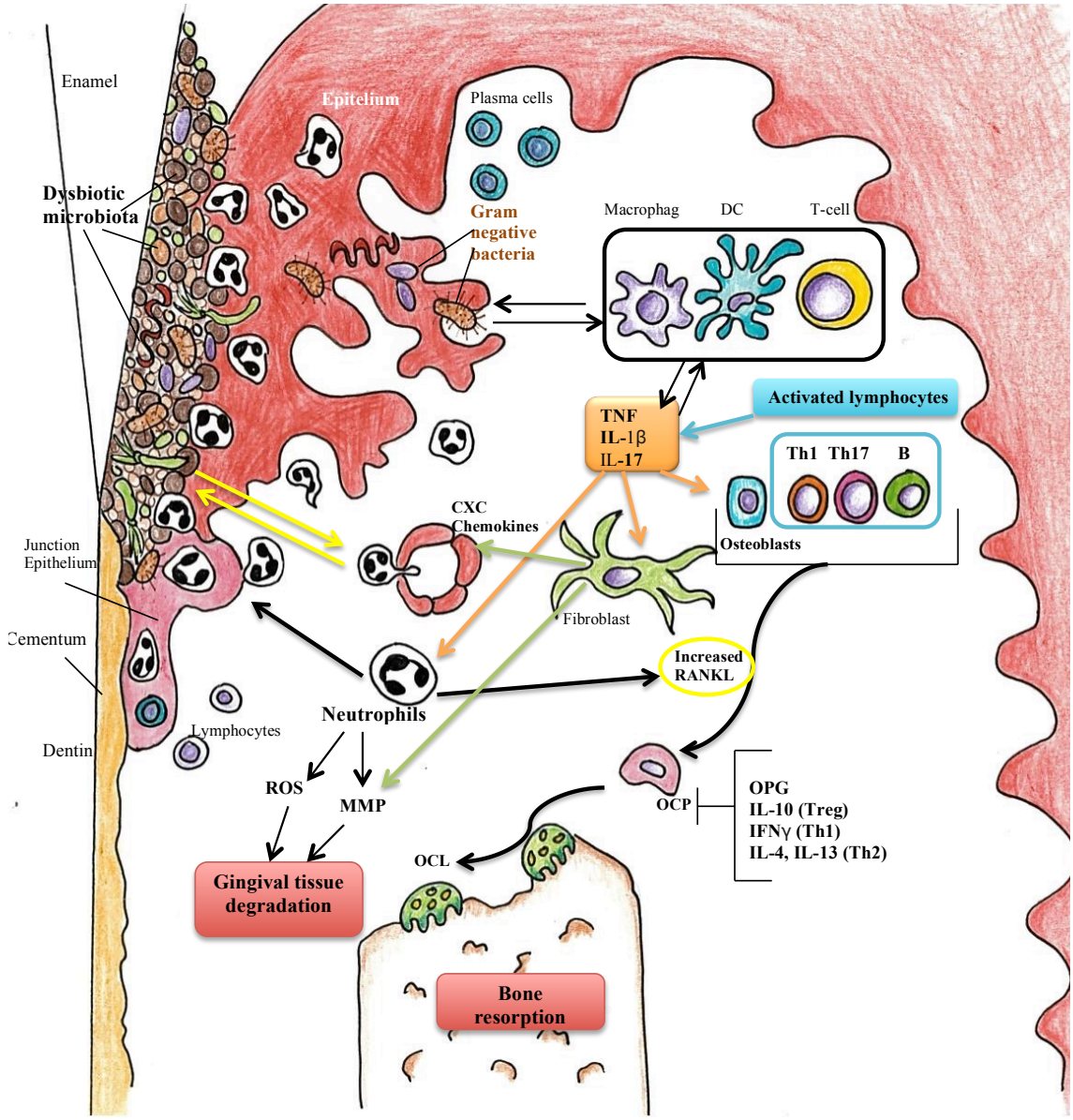

Figure 5 Inflammatory mechanisms leading to gingival tissue degeneration and bone resorption in periodontitis*. Illustration of an advanced lesion where subgingival plaque microbiota is established. Both the bizarre ridges of the thin pocket epithelium and junctional epithelium proliferate apical. Root cementum is pathologically altered and could be penetrated by bacteria [3]. The migrated neutrophils to the gingival crevice fail to control the dysbiotic microbiota, which then can penetrate further into the connective tissue and interact with immune cells, such as macrophages, dendritic cells (DC) and T cells. Innate- like lymphocytes are also one of the first cells the pathogenic bacteria interact with[4]. These immune cells produce proinflammatory mediators such as cytokines, TNF and interleukins. They also play a major role in regulating the development of Th cells that also exacerbate the inflammatory response. A signature cytokine of Th17, Interleukin 17 (IL-17) acts on innate immune and connective tissue cell types such as neutrophils, fibroblasts and osteoblast. Interleukin 17 induces production of CXC chemokines, matrix metalloproteinases (MMPs) and other tissue- destructive molecules through these interactions. Through the release of degradative enzymes as matrix metalloproteinases (MMPs) and reactive oxygen species (ROS), neutrophils can cause periodontal tissue destruction [4]. If the activated neutrophils are close enough to the bone, they could even mediate osteoclastic bone resorption through the expression of RANKL. It has also been proposed that neutrophils might have an indirect destructive effect by recruitment of the CD4+ T helper cells that produces the pro- inflammatory cytokine interleukin IL-17[4]. IL- 17 stimulates other types of cells that produce even more inflammatory cytokines and chemokines, that activates even more neutrophils and macrophages [4, 7]. This pro-inflammatory cytokine plays an important role in preserving immune homeostasis, particular at mucosal barriers[7]. Adopted from Haijshengallis et al., 2014 [4] and Mueller, 2016 [3].*

6. Proinflammatory mediators and cytokines

The increased level of proinflammatory mediators and cytokines leads to tissue destruction [3]. A consequence of this tissue destruction is formation of a pocket that offers the perfect conditions of most of the periodontal pathogens [3]. Epithelial cells, fibroblasts, dendritic cells, macrophages and T helper (Th) cells produce in response to microbes. Cytokines are central regulators of the immunoinflammatory response [15].

Table 1: Cytokines can functionally be grouped as Th1, Th2, Th17 and T regulatory (Treg) based on the different expression pattern and effects on target cells or tissues [15].

Immune cells	Cytokines	Function/ expression pattern
Th1	IFNy, IL-12	Activation of cell- mediated immunity to control intracellular pathogens and autoimmunity [15]
Th2	IL-4, IL-5, IL-13, IL-25	Drives humoral immunity to control extracellular parasites. Also, involved in allergic-type responses mediated by IgE and mast cell activation[15]
Th17	IL-1B, IL-6, IL-21, IL-22, IL-23, IL-17A	Cytokines that enhance an immune response against extracellular bacteria and fungi[15]
T regulatory (Treg)	TGFB, IL-2, IL-10	Important to maintain a balanced immune response through negative regulation of other T-helper responses [15]

A study done by Ebersole et al., 2014 [15], showed that initiation and progression of periodontitis was characterized by over-expression of Th17/ Treg cytokine genes (IL-1B, IL-6, TGFB and IL-21 and down regulation of Th1/Th2 cytokine genes IL-18 and IL-25 (Table 1) [15]. Most Th1/Th2 genes exhibited a negative correlation, whereas most of the Th17/Treg cytokine genes were positively correlated with tissue destruction genes [15].

Higher level of proinflammatory factors and matrix metalloproteinases (MMPs) activates osteoclastogenesis and destroy the collagenous structures, resulting in decreased tooth attachment (Figure 5) [10]. Th17 cytokines enhance osteoclast differentiation and activates metalloproteinases (MMPs), and the response seems to play an important role in chronic

periodontitis [15]. Both Th1 and Th2 responses are associated with either protective or destructive periodontal lesions [15].

Proinflammatory hormone Resistin [21] was found to be associated with periodontitis [22, 23]. Consequently, resistin is recently considered as important biomarker for periodontitis (19). Resistin is produced by adipocytes and also produced in abundance by various cells of the immunoinflammatory system, indicating its role in various chronic inflammatory diseases. This suggesting that resistin plays a role in obesity, insulin resistance, cardiovascular diseases, as well as periodontitis [23].

7. Periodontitis classification

The classification of periodontal diseases used today is based on a report from the International Workshop for a Classification of Periodontal Diseases and Conditions [24].

Bacterial biofilm that remains on the tooth surface for a prolonged period, may result in inflammation of the gingival soft tissues. An established lesion with distinct lateral proliferation of junctional epithelium may remain quite stable for extended periods [3]. Under normal physiological conditions and with better oral hygiene this inflammation, named gingivitis, will completely heal [25]. Gingival diseases are divided into two main groups; "*Dental plaque-induced gingival diseases*" and *"Non- plaque- induced gingival lesions",* both types of gingival diseases are with sub classifications [24].

A microbial homeostasis between the bacteria challenge and the immune response of the host, usually keep the gingivitis stable. An advanced lesion, destructive periodontitis, could develop after breakdown of both the specific and nonspecific defence mechanisms of the host [3]. Risk factors that could disturb and tip this microbial balance will further be discussed in section 9, 10 and 11. In moderate and serve periodontitis the junctional epithelium, the non-keratinized epithelium of gingival sulcus, is destroyed. This permits bacteria to enter the connective tissue and thus the circulation in significant amounts [26]. If this microbial invasion are not adequately managed by the host inflammatory response, the lesion may progress to chronic inflammation [25]. The progression are most often slow or moderate, with periods of rapid progression [3]. Prolonged, chronic periodontitis can result in mobility and loss of teeth [26]. Chronic periodontitis is the most frequent form of periodontitis [3].

Aggressive periodontitis is characteristic by rapid loss of alveolar bone and attachment loss in patients that is otherwise healthy. Both higher numbers of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* in subgingival plaque and phagocyte abnormalities are seen and it might argument to a genetic disease [3]. For many years, the differences between chronic and aggressive periodontitis have been discussed and numerous suggestions for the classification have been made. Today the two major forms of periodontitis, chronic and aggressive, are mainly differentiated by the progression rates [27].

Further, periodontitis could be classified as *"a manifestation of systemic diseases"*, *"necrotizing periodontal diseases", "abscesses of the periodontium"* and "*periodontitis associated with endodontic lesions".* The last classification is *"Development or acquired deformities and conditions"* [24].

8. Stress

8.1 Definition of stress

Stress was defined previously as*"The rate of all the wear and tear caused by life".* And as a biological and biochemical process that begins in the brain and spreads through the nervous system [28]. This process releases hormones that could affect the immune system [28]. Stress and other epigenetic modifications in response to changes in the environmental could disrupt the host-microbe homeostasis [4]. Development of periodontitis is genetic, but also significantly depending on factors as stress, among others lifestyle factors as smoking, nutrition and type-2 diabetes [9].

Selye, 1956, was one of the first to identify stress and how it effects our body, he defined stress as a nonspecific response of the body to any demand [28]. Our intern systems process all external stimulation that affects our body and send a response to the stress in return [29]. The nervous system, the endocrine system and the immune system communicate to maintain all the body functions in a balanced and controlled way. Our body strives homeostatic balance [29]. If stress is frequently repeated or prolonged, the exhaustion phase sets in. This resulting in increased susceptibility to disease [29]. For a long time scientists categorizes stress as ”good” or ”bad ” stress. Today its accepted that stress is anything that challenges the body to homeostasis [28].

8.2 How stress affects the immune system

The response to stress varies greatly between people. Levin et al., 1976 [29] found out that a little stress early in life seemed to make the test animals more resilient to later stress; called stress immunization [29].

Bacteria and viruses pathogens that invade our body, have for a long time been seen as factors that can evade our immune system and make us sick. For many years, researchers thought about the immune system as something automatic, as an automatic mechanism [28]. Well-known and well-accepted risk factors to diseases are cigarettes, obesity, lack of exercise and high blood pressure. All of these factors still count as valid, but they are only a small part of the whole picture because they only say something about the body; a small part of the person [28]. In 1980s the field of psychoneuroimmunology emerged and emotions and stress was accepted as being revealed to influence the immune system [29].

9. Molecular manifestation of stress and inflammation

Enough bacteria in the correct place can cause disease in almost anyone [28]. What decides if people exposed to the usual causes of disease get sick or not, depends on the host susceptibility or resistance [28]. Tipping of homeostatic balance in the microbial community in the oral cavity might cause changes in ecologic conditions and favour the outgrowth of periodontal pathogens, and lead to periodontitis [4].

Several factors can influence resistance, not only organic problems, but also social factors and coping ability. What make up the person disease resistant is dependent on all of such factors. The resistant patients modulate the homeostasis and the immune responses [28].

Studies shows that both psychological and neurological systems influence the immune system [29]. In wound healing experiments to test cortisol was found to reduce wound healing [30]. Also, blocking the production of corticoid was found to improve wound healing [31]. However, no data could be found dealing with cortisone effect on periodontitis directly as yet.

It has also become clear that the immune cells and their products affect the brain, and that the brain influences the responses of the immune systems. The interactions goes in both directions [29]. Important immune cells, the lymphocytes, respond chemically to hormones and neutron transmitters. Receptors for neuromodulators and neurohormones were reported in the T lymphocytes [28].

During stress the body induces immunosuppression as a defence mechanism. The production of corticotrophin-releasing hormone is the start of a chain of processes that is induced by stressful conditions. Corticotrophin realising hormone stimulates the release of corticosteroid hormones from the adrenal cortex. The hormones released from the adrenal cortex trigger some of the lymphocytes to death and inhibiting the proliferation of others [29].

With a lowered amount of lymphocytes (Low Absolute Lymphocyte Count, ALC), the body is more susceptible to infection and disease [32]. Prolonged stress results in high levels of cortisol and other corticosteroids circulation in the blood [33]. As a result, the body would develop a resistance against corticosteroids leading to failure to down regulate inflammatory response and increased risk to the patient, see Figure 6 [34].

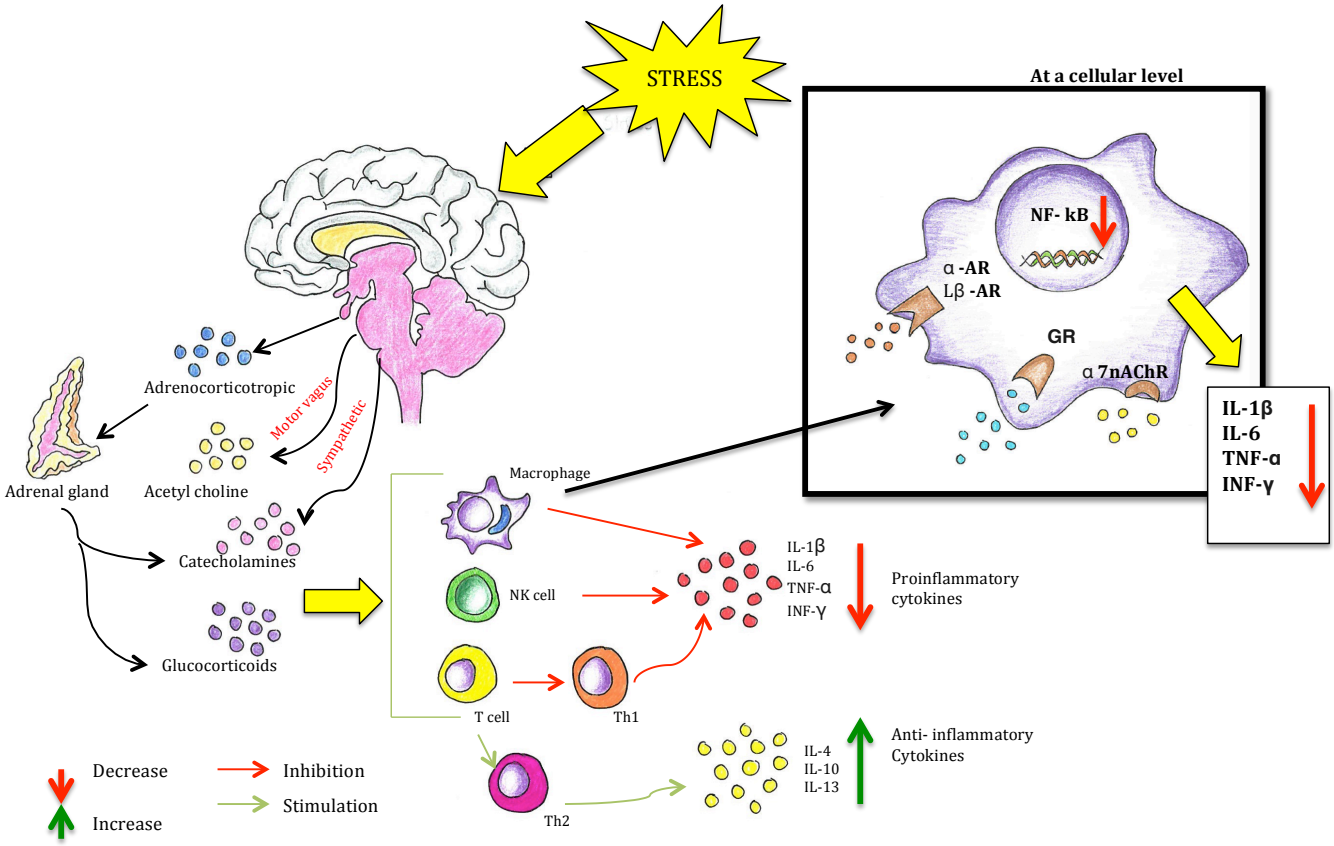

Figure 6. The mechanisms of chronic stress acting on inflammatory cytokines.
Chronic stress activated the HPA axis through and secretes Glucocorticoids. The catecholamines hormones are secreted trough the SAM axis. Both, the glucocorticoids and the catecholamines hormones act on the receptors on the surface or in the cytoplasm of the immunecells that ultimately inhibits the proinflammatory cytokines and promoting the anti-inflammatory cytokines. Motor vagus fiber also secretes these hormones, glucocorticoids and catecholamines, which both promote the shift from Th1 to Th2. At a cellular level, the stress hormones inhibit the inflammation related pathway, including NF-kB. Further the stress hormones inhibit the proinflammatory cytokines secretion. Adopted and modified from Tian et al, 2014 [33].

10. Diseases associated with periodontitis

Periodontitis is a multifactorial disease that affects among 8.1% of the adult population in Norway [35]. As described in section 5 the different periodontal bacteria can impair host response and in that way trigger a destructive change in the homeostatic balance [4]. Systemic diseases such as diabetes, obesity, stress and environmental factors such as smoking could also alone or in combination disrupted the host-microbe homeostasis [4].
Predisposition factors include genetic factors, systemic diseases such as diabetes type II or the non- insulin dependent diabetes. Factors such as smoking and oral hygiene, individual behaviour factors, are also important [25]. Periodontitis has also been strongly associated with other inflammatory and systemic disease and could ultimately lead to bone destruction [1]. The prevalence of periodontitis has been shown to be more prevalent in patients with rheumatoid arthritis (RA) [26].

10.1 Atherosclerotic cardiovascular diseases

Atherosclerotic cardiovascular diseases association between periodontitis and atherosclerotic cardiovascular diseases (ACVD) has been implicated previously, however in a study of 60,174 patients in the Netherland, no association was found [36].

10.2 Cancer

Periodontal disease was reported to have a higher significant associated risk of cancer among male never-smokers never smokers. The significant cancers were prostate cancer, colorectal cancer or melanoma [37].

10.3 Kidney disease patients

Severe periodontal diseases were more prevalent in patients with more severe CKD than in those with less severe CKD [38].

10.4 Alzheimer`s disease

Periodontitis is associated with an increase in cognitive decline in Alzheimer’s disease, independent to baseline cognitive state, which may be mediated through effects on systemic inflammation [39].

11. Diseases further aggravated by periodontitis revealed by different studies

11.1 Chronic kidney disease

A strong, association between periodontitis and increased mortality in individuals with chronic kidney disease CKD) was reported. Sources of chronic systemic inflammation (including periodontitis) may be important contributors to mortality in patients with CKD [40].

11.2 Diabetes

It was reported that periodontal infection can contribute to the low-grade general inflammation associated with diabetes (thus aggravating insulin resistance) and discussing the impact of periodontal treatment on glycemic control in people living with both diabetes and periodontal disease [41]. Moreover, observed increased levels of the proinflammation hormone resistin in periodontitis could be considered a risk for diabetes by decreasing the insulin sensitivity. Thus, periodontitis might lead to development of type II diabetes, but also suggesting that diabetes might influence the occurrence or progression of periodontitis [23] However, recent experiments concluded that resistin levels in chronic periodontitis and system diseases such as diabetes, obesity or rheumatoid arthritis was not significantly higher than the level in chronic periodontitis patients [22].

12. Non-invasive methods for early diagnosis of periodontitis

12.1 Saliva as a diagnostic fluid

The final outcome of untreated periodontitis, is destruction of the tooth-supporting structures and tooth loss [7]. The damage of the non-keratinized epithelium of the gingival sulcus, junctional epithelium, which happens in moderate to serve periodontitis, allows the bacteria and their metabolic products and enzymes to enter the circulation in significant amounts [26]. Release of the bacteria with their metabolic products and proteolytic enzymes evokes production of systemic inflammatory markers, biomarkers [26].

Saliva represents along with gingival crevicular fluid (GCF) and the blood the oral ecosystem with the micro flora and has in that way the potential to provide information on periodontal status [7]. Although saliva could represent a bio-sample that is non- invasive, there is only a

subtle agreement on some few salivary molecules that could be used as putative markers for periodontitis [20]. It is a costly, long-term process to search for a novel biomarker [20].

12.2 Biomarkers for periodontitis

"Biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or as a pharmacologic response to a therapeutic intervention or other health care interventions" [23]. Biomarkers are highly specific and sensitive indicators of disease activity and could be used for screening and risk assessment [23]. By measuring the indicators, we can get determine staging of the disease and in that way get some directions toward a appropriate treatment [23]. The diagnostics parameter used today only says something about the severity, not stage. It's therefore appropriate to find the biomarkers of the early phase [20].

Although there is only a subtle consensus on few salivary molecules that could be used as biomarkers of periodontitis, it is possible to analyse possible candidate biomarkers by considering the different biological processes that are known for periodontitis [20].

12.2.1 MicroRNA (miRNA)

MiRNA are associated with bacterial infections in the oral cavity, for example dental caries, endodontic infections and periodontitis. By targeting mRNA for cleavage or translational repression, they play an important gene regulatory role in animals and plants [42].
For periodontal disease, five miRNAs have been restricted in both in vivo and in vitro by different validation methods, that is, miR-142-3p, miR-146a, miR-155, miR-203 and miR-223. Their disease specificity, detectability and expression in saliva and their importance as non-invasive markers are not properly validated. The diagnostic potential of miRNAs seems to be not specific enough for periodontitis to be used as markers for periodontal disease [42].

As mentioned in Section 5, several pathways play a role in the pathogenesis of marginal periodontitis. Known pathways are apoptosis, matrix metalloproteinase (MMP)-REDOX/ nitric oxide (NO) activation, toll-like receptors, nuclear factor-κB (NF-κB) signalling, the network between cytokine and chemokines, the complement cascade and osteoclastogenesis, see Figure 5 [20].

In early periodontitis, the most common histological findings are related to the migration of neutrophils and activation of wound healing in gingival epithelial cells and fibroblasts, the resident cells [20]. Increased bacteria invasion and decrease tissue regeneration in these resident cells, most often leads to neutrophil activation of MMP and oxidative stress- induced apoptosis [20].

12.2.2 CRP level

Increased levels of the acute-phase inflammatory markers CRP or ProCT are seen in moderate and serve periodontitis. Higher levels are found in patients with moderate to serve periodontitis than in patents with a healthy periodontium [26]. In patients with systemic inflammatory conditions, older patients or in overweight patients, ProCT are suggested to be a better index of periodontitis than salivary or serum CRP [26].

12.2.3 Levels of UBC, JUN and MMP14

A study by Zeidán-Chuliá et al., 2015, concluded that Ubiquitin (UBC), Jun proto-oncogene (JUN) and matrix metallproteinase-14 (MMP14) are candidates as host-derived biomarkers. By using salivary fluid samples from patients to detect periodontitis at its early stage, UBC, JUN and MMP14 in combination with oral pathogenic bacteria-derived proteins are likely the optimal biomarkers [20].

12.2.4 Cytokines Level

Since interleukin 17 (IL-17) is highly associated with inflammation and bone resorption it has a potential as biomarker for periodontitis [7]. Studies by Yang et al., 2015, concluded that there was a strong association between IL-17 levels and the microbial parameters seen in periodontitis. The same study also showed that 8-hydroxydeoxyguanosine (8-OHdG) is one of the most stable product of Reactive oxygen species (ROS), that is released by neutrophils triggered by interactions between periodontal pathogens and host [7].

As mentioned in section 6, cytokines are centrals regulators of the immunoinflammatory response, see Table 1 [15]. Ebersole et al., 2014, evaluated the expression of 19 cytokine genes related to the T cell function during initiation, progression and resolution of periodontitis. Further, they related the findings to the expression of both soft and bone tissue destruction genes (TDGs) [15]. The characteristic of disease initiation/progression was over-expression of Th17/Treg cytokine genes (IL-1B, IL-6, TGFB and IL-21) and down-regulation of IL-18 and IL-25, both Th1/Th2 cytokine genes [15]. During disease resolution

decreased IL-10 and increased IL-2 levels were seen. They concluded that over- and under expression of cytokine genes were related to different T-helper subsets during initiation, progression and resolution of periodontitis [15].

A study done by Khalaf et al., 2014 [1], showed that patients with periodontitis exhibit higher numbers of periodontal pathogens and that their immune responses were significantly altered. They showed that the levels of IL-6 in saliva as well in the gingival crevicular fluid (GCF) were significantly suppressed. The T-cell-derived cytokine IL-2 did not differ between patients and controls in serum or saliva, but there was a significant suppression of IL-2 in GCF of patients [1]. Recently resistin is discovered as a potential biomarker for periodontitis influenced diabetes mellitus and diabetes induced periodontitis could be resistin [23]. Resistin is an adipocytokine with a potent quality as a biomarker for periodontitis. Various cells produce this cytokine in response to different chronic inflammatory disease, including in periodontitis. Increased levels of resistin in diseases as rheumatoid arthritis, chronic kidney diseases, diabetic retinopathy, coronary heart diseases and periodontitis are showed in studies [23]. Resistin was known earlier as a adipocyte produced cytokine, but recent studies have shown that resistin is produced by PMNs, monocyte and macrophages- cells of the immuoinflammatory system in large amounts [23].

The proinflammatory adipocytokine, resistin, could be regulated by tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and lipopolysaccharide (LPS). Significantly increased levels of resistin was observed in chronic periodontitis, compared with healthy controls [23].

13. Current and futuristic treatments and therapies for periodontitis

The aim to maintain plaque at levels compatible with health, and in that way, prevent breakdown of microbial homeostasis, is traditionally done by mechanical and chemically control of dental plaque (see Section 15) [6]. The therapy methods used today are not always effective [43]. In eliminating pathogenic microbes and their products from the periodontal pockets, the not surgical periodontal therapy (NSPT) used to day, scaling and root planning, alone is often inefficient [44].

Control of the inflammation and the host response to the microbes could, at least in principle, inhibit periodontitis [45]. By limiting the activity of proinflammatory pathways and by boosting pathways that resolve inflammation, future approach will focus on more on modifying the inflammatory response itself [46].

13.1 Good oral hygiene

The universal recommendation is to keep a good oral hygiene; this by brushing the teeth twice a day for at least 2 min [9].

13.2 Non-surgical methods

Today, it is possible to prevent this disease and even provide effective treatment that could reduce the progression of loss of the periodontal tissues and reduce rates of tooth loss [9].

Conventional periodontal therapy today focus on the mechanical control of the bacteria, and in that way get control of the inflammatory response [25]. The conventional periodontal therapy is a systematic treatment and consists of three phases. Phase I is cause- related treatment, where the main goal is to reduce the pathogenic bacteria in the oral cavity by mechanical and chemical plaque control [3]. Mechanical treatment includes removing of supra- and subgingival dental plaque and calculus by scaling and root planning by using ultrasonic scalers or hand instruments (such as curettes) or both [47] [44]. Scaling removes the plaque and calculus, while removal of bacterially or toxically contaminated root cementum is done with root planning [3]. When it comes to more challenging areas, such as presence of deep periodontal pockets or furcation areas, scaling and root planning has its limitations and are considered as less effective [47].

Phase II treatment consist of corrective procedures as periodontal surgery; gingivectomy, gingivoplasty and flap operations among others [3]. The last phase (Phase III) of the

conventional periodontal therapy is supportive periodontal therapy. Because of the high risk of recurrent infection with periodontal pathogens in a susceptible host, a life-long supportive care is recommended [3]. As an adjunct to conventional periodontal therapy chemical treatment are used today as well. Chemical plaque control by using oral rinses has been recommended as part of the oral hygiene [47].

The conventional periodontal therapy is normally effective at reducing the inflammation and improve the clinical parameters [25]. However, a long-term success of conventional periodontal therapy requires good cooperation with the patient, which often can be one of the biggest challenges. The necessity to behaviour change in the patient and to make the patient attain and sustain a lifelong good oral hygiene that includes daily plaque removal could be the hardest task for the dentist [9]. To shift the biofilm, and to prevent the worst-case final outcome of the disease that in some cases is total degeneration of the periodontal tissues and tooth loss, depends on regular maintenance and high level of oral hygiene [25]. The bedrock for successful management of periodontal disease is still mechanical plaque removal. In high-risk patients where the critical threshold for plaque accumulation to develop periodontitis is low, primary prevention by adjunctive therapy is preferable [9].

13.3. Standard surgical methods

2- 6 weeks after Phase I (cause- related treatment) is ended, a re- evaluation of the periodontal conditions are done. In cases with mild or localized moderate periodontitis, supplementary active treatment is often not necessary and Phase III (the supportive periodontal treatment) is planned [3]. Infrabony osseous lesions, furcation involvement, recessions or gingival hyperplasia, all conditions that complicates a proper oral hygiene for the patients. Furthermore, these conditions could make the eliminating of the pathogenic microbes and their products in the periodontal pockets through scaling and root planning, with the not surgical periodontal therapy (NSPT) for the dentist inefficient [3] [44]. In these cases, Phase II- corrective procedures may be indicated. Depending on what kind of conditions that complicates the control of biofilm by scaling and root planning, surgical periodontal procedures may be indicated with a determination to improve better visual control, modification of tooth and/or gingival and alveolar bone morphology and at least the aspiration to regenerate periodontal structures. Guided tissue regeneration, flap operations and gingivectomy/ gingivoplasty are all periodontal resections used today [3].

13.4 Topical treatment

It was recently reported in a study using experimental periodontitis and alveolar bone loss in rats that topical application of Polycal a mixture of polycan and calcium gluconate (2:98) has a significant inhibitory effect on periodontitis and related alveolar bone loss in experimental rats mediated by antibacterial, anti-inflammatory, and anti-oxidative activities [48]. A clinical trials study on human should open the door for such use in some clinical cases or even in the incorporation of Polycal in toothpaste preparations.

13.5 Omega-3-fatty acid and essential oil

Anti-inflammatory properties and potential use of omega-3- fatty acid was recently revied by Chee et al., 2016 [25]. A good evidence that dietary supplementation with fish oil could be a cost- effective adjunctive therapy to periodontitis [25]. A study done by Alshehri et al., 2017 [47], assessed the effect of the conventional mechanical periodontal treatment, scaling and root planning, with and without adjunctive us of an essential-oil (EO)-based oral rinse. Their patient group were type-2 diabetic patient with periodontal inflammation. They found a significant reduction in the severity of the traditional periodontal parameters (Plaque index (PI), bleeding on probing (BOP) and probing pocket depth (PPD) in patients who rinsed twice a day with EO-based oral rinse for 30 days [47]. The test group were also tested for haemoglobin A1c (HbA1c), they found significant reduction of HbA1c among the patients who used the essential-oil rinse [47]. They concluded that adjunct use of an EO-based oral rinse was more effective in the treatment of periodontal inflammation in patients with type-2 diabetes compared with using scaling and root planning alone [47].

13.6 Local inhibition of the complement system by Cp40

The compliment system is a system that coordinates the host response to infection or tissue injury. The pathways of immune and inflammatory response are activated, regulated and intensified by the compliment system. The system consists of the classic serum proteins C1-9, pattern- recognition molecules, convertases and other proteases, regulators and receptors [43].

The classical pathway, known as lectin or the alternative pathway, triggers the third complement component, C3, and induce the complement cascade [45]. The network and interacting fluid-phase and cell surface-associated molecules interact with immune mediators. It is seen increased levels of C3 cleavage in the GCF in patients with progression of gingival inflammation and thereby constituting as a potential therapeutic target. The compliment is

also seen in the pathogenesis of other inflammatory or degenerative diseases [43]. If complement is over activated or deregulated, the system forms a major link between infection and inflammatory pathology [45].

Therapeutic blockade of C3 activation /cleavage using Cp40 has blocked both inducible and naturally occurring periodontitis in studies in non-human primates. Significant lower GCF levels of proinflammatory cytokines (e.g., TNF, IL-1B, IL-17) and RANKL as well as reduced osteoclastogenesis in bone where found after treatment with Cp40 in the same study. Once Cp40 is approved in human clinical trials it would patients as adjunctive local treatment rather than a preventive one [43]. Systemic injection of Cp40 in patients will not be advisable in order to avoid affecting the general immune system of the patient.

13.7 Cytokine antagonists

It was known since 1999, that IL-1 induces osteoclast formation and bone-resorbing activity and these activities are inhibited by interleukin-1 receptor antagonist (IL-1Ra) [48]. More recently, Izawa et al., 2014 [49] using a molecular approach and IL-1Ra Knockout (KO) that IL-1Ra deficiency promoted the expression of inflammatory cytokines beyond IL-1 and altered the expression of genes involved in bone resorption in *A. actinomycetemcomitans*-infected osteoblasts. Alterations consistent with rapid bone loss in infected IL-Ra KO mice were also observed for genes expressed in bone formation and calcification. These results, clearly suggest that IL-1Ra could be incorporated in therapeutic preparations for periodontitis disease both in experimental animals and subsequently clinical trials.

13.8 Cytokine antibodies

As mentioned earlier cytokines, APRIL and BLyS were found to be associated with periodontitis, recently using antibodies Abe et at., 2015 [51] found that Ab-mediated neutralization of APRIL or BLyS diminished the number of B cells in the gingival tissue and inhibited bone loss in wild-type, but not in B cell deficient mice. This is because these two cytokines are involved in B-cell growth and differentiation contributing to periodontal bone loss and therefore could be a good target to discover appropriate inhibitors as potential therapeutic agents for periodontitis. It is also interesting to note that antibodies and blocker proteins against APRIL and/or BLyS are being clinically tested for the treatment of systemic lupus erythematosus [52, 53]. The availability of such APRIL-BLyS antibodies and blockers

makes it possible to test them in periodontitis both in experimental animals and subsequently in clinical trials.

13.9 Protease inhibitor

The different microbial proteases are known virulence factors and therefore could be potential targets for overcoming virulent pathogenic bacteria if they can be inhibited. The periodontal pathogen *Porphyromonas gingivalis* produces a unique class of cysteine proteinases, gingipains Arg-gingipain (Rgp) and Lys-gingipain (Kgp). A novel dual inhibitor was discovered (KYT-41) on experimental animals, that effectively inhibits Rgp and KgpA was proven very potent and thus very promising to treat periodontitis caused by *P. gingivalis* after the needed clinical trials on human perhaps in topical formulations [50].

13.10 Glucanase enzymes

It is suggested that glucanase enzymes (dextranase and mutase) may be used as disruption of dental plaque. In studies with human volunteers, in animals or in vitro studies, both dextranase and mutase suppress the accumulation of dental plaque [6].

13.11 Light-activated bacterial killing (Photodynamic Therapy; PDT)

In 1908 Reitz discovered that bacteria can be killed by light in the present of a sensitizing agent, but it is only recently that it has been considered to use this technology to control oral bacterial infections. Research is progressing in this area, and with better retention of the photosensitizer this could be a probable future therapeutic approach [6, 51]. More recently in experimental animals, PDT was an effective alternative to held periodontal health after scaling and root planning (SRP) treatment, and it could improve regeneration and prevent further tissue loss. PDT promoted bone recovery 7 days after periodontal intervention (SRP) [52].

13.12 Stem cell therapy

Indeed, as a result of the new momentum in stem cell research that triggered by the work of Yamanaka on induced pluripotent stem cells (iPSC) as reviewed by him [53] in applications in tissue and organ engineering and several applications in damaged tissue repair. This approach removed all the ethical concerns of using for example embryonic stem cells (ES). Currently the field of iPSC is also having potential applications in the dentistry field including periodontitis repair as recently reviewed by Malhorra 2016 [54], and Tassi et al., 2017 [55].

14. Clinical parameters used today

Early detection of periodontal disease is important for a successful therapy [9]. One of the characteristics of periodontitis is that if it is left untreated, it could ultimately end up with the loss of supra-alveolar fibres, the connective tissue, as well as loss of the supportive alveolar bone. The progressive loss usually proceeds apically [3]. Alveolar bone proper, periodontal ligament, acellular extrinsic fibre cementum (AEFC), several of the tissues of the tooth-supportive apparatus, develop all from the dental follicle and undergoes a differentiation during the odontogenesis that is dependent of cascades of genetic signals and grow factors. Hence, we can't expect regeneration of the same architecture of the tissues [3].The conventional clinical parameters used today to detect periodontitis, is based on the typical cardinal symptoms of inflammation; redness, edematous swelling, pain and impaired function. After probing four or six gingival sites of all teeth, different parameters must be assessed. A periodontal examination includes measuring the probing depth, the clinical attachment level, gingival recession, furcation involvement and tooth mobility. Also the gingival tissues tendency to bleed after being probed with a periodontal probe (with the pressure of 0,2N) is recorded. An inflammatory response in the marginal gingiva and thus bleeding after probing, are evidence for an inflammatory response to supragingival plaque but also depends on the pressure used while probing. The sulcus bleeding should be assessed with different appropriate index system [3].

As the real clinical attachment level cannot be detected by clinical probing, the probing frequently has around 1mm measurement inaccuracy, also the sulcus bleeding after probing depends not just on the presence of plaque, but also the probing pressure. Hence, these conventional parameters used to day often leads to under- or overtreatment [3]. To identify active periodontal lesions the traditional clinical parameters as gingival redness, bleeding on probing and measuring the depth of the pockets, are not very sensitive and have only a moderate specificity [3]. New clinical test systems, that potential could give us more information, have for a long time been anticipated.

It should be said that a detailed diagnosis is important before any therapy, and should be found after a carefully anamnesis, with a medical history and a dental history, followed by an extraoral-, intraoral- and functional examination before the periodontal examination, as described above. Tentative diagnosis or uncertain clinical findings, could be, if appropriate indicated, confirmed with a radiologic examination. A full status radiography is required in

cases of generalized moderate and serve periodontitis, where the different types of bone loss, bone quality and width of the periodontal ligament space among others are used as parameters and assessed [3].

As described in Section 13.2, motivation of the patient may be a big challenge. Thus, both for recording and motivating the patient it is recommended to use disclosure with for example plaque- disclosing tablets to detect the plaque on the teeth before removing the plaque and every time the patients visit for a hygiene control. The findings should be recorded, compared and the patient should be informed and re-motivated [3].

15. Discussion

Periodontitis is a disease characterized by attachment loss of the periodontal tissues [1]. It is now widely accepted that periodontitis is an inflammatory disease caused by the host response to the pathogenic bacterial biofilm [8]. However, a good balance or homeostasis of several contradicting factors is the key to healthy situation and stable gingivitis. Periodontal tissue homeostasis was likened to an 'armed peace' between host, pathogenic periodontal bacteria, and the host immune system [4]. Tipping the homeostatic balance in the microbial community in the oral cavity may cause changes in ecologic conditions and favour the outgrowth of periodontal pathogens, and lead to periodontitis [4].

Cytokines are important proinflammatory molecules that are induced by the body because of stress and bacterial infection. Cytokines have significant role in the pathogenesis of periodontitis. Initiation, progression and resolution of periodontitis include over- and under expression of cytokine genes related to various T-helper subsets. In addition, variations in individual T-helper response subset/genes during disease progression correlated to protective/ destructive outcomes [15]. Although, which cytokines exactly are involved in degeneration and progression of periodontitis and which are involved in the defence are still being clarified by various recent research.

In a recent publication by Zekeridou et al., 2017 [56], the authors found out of 12 cytokines tested in gingival crevicular fluid, after a non-surgical therapy for patients with chronic periodontitis with pocket depth PD≥5 mm, that only an increase in gm‐csf and decrease in il‐1ra levels. Moreover, cytokines Il‐1ra, il‐6, il‐8, il‐17, b‐fgf, gm‐csf, mip‐1β, and TNF‐α I, identified patients with chronic periodontitis in a generalized inflammatory state not limited to the site.
Two cytokines of the TNF ligand superfamily, namely a proliferation-inducing ligand (APRIL) and B-lymphocyte stimulator (BLyS), are up regulated in periodontitis and are associated in periodontal bone loss [57]. Another possible biomarker is TGF-β1, it was found at elevated levels both in the saliva and GCF of periodontal patients [1].

Prolonged stress results in high levels of cortisol and other corticosteroids circulation in the blood [33]. As a result, the body would develop resistance against corticosteroids leading to failure to down regulate inflammatory response and increased risk to the patient.

Destruction of periodontal tissue homeostasis leads to inflammation [8].

Any diseases in the oral cavity affect the systemic health and vice versa, making this topic more complex. Therefore, it is important to understand the molecular basis of periodontitis in order to develop specific molecular early diagnostic tools and target specific effective therapeutics. Also, the increasing awareness of antibiotic resistance seems to be a motivation to develop other ways to treat dental plaques and periodontitis without the use of antibiotics. Some of the promising tools undergoing development as discussed above, include inhibition of the complement system by Cp40, cytokines APRIL-BLyS antibodies, cysteine proteinases inhibitor such as KYT-41, and Photodynamic Therapy; PDT combined with scaling and root planning (SRP) treatment. Moreover, the applications of iPSCs research has proven to have a great potential in medicine as well in the dental field its potential for periodontitis treatment.

16. Conclusions

Periodontitis is a serious gum inflammation and pathogenic bacterial infection that damage the soft tissue and destroys the bone that supports the teeth. Periodontitis may lead to teeth loosening or loss. Poor oral hygiene could lead to the development and growth of a bacterial biofilm that establish itself and evading the host immune system. Infecting bacteria would induce cytokine that further exasperate the infected site and causing inflammation to the host. Good oral hygiene would help keep a healthy homeostasis/balance and preventing the pathogenic bacteria from forming biofilm from establishing itself thus giving the host immune system a chance to fight the pathogenic bacteria. If the bacteria do not establish itself, no host cytokine, stress or inflammation will take place.

Periodontitis can be treated non-surgically or surgically in addition to possible topical treatment. More recent techniques involve the use of specific cytokines antibodies and blockers, the inhibition of specific pathogens proteases, photodynamic therapy following scaling and root planning. For problems of serious loss of tissues and with the increasing understanding of the affect periodontitis has on systemic health, research is being developed to employ induced pluripotent stem cells (iPSCs) at least for lost tissue regeneration.

17. References

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