INTRODUCTION

Periodontal disease is caused by bacteria in dental plaque, with evidence that specific periodontal pathogens are responsible for the progressive form of the disease. However, some individuals harbor these specific microorganisms, but do not appear to show evidence of disease progression. Patient susceptibility is of utmost importance to the outcome of periodontal disease, and although periodontal bacteria are the major etiological agents, the host immune response to these bacteria is of fundamental importance ***(Seymour, 1991)***.

The clinical features associated with periodontitis were the foundation upon which these periodontal infections have historically been categorized, classified and diagnosed ***(Armitage 1991, Armitage and Cullinan, 2010)***. It is argued that chronic and aggressive forms of periodontitis are different diseases because of the differences in the following clinical features: (I) age of onset or detection, (II) rates of progression, (III) patterns of destruction, (IV) signs of inflammation, and (V) relative amounts of plaque and calculus ***(Armitage et al., 2010)***.

However, since localized and generalized chronic periodontitis appear to share numerous clinical, epidemiological and etiological characteristics, they are considered to be slightly different manifestations of the same disease. In contrast, major clinical differences between localized and generalized

aggressive periodontitis suggest that they are different diseases. The differences between the generalized chronic and generalized aggressive forms of periodontitis are less clear. From a clinical point of view, generalized aggressive periodontitis is characterized by widespread destruction of periodontal tissues in a young patient; the amount of destruction seen at an early age suggests a rapid rate of progression ***(Armitage et al., 2010)***.

Generalized chronic periodontitis is also characterized by widespread periodontal damage, but usually in an older individual; a slow rate of progression is assumed based on the relatively low ratio of damage to age. This distinction is important from a disease management perspective, as individuals with aggressive forms of periodontitis are in need of relatively urgent care ***(Armitage et al., 2010)***.

The study of cytokines in periodontal disease lesions may throw some light on this problem and may also suggest future lines of therapy. Cytokines are cell regulators that have a major influence on the production and activation of different effector cells. T- cells and macrophages are a major source, also they are produced by a wide range of cells that play important roles in many physiological responses. Cytokines are low-molecular-weight proteins involved in the initiation and effector stages of immunity and inflammation, in which they regulate the amplitude and duration of the response. They are usually produced transiently, are extremely potent, generally

acting at picomolar concentrations and interact with specific cell surface receptors, which are usually expressed in relatively low numbers ***(Balkwill and Burke, 1989)***.

IL-18 is a proinflammatory cytokine expressed by macrophages, keratinocytes, oral epithelial cells, osteoblasts, T - cells, B - cells, and dendritic cells ***(Niyonsaba et al., 2005; Stoll et al., 1997; Udagawa et al., 1997; Pizarro et al., 1999; Monteleone et al., 1999; Sugawara et al., 2001 and Okamura et al., 1998)***. IL-18 could play a role in the progression of the inflammatory responses because of its chemotactic, proinflammatory, and angiogenic features ***(Johnson and Serio, 2005)***. IL-18 is produced intracellularly from its biologically inactive precursor (pro–IL-18); pro – IL-18 is proteolytically activated to mature IL-18 after cleavage by caspase-1 in the cytoplasm ***(Niyonsaba et al., 2005***, ***Sugawara et al., 2001; Ushio, 1996)***.

It was reported that IL-18 increases neutrophil activation ***(Johnson and Serio, 2005)***. The exposure of neutrophils to cytokines or chemoattractants increases the levels of cell surface–bound proteinase 3 (***Sugawara et al., 2001; Campbell, 2000)*** which presents on the cell surface and within secretory and specific granules of neutrophils ***(Sugawara et al., 2001; Kao et al., 1988)***. It is suggested that the proteinase 3–mediated induction of bioactive IL-18 secretion from oral epithelial cells occurred via a caspase-1–independent pathway ***(Sugawara et al., 2001***). It was reported that the presence of this cytokine was a factor in the maintenance of chronic inflammatory diseases,

such as rheumatoid arthritis and inflammatory skin diseases ***(Johnson and Serio 2005; Gracie et al., 2003; Delaleu and Bickel, 2004)***. Few studies ***(Johnson and Serio 2005; Orozco et al., 2006; Figueredo et al., 2008)*** showed an association between the severity of periodontal disease and IL-18 levels.

IL-18 concentrations were significantly higher than IL-1 at both gingivitis and periodontitis sites, inferring a high significance for this cytokine in periodontal disease ***(Orozco et al., 2006)***. Higher gingival crevicular fluid levels of IL-18 were found in inflamed sites from periodontitis patients regardless of severity of disease when compared with patients with gingivitis only. Moreover, shallow pockets in periodontitis patients had a significantly higher total level and concentration of IL-18 when compared with shallow pockets in patients with gingivitis only ***(Figueredo et al., 2008)***.

Although patient susceptibility is of major importance in determining the outcome of periodontal disease, the problems in detecting susceptible individuals have not been solved. There is a great deal of variation in the microbial composition between individuals and also from site to site in the same individual, as well as variation with respect to the frequency and rate of progression of periodontal disease ***(Seymour, 1991)***.

The major goals of periodontal therapy are to suppress bacterial infection, modulate the host response and heal/regenerate periodontal tissues in order to provide a healthy periodontium favourable to the re-establishment of a long-

lasting host- compatible periodontal microbiota ***(Haffajee et al., 2006; Teles et al., 2006)***. Mechanical periodontal therapy is the most common and probably the most effective treatment for achieving periodontal health ***(Cobb, 1996; Serino et al., 2001)***. However, the adjunctive use of systemic and/or local antimicrobials has been indicated for the treatment of aggressive forms of periodontitis ***(Haffajee et al., 2006; Herrera et al., 2002; Haffajee et al., 2003)***. In particular, the combined administration of amoxicillin (AMX) and metronidazole (MET) seems to provide a significant clinical benefit in terms of periodontal attachment "gain" post - therapy and also, the administration of doxycycline yielded conflicting results.

Levels of P. gingivalis, Tannerella forsythia and Treponema denticola were statistically significantly reduced immediately after completion of antibiotic intake ***(Guerrero et al., 2005; Xajigeorgiou 2006)***. These agents have also been shown to present a synergic effect on the reduction of *Aggregatibacter actinomycetemcomitans*, a major pathogen associated with aggressive periodontitis ***(Pavicic et al., 1994)***.

REVIEW OF LITERATURE

Periodontal diseases result from an inflammatory response to bacteria located in dental biofilms. The response may be confined to the gingival tissues or may progress, leading to attachment loss. It has been suggested that disease progression is the result of a combination of factors, including the presence of periodontopathic bacteria and high levels of proinflammatory cytokines ***(Gemmell et al., 2004).*** Several cytokines have been associated with periodontitis, such as interleukin-1b (IL-1b) ***(Figueredo et al., 1999)*** tumor necrosis factor-a (TNF-a) ***(Engebretson et al., 2006)*** and more recently IL-18 ***(Orozco et al., 2006)***.

In the classical most widely used classification for periodontal diseases and conditions, over than forty different gingival disease were listed that are either dental plaque-induced or not primarily associated with dental plaque and also, seven major categories of destructive periodontal diseases were listed Chronic periodontitis, localized aggressive periodontitis, generalized aggressive periodontitis, periodontitis as a manifestation of systemic disease. Necrotizing ulcerative gingivitis/periodontitis, abscesses of the periodontium, combined periodontic-endodontic lesions ***(Armitage, 2004).***

The age of onset, or age at the time of detection, is an important feature that has traditionally been used to help place patients in either the aggressive or chronic periodontitis category. The 1999 classification recommended deletion of age

- dependent terms such as "adult" and "juvenile" periodontitis since age is not an appropriate descriptor for use in diagnostic categories and instead of it he used the terms "chronic" and "aggressive" periodontitis ***(Armitage, 1999).*** (Table 1):

Table (1): ***Armitage 1999*** classification of periodontal diseases and conditions (Appreviated version).

I- Gingival Diseases:*
A. Dental plaque induced.
B. Non-plaque induced.
II. Chronic Periodontitis*
A. Localized
B. Generalized
III. Aggressive Periodontitis*
A. Localized
B. Generalized
IV. Periodontitis as a Manifestation of Systemic Diseases:
A. Associated with hematological disorders
B. Associated with genetic disorders
C. Not otherwise specified (NOS)
V. Necrotizing Periodontal Diseases
A. Necrotizing ulcerative gingivitis (NUG)
B. Necrotizing ulcerative periodontitis (NUP)
VI. Abscesses of the Periodontium
A. Gingival abscess
B. Periodontal abscess
C. Pericoronal abscess
VII. Periodontitis Associated With Endodontic Lesions
A. Combined periodontic-endodontic lesions
VII. Periodontitis Associated With Endodontic Lesions
VIII. Developmental or Acquired Deformities and Conditions
A. Localized tooth-related factors that modify or predispose to plaque-induced gingival diseases/periodontitis
B. Mucogingival deformities and conditions around teeth
C. Mucogingival deformities and conditions on edentulous ridges
D. Occlusal trauma
***Can be further classified on the basis of extent and severity. As a general guide, extent can be characterized as Localized = ≤30% of sites involved and Generalized = >30% of sites involved. Severity can be characterized on the basis of the amount of clinical attachment loss (CAL) as follows: Slight = 1 or 2 mm CAL, Moderate = 3 or 4 mm CAL, and Severe = ≥5 mm CAL.**

In their consensus report**, *Lang et al. (1999)*** agreed on classifying of aggressive periodontitis into Localized aggressive periodontitis and generalized aggressive periodontitis.

Table (2): Primary and secondary features of aggressive periodontitis ***Lang et al. (1999).***

Primary features of Aggressive periodontitis (Always Present): I- Except for the presence of periodontitis, patients are otherwise clinically healthy. II- Rapid attachment loss and bone destruction. III- Familial aggregation.
Secondary features of Aggressive periodontitis (Often Present): I- Amounts of microbial deposits are inconsistent with the severity of periodontal tissue destruction. II- Elevated proportions of *Actinobacillus actinomycetemcomitans* and, in some populations, *porphyromonas gingivalis* may be elevated. III- Phagocyte abnormalities. IV- Hyper-responsive macrophage phenotype, Including elevated levels of PGE2 and IL-1β. V- Progression of attachment loss and bone loss may self-arresting.

Table (3): Specific features of localized and generalized aggressive periodontitis which are used to differentiate between them ***(lang at al. 1999).***

Localized Aggressive periodontitis: A- Circumpubertal onset. B- Robust serum antibody response to infecting agents. C-Localized first molar/incisor presentation with interproximal attachment loss on at least two permenant teeth, one of which is a first molar and involving no more than two teeth other than first molars and incisors.
Generalized Aggressive periodontitis: A- Usually affecting persons under 30 years old but patients may be older. B- Poor serum antibody response to infecting agents. C- Pronounced episodic nature of the destruction of attachment and alveolar bone. D- Generalized interproximal attachment loss affecting at least three permenant teeth other than first molars and incisors.

Localized and generalized chronic periodontitis are usually considered to be two clinical expressions of the same disease. In both cases, there are similar signs of inflammation (e.g. redness, swelling, bleeding on probing) associated with moderate to heavy deposits of plaque and calculus. They also share slow rates of progression, affect similar populations (e.g. age range, gender), and are associated with similar genetic and environmental risk factors. Except for a general tendency to

exhibit bilateral symmetry ***(Mombelli and Meier, 2001)***, no consistent pattern of destruction is usually observed.

The rate at which loss of supporting periodontal tissues occurs has long been considered an important characteristic by which chronic and aggressive forms of periodontitis can be clinically distinguished. Chronic periodontitis has traditionally been viewed as a slowly progressing disease, whereas aggressive forms of periodontitis progress at a rapid rate. ***Baer (1971)*** estimated that the loss of attachment in aggressive periodontitis patients progressed three or four times faster than in cases of chronic periodontitis.

The reasons for this difference are unclear. Further, use of full-mouth averages probably had a diluting effect, especially in the case of localized aggressive periodontitis where the majority of sites are unaffected and show no attachment loss. The most compelling argument indicating that aggressive periodontitis progresses at a rapid rate comes from case series and epidemiological reports showing extensive periodontal damage at some sites in adolescents and young adults ***(Burmeister, 1984, Liljenberg and Lindhe, 1980, Saxe´n, 1985).***

There is a long-standing clinical impression that the rate of disease progression slows down or stops entirely in a small percentage of patients with localized aggressive periodontitis ***(Baer, 1971, Lang, 1999). Baer (1971)*** referred to this phenomenon as “burn out” of the disease.

It is possible that instances where localized aggressive periodontitis appears to spread to adjacent teeth and acquire a generalized pattern of destruction are due to the development of a new periodontal infection rather than the spread of an existing one. This possibility is supported by the observation of multiple types of periodontitis in the same family ***(Long et al., 1987; Marazita et al., 1994 and Spektor et al., 1985)*** or in a single individual ***(Shapira et al., 1994).***

In cases of chronic periodontitis, there is no consistent pattern to the number and types of teeth involved. The disease can be localized to a few teeth or can affect the entire dentition. There is a slight tendency for the destruction to exhibit bilateral symmetry ***(Mombelli and Meier, 2001)***, but there is no well-defined pattern in most cases. In cases of generalized aggressive periodontitis, most permanent teeth are usually affected. There are no evidence-based criteria to determine when a localized periodontal infection becomes generalized. The classification of ***Lang et al. (1999)*** suggested that the pattern of damage in generalized aggressive periodontitis includes situations where there is "generalized interproximal attachment loss affecting at least three permanent teeth other than first molars and incisors".

This is similar to the criteria used by ***Burmeister et al. (1984)***, who suggested that a generalized pattern of destruction is present if there is "attachment loss on 8 or more teeth, at least 3 of which were not first molars or incisors". These case definitions may be useful for the purposes of epidemiological

investigations but they lose most of their clinical utility in the diagnosis and management of an individual patient. For example, if only eight teeth are affected, most clinicians would characterize the disease as a localized rather than a generalized condition. It was the consensus of the group at the 1999 Classification Workshop that the extent of the disease be considered localized if ≤ 30% of the sites (or teeth) are affected, and generalized if > 30% of the sites (or teeth) are involved ***(Armitage, 1999).***

One of the features of localized aggressive periodontitis described originally was the relatively low level of gingival inflammation (e.g. redness, swelling) compared with other forms of periodontitis ***(Baer, 1971, Gottlieb, 1921, 1923, 1928, Orban and Weinmann, 1942).***

Burmeister et al. (1984) examined a population of these patients and found that the gingival index, gingival bleeding and suppuration scores at sites with attachment loss were equally high in patients with localized or generalized forms of aggressive periodontitis. In localized aggressive periodontitis, the biofilms that form on tooth surfaces are often quite thin, but these deposits are usually quite thick and abundant in the other forms of periodontitis ***(Listgarten, 1976).***

In many patients with localized aggressive periodontitis, there are only thin deposits of dental plaque (i.e. biofilm), with little or no calculus ***(Baer, 1971, Liljenberg and Lindhe, 1980, Listgarten, 1976).*** However, sites affected by the disease are

not biofilm-free. Electron microscopic observations of teeth extracted because of localized aggressive periodontitis revealed that root surfaces were covered with thin deposits of gram-negative coccoid and filamentous bacteria together with other microorganisms. The microbiota on the root surfaces was described as "relatively sparse and simple" ***(Listgarten, 1976).*** In contrast, teeth with chronic periodontitis usually have very complex and thick deposits of polymicrobial communities on affected root surfaces ***(Listgarten, 1976).*** In addition, population surveys of patients with localized aggressive periodontitis have shown that there are clinically detectable biofilms at affected sites ***(Burmeister, 1984).***

In their review, ***Smith et al. (2010)*** discussed and compared the nature of the inflammatory infiltrates found in cases of chronic and aggressive forms of periodontitis, and found no apparent histopathological explanations for the different rates of destruction observed in chronic and aggressive forms of periodontitis. Based on currently available data, it appears that the microbiota associated with localized aggressive periodontitis is somewhat different from that associated with either generalized aggressive or chronic forms of periodontitis ***(Armitage and Cullinan, 2010).*** However, there are many microbiological similarities between the two diseases ***(Armitage, 2010).***

Oral bacteria are initially acquired by contact with an infected family member at birth or at later life stages ***(Tuite-McDonnell et al., 1997).*** The gingival sulcus, and especially

the col region, which forms the bridge between adjacent gingival papillae, offer protected niches that favor bacterial settling. Pioneer colonizers include oral species as *Streptococcus, Veillonella, Prevotella, Neisseria, Gemella, Actinomyces and others* ***(Palmer et al., 2003)*****.**

In the study of ***Haffajee et al. (2008)*** to examine microbial communities in supragingival biofilm samples, they found that a red complex community was formed that contained the three species identified as the red complex in subgingival plaque, *T. forsythia, P. gingivalis, and T. denticola. Eubacterium nodatum* was also part of this complex and *Treponema socranskii* was loosely associated with these four species. A number of species previously identified in subgingival plaque as orange complex species were also detected as part of an orange complex in supragingival plaque. These included *Campylobacter showae, Campylobacter rectus, Fusobacterium nucleatum subsp. nucleatum, F. n. subsp. vincentii, Fusobacterium periodonticum, F. n. subsp. polymorphum, Campylobacter gracilis, Prevotella intermedia, and Prevotella nigrescens. These taxa were joined by Gemella morbillorum, Capnocytophaga ochracea, Selenomonas noxia, and Prevotella melaninogenica.*

A yellow complex was formed primarily of the *Streptococcus species S. mitis, S. oralis, S. gordonii, S. sanguinis and, somewhat separately, S. anginosus, S. intermedius, and S. constellatus.* These species were joined *by Leptotrichia buccalis, Propionibacterium acnes, Eubacterium*

saburreum, Peptostreptococcus micros, and Aggregatibacter actinomycetemcomitans. A tight cluster of *Actinomyces* species was formed including *A. israelii, A. naeslundii1, A. odontolyticus, A. gerencseriae, and A. naeslundii2.* A green complex consisting of *Capnocytophaga sputigena, Eikenella corrodens, and Capnocytophaga gingivalis* was formed as well as a loose purple complex consisting of *Neisseria mucosa and Veillonella parvula.*

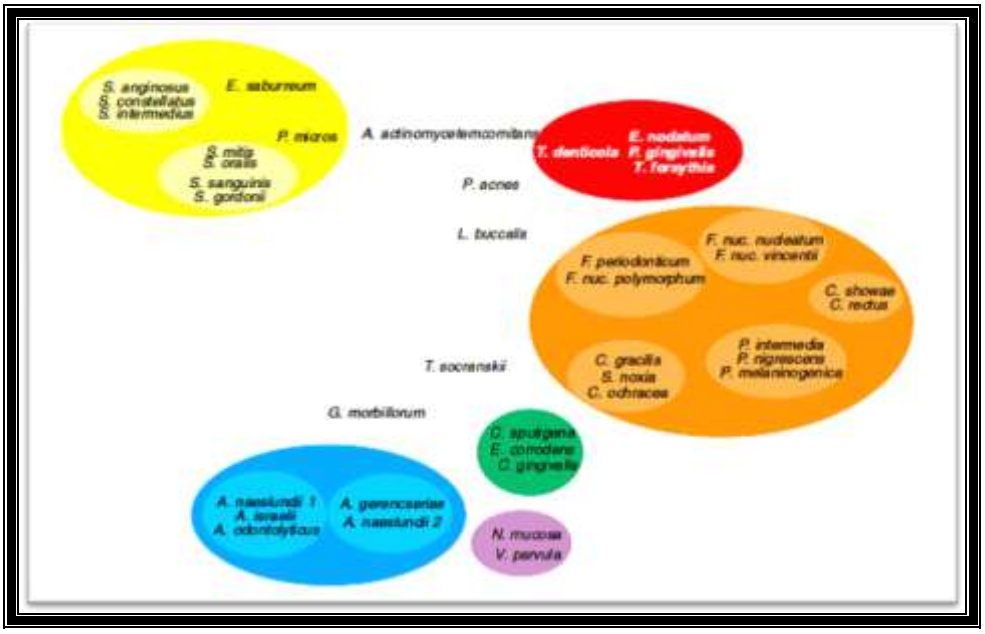

Fig (1): Diagrammatic representation of the relationships of species within microbial complexes and between the microbial complexes in supragingival biofilm samples ***(Socransky and Haffajee 2005)***.

During biofilm maturation, bacteria interact with each other within and between species via surface-associated structures (co-aggregation), leading to a unique spatial organization ***(Listgarten, 1976).*** As part of a sophisticated ecological system, biofilm residents communicate through