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Pathogenesis of Periodontitis: An Overview

Wael Khalil [a*], Georges Aoun [b], Marwa Jaffal [c], Maryse Nassif [d] and Mazen Kurban [e]

[a] Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Lebanese University, Lebanon.
[b] Department of Oral Medicine and Maxillofacial Radiology, Faculty of Dental Medicine, Lebanese University, Lebanon.
[c] Abdelkarim Al-Khalil Street, Chyah, Beirut, Lebanon.
[d] Department of Prosthodontics, Faculty of Dental Medicine, Saint-Joseph University, Lebanon.
[e] Departments of Dermatology and Biochemistry and Molecular Genetics, American University of Beirut, Lebanon.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Periodontitis is the severe inflammation of the tissues surrounding and supporting the tooth like gingiva, alveolar bone, and periodontal ligament. Many studies have tried to explain the pathogenesis of periodontitis focusing in many parameters such as the roles of the host pathways, the molecular and genetic factors, the bacterial biofilm mass, and the patient's susceptibility.
The main objective of this article is to review the most relevant and comprehensive models of the pathophysiology of periodontitis and emphasize factors including the presence of systemic conditions and genetic that play a crucial role in the pathogenesis of chronic and aggressive periodontitis.

Keywords: Pathogenesis; periodontitis; genetic factors; systemic conditions; host pathways; molecular factors; bacterial biofilm.

**Corresponding author: E-mail: waelkhalil74@hotmail.com;*

1. INTRODUCTION

Periodontitis is the severe inflammation of the tissues surrounding and supporting the tooth [1]. Many classifications have been described for periodontitis, two are the most relevant.

The first is based on pathogenesis (classification of 1999) and include: a) necrotizing periodontitis, b) chronic periodontitis, c) aggressive periodontitis, and d) periodontitis as a manifestation of a systemic disease.

As for the second one, it is based on staging (2017).

All forms of periodontitis, no matter the type or classification, can lead eventually to tooth loss if left untreated [2] (Fig. 1).

Periodontal pockets that are considered characteristics of the disease become evident. They result from severe inflammation leading to alveolar bone loss [3] (Fig. 2).

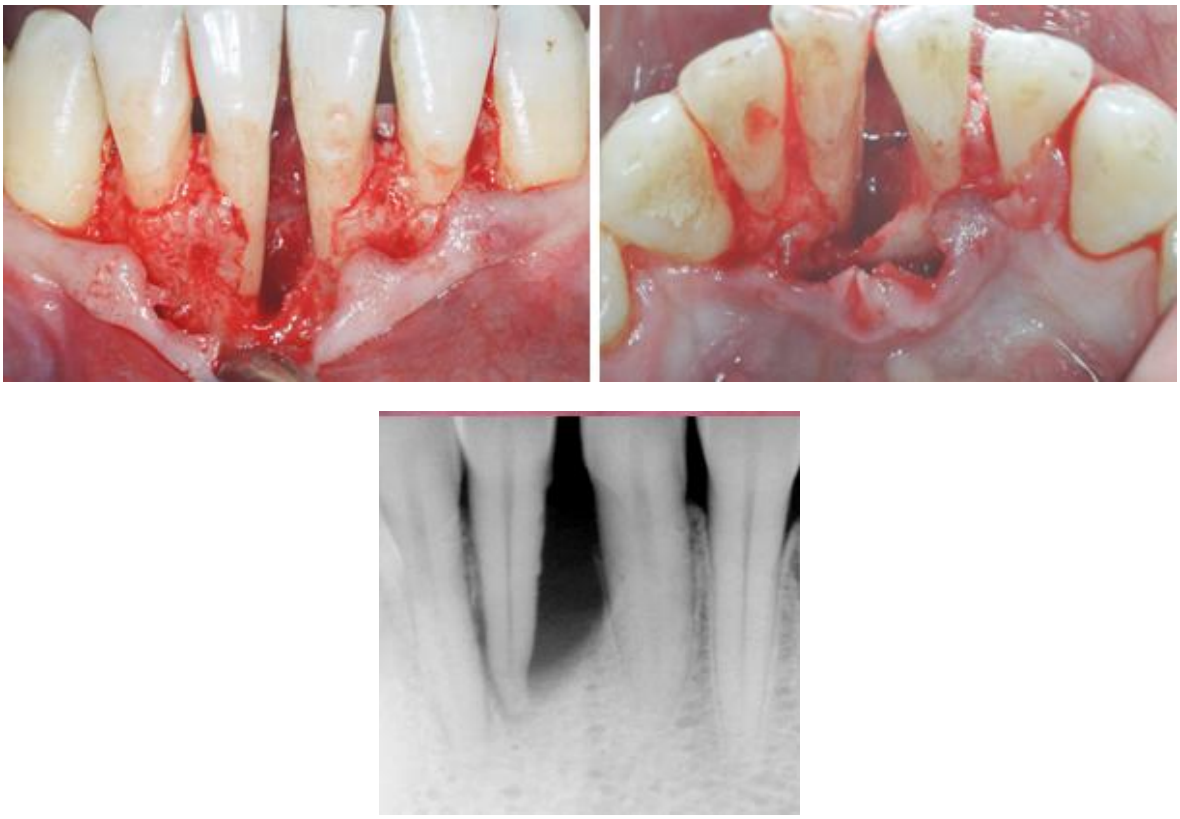

Fig. 1. Localized periodontitis

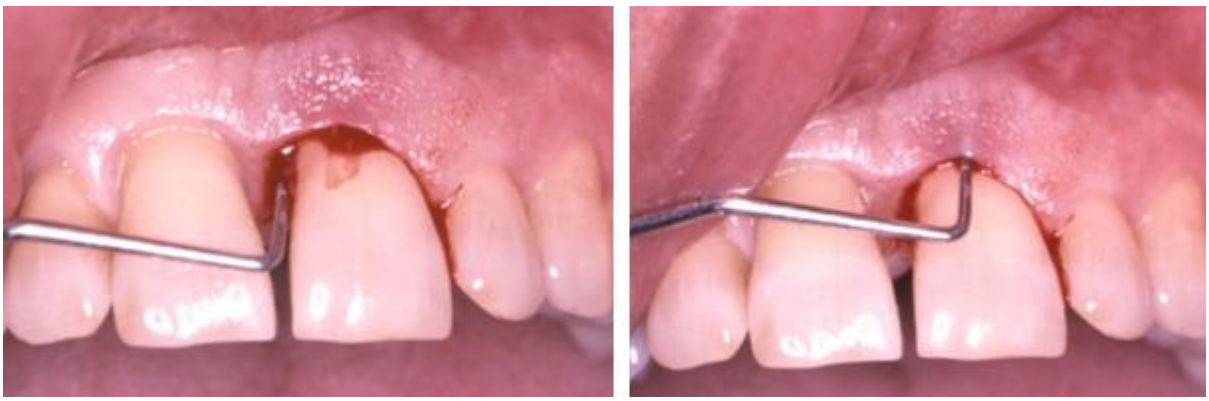

Fig. 2. Periodontal pockets

2. PATHOGENESIS

At the time where many studies aimed to explain the physiopathology of periodontitis, we would like to focus on two main models, which are the most comprehensive.

2.1 Page and Kornman Model

In 1997, Page and Kornman considered a model for pathogenesis of periodontitis which was based on findings from previous 10-15 years [4]. In their model, the authors focused on two major points:

- The role of the host pathways.
- The role of molecular and genetic factors.

According to the authors, periodontitis had been described as a series of "cellular" events that affect the oral cavity and surrounding tissue. Even though the authors approve on the previous approach which always related the pathogenesis to host mechanisms, they claimed that further discoveries should be done to update this concept. To clarify their point, they mentioned the role of the host immune response in triggering the damage to the tooth supporting tissues. In that time, this idea was considered revolutionary since the immune response had been always considered as a protective agent for the tissues against aggression and damage. Yet, Page and Kornman insisted on their observations and mentioned the role of both innate and adaptive immune responses in initiating and supporting the destructive feature of periodontitis. On the other hand, microbes, mainly bacteria, are for sure essential for the initiation of the immune response characteristic for the disease; however the extent of the damage resulting from this inflammation is greatly affected by the host immune mechanisms [4].

In addition to that, the authors described the presence of risk factors that may predispose the individual for more damage in periodontal disease. They found out, with the help of the advance in genetic research, that genetic predisposition may be a risk factor with great impact on the immune reaction. Furthermore, they described some environmental factors as risk factors that can contribute to the pathogenesis of the disease.

Now from the bacterial side of the story, this model states that microbes attack the host immunity through antigens and lipopolysaccharides (LPS). In return, the host defends itself by antibodies and polymorphonuclear cells (PMNs). Definitely, the environmental, acquired, and genetic factors can control the degree and extent of the host's response against the microbial aggression by inducing and influencing the release of cytokines, prostanoids, and matrix metalloproteinases (MMPs). Similarly, these risk factors, whether environmental, genetic, or acquired, affect also the bone and connective tissue metabolism, and therefore, the extent of tissue destruction and clinical symptoms of periodontitis. In their model, the authors mentioned "tobacco smoking" as an environmental risk factor for periodontitis [4].

2.2 Meyle and Chapple Model

According to Meyle and Chapple, the pathogenesis of periodontitis depends mainly on two main factors: the bacterial biofilm mass and the patient's susceptibility. Therefore, we distinguish three scenarios that explain this pathogenesis: the first scenario is characterized by symbiosis in which the biofilm is limited and contains gram positive aerobic bacteria that release N-formylmethionyl-leucyl-phenylalanine (FMLP). The PMNs of the innate immune system react by releasing complement molecules leading to reversible and spontaneous inflammation resolved when plaque is removed without any intervention. In case this biofilm extends in time and space, the second scenario; incipient dysbiosis, occurs where gram negative anaerobic bacteria, represented by *Fusobacterium,* release antigens and LPS. The immune reaction in this case is proportionate where the adaptive immune system, represented by B and T lymphocytes, reacts by releasing antibodies leading to gingival inflammation. This inflammation is reversible and resolves when plaque is removed by good brushing or dentist intervention. In susceptible patients; in which some genetic, epigenetic, lifestyle and environmental factors exist like systemic disease, smoking, malocclusion etc…, this dysbiosis and extended biofilm will cause more harsh tissue damage. These damaged cells will release damage-associated molecular pattern (DAMPs) and haem which will lead, in one hand, to a disproportionate inflammatory reaction represented by cytokines, prostanoids, MMPs, and reactive oxygen species stress (ROSS). On the other hand, haem production will favor the growth of *Porphyromonas* bacteria. All these factors will lead to an irreversible non-resolving

inflammation and bone destruction typical for periodontal disease. The Fig. 3 schematizes the Meyle and Chapple model of pathogenesis of periodontitis [5] (Fig. 3).

In their explanation of the host-biofilm relationship, Meyle and Chapple focus on 3 main points: the oral biofilm, the host response and local inflammation, and the types and behavior of different immune cells.

2.2.1 The oral biofilm

The oral biofilm is not composed exclusively of the specific bacterial species that characterize periodontitis; it is rather composed of different microbial types in which viruses may exist too. Surprisingly, many bacterial species that characterize the healthy oral cavity are also abundant within the periodontal biofilm. Therefore, periodontitis is not caused by specific microbes, but it's the disequilibrium that occurs between the host and the existing microbes of the oral biofilm that initiate and maintain the inflammatory pathways typical for periodontitis. In other words, microbes that do not cause harm in normal conditions might cause inflammation when the microbe-host equilibrium is not maintained. However, the reasons behind this disruption of equilibrium are still unclear in the literature, but some studies suggest that some oral commensal bacteria act as protectors for this equilibrium, thus preventing dysbiosis.

The aim behind this model was not to differentiate between the normal commensal and the pathogenic bacteria; it rather focused on the previously mentioned equilibrium. In addition, as both commensals and pathogenic bacteria are present in the oral biofilm, distinguishing and separating between them is quite difficult. Therefore, this model is concentrated on the dysbiosis and the reasons behind it are rather than on the specific microbes that have already a confirmed role in periodontitis.

In the same context, this model also discussed the role of some ubiquitous viruses. These viruses include cytomegalovirus, Epstein Barr virus, and herpes simplex virus 1 (HSV1). HSV1 is known by its ability to reside in the trigeminal ganglion without causing a disease until the host becomes susceptible or the tissue becomes damaged. This virus is considered a good example of viruses that may become dysbiotic

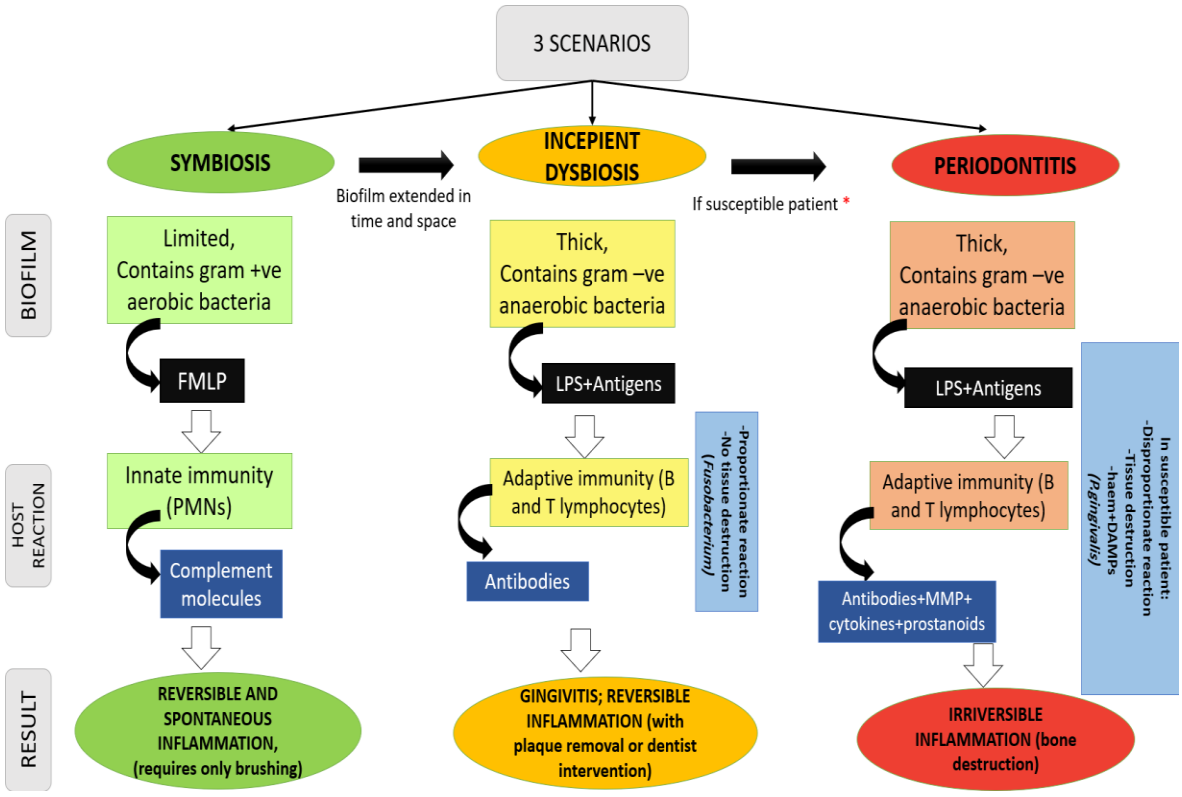

Fig. 3. Schema summarizing the pathogenesis of periodontitis according to Meyle and Chapple model

when the adequate conditions meet. Interestingly, HSV1 has been shown to be abundant in periodontal lesions compared to healthy oral cavity. Yet, the mechanisms through which viruses can activate the inflammatory pathways are diverse. One explanation suggests that viruses can activate interferon type 1 in neutrophils, and another one states their ability to induce complex systemic effects especially in immunocompromised patients. Indeed, the complex systemic mechanisms require further studies and investigations.

2.2.2 The host response and local inflammation

In their discussion of the host response, Meyle and Chapple describe the balance between a "proportionate" and a "disproportionate" host responses. The proportionate response is associated with clinical health, while the disproportionate response is characterized by tissue destruction resulting from disruption of the balance between microorganisms and host immunity. However, the proportionate or the controlled response may become disproportionate. It has been suggested that this may be caused by activation of pathways that lead to leakage of nutrients needed for microbial growth through their specific capillaries. This will lead to increased microbial growth that when combined with the release of certain endogenous molecules induce the secretion of pro-inflammatory cytokines and interleukins mediated by caspase-1. As a result of histamine release, vasodilation occurs which allows the migration of neutrophils to the biofilm site. In this context, many studies, conducted on both humans and mice, have shown that neutrophils migration is necessary for the maintenance of healthy periodontal tissues. However, this neutrophilic migration requires regulation which is achieved by the regulatory endothelial protein, DEL-1. On the contrary, an uncontrolled diapedesis or chemotactic migration of neutrophils is coupled with compliment release by the dilated capillaries. This will lead to the production of serum tissue fluid which has a role in carrying inflammatory peptides like antibodies along with other agents into the gingival crevice. Therefore, this will be manifested by swelling and retention of the gingival crevicular fluid within the sulcus.

It should be noted that some microbes can increase the severity of inflammatory response by activating more complement proteins and macrophages. However, some individuals may have an exaggerated inflammatory response due to the local environment regardless the pathogenicity of the microbes. To clarify, Meyle and Chapple give the example of diabetes, where the metabolic dysregulation can increase the inflammation and tissue destruction in spite of the type of microbes involved in the process.

2.2.3 The types and behavior of different immune cells

In their discussion of cells, the authors of this model mentioned 3 main groups of cells: Keratinocytes/Dendritic cells, Natural Killer cells, and T/B lymphocytes.

a) **Keratinocytes/Dentritic cells:** In addition to their role as "physical barriers", keratinocytes can play an important role in eliciting and maintaining inflammation. When they get activated by bacteria and viruses, they activate the release of pro-inflammatory cytokines such as interleukin 1 alpha, interleukin 1 beta, interleukin 6, tumor necrosis factor, and defensins. Mentioning defensins, Meyle and Chapple discuss the activation of dendritic cells which are very important antigen presenting cells and critical regulators of both innate and adaptive immune responses. However, the role of dendritic cells whether in the induction or prevention of inflammation is uneasy to be determined because they have also a role in controlling the immunity. At the same time, the up-regulation of their function may lead to as adverse inflammatory response characteristic of periodontitis.

b) **Natural Killer cells:** Concerning Natural Killer cells, the authors focused on interferon gamma. A study done on mice showed that groups lacking interferon gamma have shown decreased bone loss following a *Porphyromonas gingivalis* infection. To explain, interferon gamma has been already known by its role in growth and activation of Natural Killer cells. Therefore, it can be hypothesized that this group of immune cells plays a major role in the pathogenesis of periodontal disease.

c) **T and B lymphocytes:** Taking into consideration the different subsets of lymphocytes that are involved in immunity, it would be vital to look at the functions of these in periodontitis. Moreover, it is essential to identify the different cytokines which are involved in the activation of the different subsets.

On the other hand, many other interleukins have been identified to be secreted by the mentioned subsets of lymphocytes. However, for the sake of the specificity of the topic, we focused on the interleukins which may have roles in periodontitis.

Studies have shown that regulatory T-lymphocytes (TReg lymphocytes) may be present within the periodontal tissues. In addition to their states immunosuppressive function, these cells may contribute to many diseases and conditions such as cancer and autoimmune disorders. However, even with all the established studies, further investigations should be done in the context of their role in periodontal disease.

2.3 Other Factors Contributing in Pathogenesis of Periodontitis

Within the pursuit of explanation of the pathogenesis of periodontitis, new studies have discussed other important factors that may be involved in this disease. Even if these factors are poorly discussed in the literature and require further investigation, it is essential for us to mention them here as current researches are being conducted. These factors include the role of Micro RNAs and the role of periodontally driven systemic inflammation.

2.3.1 Micro RNAs

These molecules act by binding and degrading the messenger RNA (mRNA), thus they negatively regulate the protein expression. They have been found in the periodontal tissues, but their exact role in the contribution of periodontitis is still unclear. However, studies have clarified till now that micro RNA can induce the dysregulation of both innate and adaptive immune responses, and therefore, they can facilitate the development of a chronic inflammatory state [6-8]. As the gingival tissue is not made up of a single cell type but of a mixture of cell types and subsets, identifying micro RNA molecules in the gingival tissues and their actions would not help in determining their specific role and pathways in which they are involved in. Moreover, as these molecules are known for their roles in cancer and some systemic disease, this would shed the light on common pathogenesis pathways between periodontitis and other systemic conditions through micro mRNA molecules [5].

2.3.2 Periodontal driven systemic inflammation

As previously mentioned, periodontitis may be associated or even caused by several systemic diseases. However, some systemic conditions may be driven and caused by periodontitis by a mechanism called “the metastatic inflammation”. This inflammatory state either involves the liver and causes the release of C-reactive protein (CRP), or activates the dissemination of pathogens to the systemic circulation. Indeed, both of these observations require further verification for their ability to cause systemic disease.

Whenever an inflammation starts in the oral cavity, the first thing to happen is the crawling of neutrophils to the injury site. This is what happens in case of gingivitis or periodontitis where injury site is represented by the site of plaque or microbial growth.

Neutrophils have a major role in the initiation and the progression of inflammation that characterizes gingivitis and periodontitis. The interaction between the endothelial cells and neutrophils is a crucial determinant of the speed and efficiency of the inflammatory response. Additionally, macrophages and dendritic cells are also involved [9,10]. Consequently, an orchestrated system of cytokines attracts lymphocytes to the injury site. In addition to Natural Killer cells, B cells, helper T cells, and cytotoxic T cells, regulatory T cells are also detected in the sites of injury [11-13]. This sheds the light on the possible involvement of this subset of T lymphocytes in the pathophysiology of periodontitis, probably by creating a chronic inflammatory state. This indeed deserves future investigation, especially that interleukin 10 (Il-10) was shown to be abundantly present in periodontal oral cavities [14].

At this context, understanding the mechanisms involved in the activation of innate immune cells (neutrophils, monocytes and dendritic cells) is crucial for comprehending the pathways involved in increasing, as well as decreasing, the severity of the inflammatory response characteristic of gingivitis and periodontitis. More specifically, lights should be shed on the markers involved in the crawling and extravasation of neutrophils that can regulate the extent and severity of inflammation and its progression to alveolar bone loss characteristic of periodontitis [15]. So, we will discuss the initiation of the inflammatory

response by discussing the recruitment and activation of neutrophils.

In fact, as neutrophils adhere to the endothelial cell surface of blood vessels, an interaction between them is initiated by high affinity adhesion between endothelial cell surface markers, the P and E selectins with glycoproteins on the surface of neutrophils. This secures a site for transmigration of neutrophils within blood vessels. The main neutrophilic macromolecule involved in this interaction is the lymphocyte-function-associated antigen 1: (LFA-1) integrin (CD11a/CD18). Through this molecule, neutrophils interact with endothelial factors, and this will subsequently regulate the crawling of neutrophils [16].

Furthermore, the extravasation of neutrophils which is regulated by cytokines, such as chemokines; these are the major cytokines involved and they act by regulating the expression of endothelial molecules. Moreover, some tissue derived chemokines can also regulate the expression of the aforementioned LFA-1 integrin, and hence regulate the extravasation of neutrophils [17,18].

In addition, recent studies have shown that the developmental endothelial locus (Del-1) may have a role in the transmigration of neutrophils in response to infection. It has been shown that deficiency in this marker led to severe inflammation accompanied with severe alveolar bone loss. To confirm this, local treatment by recombinant Del-1 stopped the alveolar bone resorption and prevented further neutrophilic infiltration [19].

Another signaling molecule that affects the activity and migration of neutrophils is interleukin 17 (IL-17). Their activity is based on the activation and recruitment of neutrophils to the inflammation site, more specifically; they activate the phagocytic/antigen presentation of neutrophils [20].

These two molecules, Del-1 and IL-17, function in opposite manners. As IL-17 acts as an activator of inflammation, Del-1 inhibits the neutrophilic activity; hence it decreases the inflammation levels [21].

However, it is important to keep in mind that the inflammatory response is in the first place caused by the microbes growing in the dental plaque [22]. Therefore, it is very important to study and discuss the roles of the microbes themselves in the activation and control of the immune response.

What is surely known is that the interaction between microbes and immune cells involves surface receptors on the immune cells. These are known as pattern recognition receptors (PRRs), which in turn will recognize the conserved molecular structures, the PAMPS, on the microbial surface of the pathogens. For this inflammatory response to progress and continue, the host immune cells must recognize nucleic acids released by bacteria, viruses, and the host cells as well. This is done, along with many others, by Toll like receptor-9 (TLR-9) which will activate the innate immune cells involved in inflammation after detecting the microbial DNA. However, genetic polymorphism in this regard is very important and affects the level of inflammation indeed. Any genetic variation in TLR-9 gene for example will result in different immune response against microbes of the oral cavity between individuals. This may give a possible explanation for the different initiation and progression of periodontal disease among different individuals having similar lifestyle habits [16,23].

2.3.3 Genetic factors

It is well-known that aggressive periodontitis is more strongly associated with genetic factors compared to chronic periodontitis. Even though some genetic factors might direct an association between chronic periodontitis and systemic diseases; the genetic factors that are associated with aggressive periodontitis are clearer and more straightforward.

Previously conducted studies support the fact of genetic factors related to aggressive periodontitis (AgP), however, it's unlikely that all forms of AgP share the same genetic variation [24,25]. This idea is based on the fact that several general diseases and syndromes share the same clinical features but have different genetic background. Based on the formerly confirmed knowledge of how AgP affected subjects have defective PMNs functions with increased levels of inflammatory mediators responding to LPS stimulation, several gene modifications on different loci were proposed to be the origin of AgP.

It has been suggested that allelic variations in the Fc receptor for IgG2 may play a major role in decreasing the PMNs ability to fight

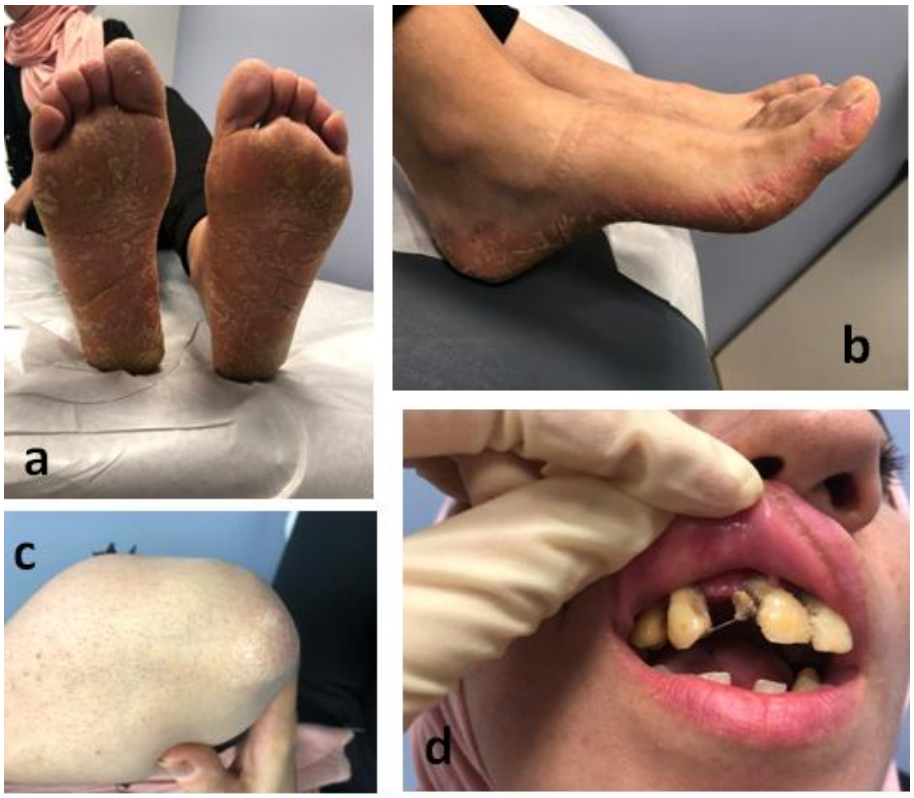

Fig. 4(a, b and c). skin redness and thickening; d). aggressive periodontitis

Actinobacillus actinomycetemcomitans infections. Moreover, PMNs expressing the R131 allotype of FcγRIIa show a weak phagocytic activity against *Actinobacillus actinomy-cetemcomitans* [26].

Going more deeply into the genetic variations, the most famous genetic variant causing AgP was the Intronic SNP rs1537415 in glycosyl transferase 6 domain containing 1 (GLT6D1). It was identified using GWAS (Genome wide association study). In addition, genes governing the immune response have been also investigated as AgP is an inflammatory disease. The most famously discussed are defensins, in which rs2738058 gene of both variants: defensin α1 and α3 has been shown to carry a genetic risk for AgP. Similarly, other immune-related genes including IL-10, CXCL5, and PF4 were proved to be related to AgP too. Nevertheless, as the involvement of IL-10 in many immune functions was confirmed by many studies, it would be plausible to hypothesize that those immune functions can be physiologically related to the pathogenesis of AgP. These functions may be related to immunosuppression governed by Regulatory T cells (Treg cells).

Recently, using Whole-Exome Sequencing followed by functional analysis was very helpful in identifying genetic risk factors for AgP. As a result, three factors have been identified:

- G protein coupled receptor 126 (GPR126), where the protein receptor encoded by this gene is already known to elevate cyclic adenosine monophosphate (cAMP) and to activate protein kinase A (PKA). The cAMP/PKA pathways are involved in inhibiting bone remodeling following periodontal damage.
- Sphingomyelin Phosphodieasterase 3 (SMPD3): The protein encoded by a variant of this gene, namely sphingomyelinase 2 (nSMase 2) is greatly involved in skeletal development as well as in the differentiation of alveolar bone and odontoblasts.

Genes associated with Papillon-Lefèvre Syndrome (PLS): PLS is an autosomal recessive syndrome first described by two French physicians: Papillon and Lefèvre in 1924. It is characterized by redness, thickening of soles and palms, and aggressive periodontitis [27] (Fig. 4). The defect is genetic and it happens in

chromosome 11q14.1q14.3, specifically in Cathepsin C [28].

3. CONCLUSION

Even though periodontitis is specifically manifested by loss of tooth-supporting tissues, it should not be considered as an exclusively localized tooth-related infection. This disease should be rather investigated and considered as a systemic disease based on the facts and links it showed with many systemic diseases, especially the autoimmune ones. These latter diseases may share with periodontitis a similar pathway in their pathogenesis; however, we should not ignore the essential role of bacterial biofilm in triggering periodontitis. Yet, there exist other factors, including the presence of systemic conditions and genetic factors that play a crucial role in the pathogenesis of chronic and aggressive periodontitis respectively. Based on this, further investigations should be done to understand this multifactorial condition in order to establish an individualized treatment plan that would prevent loss of teeth because of periodontitis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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