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GENETIC AND ENVIRONMENTAL FACTORS INVOLVED IN THE DEVELOPMENT OF PERIODONTAL DISEASE

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ABSTRACT
The goal of this work was to make a search on the genetic and environmental factors involved in the development of periodontal disease, in order to have a better understanding and therefore be able to give a better treatment to our patients. One of the most common immune/inflammatory disease of infectious origin is the periodontitis. This disease can have a negative impact in health and life quality, since patients can lose their teeth. Chronic and aggressive periodontal diseases are complex diseases with multifactorial etiology, that result in the destruction of the supporting structures of teeth. The immune system of the host plays an important role in this process. As environmental risk factors are smoking habits, nutrients and food diet, obesity and involved metabolic syndromes, stress and depression.
Concerning genetic risk factors, several studies show the existence of familial aggregation and polymorphisms of diverse genes as well as epigenetic changes have been associated with increased susceptibility to periodontitis.

KEYWORDS: Periodontitis; genetic risk factors; environmental risk factors.

INTRODUCTION
Knowledge about periodontal disease has increase in the last years, and it has been found that its pathogenesis is very complex, and the presence of virulent microorganism is not the only cause of this disorder.[1]

It is well established that periodontal disease is predominantly a bacterial infection involving the dental biofilm or dental plaque. Several studies have identified the main pathogens of the subgingival microbiome and found that the biofilm that causes this disease is site-specific, a complex polymicrobial community, resistant to the host defense mechanisms and to antimicrobial agents.

However, today, it is accepted that the susceptibility to periodontal disease varies greatly between individuals who have the same pathogenic microflora.[2] Years ago, researchers believed that all individuals were equally susceptible for periodontal disease[3], but with the development of new methodology such as being able to asses depth pocket and clinical attachment loss, several epidemiological studies found differences in susceptibility among different individuals.[4] It was found that some individuals throughout their life presented this disease and many others did not, pointing to the possibility of the existence of other risk factors playing an important role in development of periodontitis.[5]

In the last decades, the believed concept concerning risk factors involved in the initiation and progression of periodontal disease has changed drastically. It was first accepted that the periodontal disease was directly triggered by microbial agents. Later, it was identified the importance of the immune system and the inflammatory response of the host to bacterial infection responsible for periodontitis. Nowadays, it is believed that this condition is a multifactorial disease where genetic and environmental factors are involved.[6]

The susceptibility to periodontitis and other inflammatory diseases seems to change according with the interaction of genetic and environmental factors during life. Some risk factors can be modified, such as depression, psychological stress, obesity, smoke and alcohol. These factors increase the inflammatory response and modify gene expression through a variety of biological mechanisms such as epigenetic modifications and gene - environment interaction. Greater knowledge concerning genetic and environmental risk factors can help the development of new therapeutic strategies for these patients, decreasing the risk of tooth- loss[7], that would lead to poor masticatory function and consequent poorer nutritional status, low self-steam and life quality and negative general health impacts.[8,9]

1. Periodontitis etiology and pathogenesis

The major etiological factor triggering gingival inflammation and progression of the inflammatory process is bacterial biofilm. The biofilm is complex and seems to have many ecological advantages, such as environmental protection, nutrients, metabolic cooperation and the acquisition of new genetic traits.[10,11] In 1994, Socransky and Haffajee identified some of the most important microorganisms associated with the periodontal disease such as: *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Campylobacter rectus*, *Micromonas micros*, *Streptococcus intermedius*, *Eubacterium nodatum*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans* and *Prevotella intermedia*. This study also found that some bacteria present in tooth plaque are more pathogenic than others.[12]

Moreover, some studies show that viruses can affect the hemostasis of the microbial community leading to changes in microbial composition.[13] Phages appear to play a crucial role in the evolution, diversity and abundance of bacteria in ecosystems[14,15], and seem to be strongly implicated in the pathogenesis of the periodontal disease (specially herpes virus and cytomegalovirus).[16]

However, periodontal disease is much more complex than biofilm (bacteria or viruses), since genetic risk factors interfere with the host immune and inflammatory response, which can lead to subgingival alterations, favoring the proliferation of periodontal pathogens.[17]

The immune defense system responds to behavioral, biological and environmental factors, such as obesity and smoking. Work of Cekici et al. [18] concluded that chronic inflammation occurs due to dysregulation of the inflammatory and immune process that leads to host mediated connective tissue damage and alveolar bone loss.[18]

2. Aggressive and chronic periodontitis

Classification of periodontal diseases has suffered many changes throughout the years, and the last classification, used for many years, dates from 1999 where periodontitis was reclassified as chronic, aggressive (localized and generalized), necrotizing and as a manifestation of systemic disease.[19]

A lot of studies have emerged since that classification and in 2017 a new classification of periodontitis was stablished. From that date, three forms of periodontitis can be identified: necrotizing periodontitis, periodontitis as a manifestation of systemic disease, and the forms of the disease previously recognized as “chronic” or “aggressive”, now grouped under a single category, “periodontitis”.[19]

Since this is a recent classification and most studies used in this review were published before and have still used previous classification, this work refers to this disease with its old classification.

2.1. Chronic periodontitis

Chronic periodontitis is a set of inflammatory conditions that affect tissues surrounding teeth. It is a plaque-induced disease, where the immune host response plays an important role. Some authors claim that it is initiated by plaque-induced gingivitis, a reversible condition, which, if not treated, can give rise to chronic periodontitis, which is considered irreversible.[20]

Among clinical features of chronic periodontitis, it is possible to find the following: redness or bleeding of gums, loss of insertion to the level of the bone, gingival margin recession, alveolar bone loss. In more advanced cases there is still increased dental mobility, furcation exposure and eventual dental loss.[20]

The prevalence of chronic periodontitis is higher in adults, being directly related to oral hygiene and plaque levels. Some local factors such as smoking, stress and systemic disease can predispose individuals to the development of this condition. These factors will be discussed later.

The biofilm found in chronic periodontitis. contains a large variety of bacteria and subgingival calculus are usually found in this type of periodontitis.[20]

Progression of chronic periodontitis is usually slow and moderate. This condition can be classified according with the extension of the affected region: localized when less than 30% of the sites are affected; or generalized when more than 30% of the sites are affected.[20]

Moreover, the severity of the disease can be classified by measuring the loss of teeth insertion with the probe: mild if the loss is between 1-2 mm, moderate between 3-4 mm and severe when it is 5 mm.[20]

2.2. Aggressive periodontitis

Aggressive periodontitis includes a group of rare, rapidly progressing and frequently severe forms of periodontitis that generally affects young individuals (30 years of age or less), but it can also develop in older people.[21]

Often, clinical manifestations start at an early age in opposition to chronic periodontitis that takes time to develop and occurs at older ages.[21] This means that the etiological agents are able to cause clinical signs in a short period of time.

In aggressive periodontitis a highly virulent microflora including mainly elevated proportions of *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* is present usually together with a high level of susceptibility of the individual, leading to a rapid loss of tooth insertion.[21]

In this type of periodontitis rapid loss of insertion and bone destruction are observed and the number of microbial deposits is incompatible with the destruction gravity and the extent of loss of surrounding tissue.[21]

Aggressive periodontitis can be classified into localized aggressive periodontitis or generalized aggressive periodontitis. The localized type is usually present in first molars and incisives and it does not affect more than two teeth other than those mentioned above.[21]

3. Susceptibility Risk Factors

There is still an enigma concerning the development of this disease because of the selective susceptibility between individuals. A great variety of risk factors are involved in its manifestation and progression, including environmental local factors such as the microbial composition of the plaque, where a diverse variety of microorganisms play an important role.[22]

Other environmental factors associated with lifestyle, such as smoking, nutrition (consumption of sugar, obesity), stress, depression, educational factors, race and inherited genetic variants. can also be involved in the development of this condition.[23-25]

Some studies refer the influence of age and gender on periodontitis development. Aging is associated with the decline of health that increases the risk of chronic diseases like cancer, diabetes and atherosclerosis.[26] This decline in health and physical activity also involves poor dental hygiene that can increase the risk of periodontitis development. This condition can also be associated with the other chronic conditions described before.

Concerning gender, for some time, it has been recognized that males of all ages, ethnic groups and geographic locations have more periodontal disease than women. However, since no inheritance differences have been observed between the two sexes, the increased incidence of periodontitis in males can presumably be a consequence of different lifestyles between men and women, like smoking, alcohol consumption and different food diet habits that can influence the development of this disorder.[27]

3.1. Environmental Risk Factors

Smoking

Smoking tobacco is a behavior with serious consequences for health including oral health. According with the International Classification of Diseases (tenth revision {ICD-10 F17}), when smoking becomes a habit and nicotine dependence is established, it is classified as a chronic medical disorder. Tobacco contains a large amount of toxins associated with cardiovascular diseases, various types of cancer and other chronic diseases, which makes it a potential risk factor for mortality as was found in the study made by de Center for disease control and prevention.[28]

More than 4,000 toxic substances have been found in cigarette smoke, such as oxidizing radicals, carbon monoxide, carcinogens (nitrosamine) and nicotine (which is addictive).[29]

Several studies have shown that periodontal support tissues can suffer adverse effects as a result of smoking, increasing 2 to 5 times the risk of periodontal disease.[30] Some studies found an association between tobacco consumption and the depth of periodontal pockets.[31]

The adverse effects found between tobacco consumption and periodontal disease can be categorized according with the effect of tabaco in microbiota and periodontal pathogens, in gingival blood flow, in the immunological area phagocytosis of polymorphonuclear neutrophils, in cytokines production (interleukin-1), in CD3, CD4 and CD8 and subsets of T cells and in healing of periodontal disease.[32-34]

It has been found that smokers present subgingival infections with specific periodontal pathogens such as *P. gingivalis*, *T. denticola* and *T. forsythia*, which increases both the risk of developing the disease and its progression.[32-34]

Moreover, smoking leads to peripheral vasoconstriction, decreasing gingival bleeding. This can also explain the existence of oxidation in the periodontal pocket and therefore the proliferation of a big number of anaerobic bacteria such as *P. gingivalis* and *T. denticola*.[35-37]

The use of tobacco modifies local and systemic inflammatory response, leading to a higher number of cytokines, achieving an exacerbated inflammatory response.[32,38]

Another evidence linking smoking with the etiopathogenesis of periodontal disease is that nicotine affects neutrophils function, since nicotine enhances neutrophils degranulation, increasing their sensitivity towards bacteria.[39]

Obesity

Obesity and overweight are a serious public health problem and have been increasing in recent years.[40] Several studies have found higher severity and prevalence of periodontal disease in individuals with overweight and obesity.[41]

These conditions have an adverse effect on the general state of health, being responsible for the development of insulin resistance and chronic inflammatory state. It is believed that the association between periodontal disease and obesity results from the chronic state of inflammation present in obesity that increases susceptibility for periodontal disease.[42]

It has been found differences between the oral microbiota of obese individuals and of nonobese. A

significantly higher number of *T. forsythia* in the obese individuals has been found, and the increased presence of this bacteria can lead to increased susceptibility for initiation and progression of periodontal disease.[43]

Moreover, obese individuals developed more often several types of infections (post-operative and nosocomial infections) than normal weight people.[42,44] This can be explained by the participation of adipose tissue in inflammation and immunity.[42,44] In obesity state, adipocytes are metabolically active and release a big variety of proinflammatory factors.[45] In addition, in this state increased number of macrophages are present, that may also contribute to the release of inflammatory mediators.[46]

Work of Genco et al.[47] showed that overweighed individuals presented a higher level of tumor necrosis factor. This study also found that obese subjects with insulin resistance presented a more severe periodontitis, suggesting that the release of this proinflammatory factor by adipose tissue can contribute to insulin resistance and consequently to periodontal disease.[47]

Metabolic Syndrome

The metabolic syndrome is a cluster of metabolic and physiological alterations including excess body fat around the waist and abdominal area, increased blood pressure, elevated plasma glucose and, in certain individuals, altered cholesterol levels. Consequently, this syndrome increases the risk of stroke, diabetes, heart disease and type 2 diabetes.

Risks factors for metabolic syndrome include race, age, obesity, history of diabetes and diseases such as cardiovascular disease, hypertension and polycystic ovary syndrome.[48]

Several studies focused on looking for evidence of association between metabolic syndrome and periodontal disease. One of the first performed studies[49] examined the relationship between five signs/symptoms of metabolic disease and periodontitis: high plasma levels of triglyceride and glucose levels, low level of high-density lipoprotein, obesity and high blood pressure. These researchers found that patients with 4 of these signs/symptoms presented deepest pockets. Moreover, the signs with highest effect were altered high-density lipoprotein and fasting plasma glucose.[49]

The mechanism explaining the association between metabolic syndrome and periodontal disease, seems to be close to the mechanism of obesity since there is a chronic systemic inflammatory response resulting from the presence of some signs such as hyperglycemia, reduced high density lipoprotein and, as mentioned before, obesity. These patients show higher number of proinflammatory molecules causing an elevated systemic inflammatory response. Consequently, the destructive immunopathologic response of these individuals increases, resulting in a higher tissue destruction.[50,51]

However, there are still unanswered questions concerning which symptoms have the strongest association with periodontitis, but there is reasonable evidence to expect that obesity and diabetes will strongly affect the susceptibility or progression of periodontal disease.[49]

Moreover, the relationship between periodontal disease and diabetes applies in both directions. It has been observed that diabetes increases the risk of periodontitis development and it has also been found that after periodontal treatment diabetic patients experience an improvement of plasma glycemic control.[52]

Diabetes

Diabetes mellitus belongs to a group of metabolic diseases that occur in several forms, being characterized by hyperglycaemia that can result from defects in insulin production, insulin action or both. Diabetes is associated with damage and consequent disfunction of several organs.[53,54] Among symptoms developed by individuals with marked hyperglycaemia, are polyuria, polydipsia, weight loss, polyphagia and blurred vision. Patients with chronic hyperglycaemia may have higher susceptibility to infections. Other long-term complications include retinopathy with potential loss of vision, neuropathies with risk of feet ulcers and amputation and nephropathy leading to renal failure.

Considerable evidence has been found for diabetes as a risk factor for development of periodontal diseases. It has been observed that diabetic individuals with periodontal disease, when submitted to periodontitis treatment have a consistent reduction in glycated hemoglobin. For this reason, it is considered the existence of a bidirectional relationship between diabetes and periodontitis since this interrelationship works in both directions.[7]

Persistence of hyperglycaemia leads to an exaggerated immuno-inflammatory response to pathogens of periodontal disease resulting in faster and severe destruction of periodontal tissue.[55-57]

Several studies have been published on the effects on glycaemic control after periodontal treatment. Some studies found an improvement in glycaemia control in patients with type 2 diabetes that were submitted to periodontitis treatment.[57,58] However, no consensus was reached regarding treatment effects in type 1 diabetes.[57,58]

It has also been found that inflammation and infection can lead to insulin resistance.[45,59] This finding supports the effect on glycaemic control of periodontal infection treatment, due to the decrease in inflammation.[45,59]

Nutrients and Food Diet

Many dietary nutrients can play an important role in the development of some inflammatory conditions like low levels of certain micronutrients, especially vitamin D or consumption of monosaccharides and disaccharides, since they may increase the risk of some inflammatory condition such as inflammatory bowel diseases, Crohn's disease and ulcerative colitis.

Several dietary regimes may modify disease symptoms, in part through their actions on the gut microbiota.[60,61]

Other studies have proven that diet can modify the risk of development of chronic diseases such as cardiovascular disease and cancer, but, so far, no specific linkage between diet and periodontal disease was established.[62]

Moreover, the role of dietary calcium in the development of this condition was studied and researchers found statistically significant association between low intake of dietary calcium and more severe level of periodontal diseases (specially in women).[63]

Some studies show that consumption of vitamin D and calcium can help in the treatment of periodontal disease, having beneficial effects on tooth retention.[64]

Singh-Dang et al.[62] emphasized the importance of the interaction between diet and genotype of the individual. This interaction can have a higher connection with the development or severity of periodontitis and not just nutrients alone. So further studies should be made to have a clear answer for the association between dietary and periodontal disease.

Stress and Depression

Studies show evidence of psychological stress playing an important role in the development of major depression. Major depression is a severe widespread psychiatric disorder, life-threatening and highly prevalent, that is becoming one of the major causes of death worldwide.[65] It is the fifth among the leading causes of global disease in the ranking established by Mathers & Loncar.[66]

Chronic stress and depression have negative impacts in the inflammatory response of the host. It can increase the risk of diseases such as diabetes, atherosclerosis, cardiovascular disease and other systemic conditions. Consequently, it can modify the host defense and progression of periodontitis.[67]

Depression can also be associated to changes in health-related behaviors. In this way, it might lead to poor oral hygiene, bad food diet, fewer dental visits and increased smoking, contributing to increased predisposition for periodontal disease.[67]

Moreover, other studies also showed that depression delayed the wound healing by adversely affecting the immune system.[68]

Three studies looked at the biological mechanism of stress in periodontal disease. One of these studies showed that cortisol levels were associated with severity and extent of the disease. Higher cortisol levels were indicative markers of stress and were associated with higher levels of periodontal disease.[69] The second study[70] demonstrated a positive relationship between depression, cortisol and β-endorphins and the development of periodontal disease and consequent tooth loss.

In the third study, researchers observed that patients with salivary cortisol have an important association with attachment loss in periodontal pocket and tooth loss. This can be due to an altered immune response that facilitate increased colonization by pathogenic bacteria and breakdown of the periodontal attachment.[71]

3.2. Genetic Risk Factors

Periodontal disease is initiated mainly by microorganism in the subgingival biofilm, but other risk factors can play an important role in its development and progression. Nowadays, it is evident that genetic factors are also involved in the susceptibility for this disorder.

Genetic factors regulate the innate immune system and certain polymorphisms may affect the effective response of the immune system and render it unable to successfully protect from pathogens assaults. In this way, genetics factor may have a stronger role in aggressive periodontitis than in chronic periodontitis.[72]

Familiar aggregation and twin studies

Many studies have observed that the prevalence of aggressive periodontitis is high among certain families, which show a prevalence of 40 to 50%.[73-75]

Study of Butler[73] observed in a family with one brother and a sister having aggressive periodontitis (also called juvenile periodontitis), the same pattern of bone loss in the first molar and hard and shiny root surfaces with little or no calculus attached in the deep pockets.[73] This last observation is very important since, as discussed above, one of the major etiological factors involved in initiation and progression of inflammation is the bacterial biofilm and, in this study, it is not presented, suggesting that genetic factors must be involved in susceptibility to aggressive periodontitis.[76] This susceptibility points to familiar aggregation but may also reflect that families are exposed to similar environmental factors, such as diet, nutrition, oral hygiene, pollution and smoke (active and passive). Moreover, some pathogens can also cluster in families.[77]

It has been proposed that aggressive periodontitis can be inherited as an autosomal recessive, autosomal dominant or X-linked trait but there are still no clear results.[75]

It has been shown that localized aggressive periodontitis is related to leukocytes disfunction in certain races and that this dysfunction can be genetically inherited.[75]

Concerning chronic periodontitis, few studies on family aggregation have been published, since this type of periodontitis is less common. Nevertheless, one of these studies [78] concluded that parents with poor periodontal health tend to have children with poor periodontal health. These researchers found that both genetic factors and environmental factors are shared in the family but were not able to distinguish between the environmental and genetic factors that predispose to the development of periodontal disease.[78]

Michalowics et al.[77] studied dizygotic and monozygotic twins and concluded the existence of genetic factors in inheritance of periodontal disease. This study found that 38 to 82% of the population variability for measures of depth of probe (periodontal pocket), insertion loss, gingivitis and dental plaque of periodontal disease can be attributed to genetic factors.[77]

Further studies found discordance between twins regarding the severity of attachment loss, suggesting that the role of genetics in the development of chronic periodontitis between twins may have been overestimated.[75,79]

Polymorphisms

Nowadays, researchers are showing a lot of interest in the role of genes and their variants (polymorphisms) in the development of periodontal disease, the response of the host and its progression.

It has been demonstrated that genetic polymorphisms are determinant for the result of a disease, since they can cause changes in gene expression and synthesis of coded proteins or can cause changes the protein structure and lead to alterations in the innate and adaptive immune response. Hence, multiple genes and their polymorphisms may have a contribution to the susceptibility and severity of the disease.[80]

Calprotectin

Calprotectin is a proinflammatory mediator involved in the regulation of several cell processes like cell cycle progression and differentiation. It is known to participate in multiple regulatory functions in periodontitis and other inflammatory diseases such as cystic fibrosis. This molecule belongs to the calcium-binding protein family and is a heterodimer constituted by two subunits (S100A8 and S100A9). It is released by activated neutrophils and leukocytes.

A study was conducted to investigate the relationship between aggressive periodontitis and the level of plasma calprotectin, and to determine the influence of *S100A8* gene polymorphisms and the level of calprotectin in patients with aggressive periodontitis. It was found that individuals with aggressive periodontitis have a significant level of calprotectin in plasma.[81,82] Moreover, the percentage of allele rs3795391 of the *S100A8* gene was significantly higher in patients with aggressive periodontitis than in controls, while the frequency of the rs3806232 polymorphism was lower in patients when compared with controls.[81,82] These differences were observed in male patients. These findings suggest that these two single nucleotide polymorphisms of the *S100A8* gene, might be associated with susceptibility to periodontal disease and gender can play a role in individual predisposition.

It has been demonstrated in other studies that the combined effects of gender and polymorphism can interfere with the susceptibility to certain diseases like lung cancer and heart disease.[83]

Other studies found a higher level of calprotectin in the crevicular fluid than found in plasma. This observation can indicate that abundant calprotectin present in periodontal tissue is the reason for the high level found in plasma.[84,85]

Vitamin D

Vitamin D is a steroid molecule that regulates the expression of many genes. It also plays an important role in bone metabolism and in the homeostasis of phosphorus. The best indicator of vitamin D levels in an individual is blood concentration of the calcifediol hormone.[86]

Liu et al. (2009) found that plasma calcifediol levels in patients with aggressive periodontitis were significantly higher than in healthy controls.[87]

Vitamin D has pleiotropic effects, and this explains the widespread presence of vitamin D receptors (VDRs) throughout the body. VDR receptor is not only found in tissues involved in calcium homeostasis but also in a variety of cell lines involved primarily in immune regulation, including the mononuclear cells, dendritic cells, antigen-presenting cells, and activated B lymphocytes and CD4+ T cells. Therefore, it is thought that it can play an important role in inflammatory and autoimmune disease. Several reports link low vitamin D levels with various autoimmune diseases.[88]

Several studies have investigated the association between VDR polymorphisms and periodontitis in different populations. These studies observed that the frequency of the rs731236 allele, the less abundant allele in the population, was significantly higher in patients with periodontitis than in controls. These findings were seen

in Caucasian individuals from the UK, Chinese and Italians.[89-91]

However, Park et al. [92] did not observe association of that polymorphism with susceptibility to aggressive periodontitis in Korean individuals. On the other hand, these researchers found higher levels of another polymorphism (rs2228570) in patients with this condition.[92]

Another study found the association of the rs731236 allele with chronic periodontitis but not with aggressive periodontitis in an Asiatic population, but this was not observed in white individuals.[93] Moreover, the rs2228570 polymorphism was found to be a risk factor for aggressive periodontitis in the same population.[93] Other tested polymorphism did not show significative association with susceptibility to any type of periodontitis.[93]

Cytokines

Interleukin-1 is a potent immunomodulator and proinflammatory cytokine. This cytokine has been associated with the pathogenesis of autoimmune and infectious diseases. It has also been suggested as a risk factor for aggressive periodontitis.

Many studies have investigated the association of aggressive periodontitis and interleukin-1 polymorphism. Results were not consistent or did not have enough evidence of this association in Caucasian individuals.[94] However, significant association in other ethnic groups was observed. This was the case of the study of Guzeldemir et al.[95] where *IL-1* gene polymorphisms were associated with increased susceptibility to aggressive periodontitis in the Turkish population.

Another cytokine possibly involved in susceptibility to periodontitis is interleukin-6. This cytokine also has proinflammatory and inflammatory functions. Some studies have been conducted to evaluate the association of *IL6* gene polymorphism with periodontal disease.

One of these studies observed that *IL-6* -1363 polymorphism was associated with aggressive periodontitis in patients from all ethnicities, while -1480 and -6106 polymorphisms were present in Caucasian individuals with localized aggressive periodontitis.[96] Moreover, a meta-analysis study performed by Shao et al. [97] concluded that the *IL-6* -174 allele did not interfere with chronic periodontitis, however, was associated with increased risk of the aggressive form. On the other hand, the -572 polymorphism affected the pathogenesis of both types of periodontitis.[97]

Another work of Nibali et al.[98] concluded that *IL-6* polymorphisms were moderately associated with susceptibility to periodontal disease. In Caucasians, -1480 and -6106 polymorphisms slightly increased the risk of periodontitis and this association was stronger for localized aggressive periodontitis.[98] These researchers believed that this association resulted from their influence on IL-6 tissue levels.

Moreover, Nibali et al.[99] were able to associate some IL-6 polymorphisms with the presence of certain bacterial species in subgingival biofilms of individuals with severe forms of periodontitis. The *IL-6* -6106 polymorphism was associated with the presence of *A. actinomycetemcomitans* and concomitant presence of *A. actinomycetemcomitans* and *P. gingivalis*, as well as the *IL-6* -174 polymorphism.[99] This data agrees with the hypothesis of periodontitis susceptibility being increased by a complex interaction between the microbiome and the host genome.

Epigenetics

Epigenetics refers to the interactions between environmental factors and genes that influence in their expression. These interactions are independent on DNA sequences and occur mainly by DNA methylation and changes in the chromatin structure.

As referred by Ubeda & Wilkins[100], epigenetic modifications can be established in different cell lines and can be responsible for different expressions in different tissue types.[100]

Usually, DNA methylation occurs in a region of DNA that contains cytosine followed by guanine nucleotides (CpG islands) in the linear sequence of bases along its 5' → 3' direction.[101]

It is known that methylation of a gene is associated with inactivation of its expression and that patterns of methylation can be inherited from the mother or acquired during life. Acquired methylation can be associated with systemic exposure such as smoking, that seems to affect the inflammatory state of the periodontal tissue in response to injury or infection.[101]

Work of Zhang et al.[102] showed evidences of post-translational methylation of genes, in periodontal disease. These researchers reported that chronically inflamed periodontal tissues exhibited an increased generalized methylation affecting levels of prostaglandins, as compared with non-inflamed periodontal tissues. This observation indicates that this effect can be significant for the chronicity of the periodontal disease.[102]

It has been suggested that the presence of bacteria can trigger changes in the epigenome of epithelial cells and subsequently in inflammatory cells, by inducing alterations in signalling pathways and gene expression. In fact, pathogens usually associated with periodontitis such as *P. gingivalis* and *F. nucleatum* can induce histone acetylation. Furthermore, activation of pathogen recognition receptors and Toll-like receptors (TLR) by these bacteria further contribute to histone modifications

in oral epithelial cells.[103] Toll-like receptors have an important role on the activation of the innate immune response, since they are able to recognize pathogen molecules such as bacterial lipopolysaccharide. So, dysregulation of the expression of these receptors will probably affect host immune response towards periodontal pathogens and can lead to increased inflammation and hence periodontitis susceptibility. Work of Oliveira et al.[104] did not see significative differences in the methylation pattern of the *TLR4* and *TLR2* genes between healthy individuals and periodontitis patients. However, study of Faria Amormino et al.[105] observed a higher degree of methylation in the *TLR2* gene in periodontitis patients when compared with controls, that was directly related with the number of inflammatory cells. These findings indicate that differences in these studies results probably result from the degree of inflammation of sample cells used.

Another study showed that the presence of *P. gingivalis* in gingival epithelial cells induced DNA methylation.[106] Martins et al.[103] observed that the pathogen besides inducing histone acetylation, also activated the transcription factor nuclear factor-kb (NFkB) in oral epithelial cells. This transcription factor is involved in activation of the innate immune system, osteoclast differentiation and induces matrix metalloproteinases and adhesion molecules.[103] Moreover, it was seen that NFkB binding sites in the promoter region of the *LTR2* gene were methylated, probably affecting the binding of that transcription factor.[104]

Takai et al.[107] observed that long-term treatment of periodontal fibroblast cells with P. gingivalis leads to hypermethylation of diverse genes involved in the formation of the extracellular matrix. It is believed that this hypermethylation reduces the production of matrix proteins such as cell surface receptors, affecting in this way adhesion of cells to the extracellular matrix and consequent loss of supporting tissue observed in periodontitis.

Other studies observed a decreased level of methylation in promoter regions of genes coding for cytokines in gingival tissue from patients with aggressive periodontitis.[108,109] This is in accordance with the fact that cytokines play an important role in the host immune response towards infecting bacteria. Schulz et al.[109] suggested that the increased gene expression resulting from their hypomethylation may be related to the loss of periodontal attachment in periodontal disease.

Data even showed that these epigenetic changes can differ among different tissues from the same patient.[110,111]

DISCUSSION AND CONCLUSION

Previously it was believed that periodontal disease was only developed thanks to microbial factors and that all individuals were equally susceptible to its development. This believe changed gradually due to years of research that observed that some individuals do not suffer from this disease throughout their lives while others developed it and with different degrees of severity. These observations allowed to accept that the host immune response must play an important role in this condition.

Nowadays, this disease is seen as a multifactorial disorder, in which many environmental and genetic factors contribute to the susceptibility and development of periodontal disease.

This work allowed the identification of factors that affect the susceptibility and development of periodontitis. Among these factors is tobacco that can increase its incidence 2 to 5 times. Smoking affects oral microbiome, the gingival blood flow, and also leads to vasoconstriction, leading to oxidation in the periodontal pocket. All these changes exacerbate the immune response leading to higher release of cytokines and affecting neutrophils function.

A similar mechanism is observed in cases of individuals with obesity or metabolic syndrome that increases their susceptibility to periodontitis due to a chronic inflammatory response. Obese individuals show the release of a variety of proinflammatory factors due to activation of adipocytes while in the metabolic syndrome this same release was found, but due to the hyperglycemic state, to low levels of high-density lipoprotein and to obesity.

Food diet regimen can also interfere with periodontitis susceptibility being affected by low calcium consumption. Other factors that have been associated with periodontal disease are stress and depression. High levels of cortisol in saliva within the periodontal pockets of the patient with periodontitis have been found, being this hormone indicative of a stress condition. Depression interferes with mood and attitude of individuals and can lead to decreased health care and oral hygiene that can contribute to periodontitis. Depression may also affect the immune response of the organism, delaying bone healing.

Concerning genetic factors, it has been found that polymorphisms of certain genes can increase periodontal disease susceptibility. This is the case of the S100A8 gene coding for one subunit of calprotectin. Some polymorphisms of this gene are preferentially found in patients with aggressive periodontitis. Another example is the case of polymorphisms of the gene coding for vitamin D receptors.

Many studies also point out the relationship between polymorphisms of genes coding for some interleukins and the susceptibility to periodontal disease, since these molecules are potent immunomodulators and proinflammatory cytokines.

Moreover, epigenetic factors such as DNA methylation and histone acetylation that alters chromatin structure are known to affect gene expression. Studies have found that chronically inflamed periodontal tissue had increased levels of methylation in genes leading to altered levels of prostaglandins that may favor the chronicity of this disease. Several studies indicate that such epigenetic changes influence production of signaling molecules and their molecular signaling pathways, affecting host immune response and influencing tissue degradation during periodontal disease.

All these factors can affect the patient's susceptibility to periodontal disease. So, the elimination of some of the environmental factors that can be modified, can help in the combat of periodontitis.

Knowledge about the involved etiological factors can help to better understand this multifactorial disease, that should be treated as such, trying to reduce factors that interfere with the applied treatment. The dental doctor should suggest to patients several changes in lifestyle such as diet, exercise, stop smoking, stress reduction, helping in this way in prevention of periodontitis.

A lot of progress in the genetic field is still needed, aiming that one day it will be possible to determine the susceptibility of each person to a certain disease such as periodontitis and hence help in preventing its development.

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