Aggressive Periodontitis Etiology, Pathophysiology, and Treatment: A Recent Review

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ABSTRACT

Periodontitis is a microbially driven inflammatory disorder that affects the periodontium and continues to be a major dental health problem worldwide. The aggressive form, formerly known as juvenile periodontitis, is a pathological condition in which rapid destruction of the periodontal tissues and bone occurs at youth, resulting in loss of teeth. Factors such as lifestyle, host response genetic defects, and subgingival microbial consortium are responsible for the progression of the disease. This devastating loss of face esthetics and oral function affects younger patients emotionally, mostly adolescents, and requires costly and invasive treatments such as implants. Fortunately, recent discoveries regarding early diagnostic tools and biomarkers were proven to be effective in controlling aggressive periodontitis (AgP) progression and limiting it at its early stages. Other modified therapies such as bone augmentation and flap surgery has also ameliorated dental clinical parameters and minimized the necessity for dental implants. Each periodontal treatment is assigned depending on the stage and the severity of the disease, and for this reason, early management is crucial. This was achievable thanks to novel diagnostic methods such as advanced cone beam computed tomography (CBCT) imaging and high throughput analysis of gingival crevicular fluid (GCF) biomarkers. The review discusses and compares the latest case studies on the use of different periodontal therapies to treat AgP. Recent research about its pathogenesis and etiological factors such as microbial and genetic association is also highlighted.

Keywords: Aggregatibacter actinomycetemcomitans, Aggressive periodontitis, Cone beam computed tomography, Implants, Leukotoxin.

International Journal of Experimental Dental Science (2019): 10.5005/jp-journals-10029-1189

INTRODUCTION

Periodontitis is an inflammatory disease that is infection-induced and causes loss of alveolar bone, connective tissues, and tooth-supporting tissues. As it progress rapidly, it results in loss of tooth attachment and consequently tooth loss. However, aggressive periodontitis (AgP), which is also abbreviated simply as AgP, is a type of periodontal disease that affects young healthy individuals. It was first discovered by Gottlieb in 1923, who believed that it was a degenerative, noninflammatory condition. To describe this periodontal disorder in young individuals, Weinmann and Orban introduced the term periodontosis in 1942. However, 20 years later, it was confirmed that there is no evidence for noninflammatory periodontal diseases. As more was ascertained on the etiology of AgP, Butler replaced the term periodontosis in 1969 by juvenile periodontitis. There are two forms of AgP, the generalized form (G-AgP) and the localized form (L-AgP), which have been distinguished in terms of number and type of teeth affected. L-AgP usually affects only incisors and first molars. The aggregation of this disease within families could be elucidated by a genetic predisposition, which is linked to susceptibility to the disease. The prevalence of AgP varies widely between many ethnicities. In a study involving 11,007 American adolescents aged less than 17 years, black teenagers were 15.1 times more likely to be affected than white teenagers. Besides, females are reported to be more affected than males. Chronic periodontitis (ChP) differs from juvenile periodontitis as it is a slowly progressive form that is more prevalent in adults. Unlike the aggressive form, it is generally associated with marked biofilm and calculus accumulation. Biofilm bacteria play a significant role in the pathogenesis of periodontitis. This is supported by the fact that subgingival microbiome shifts differently between ChP and AgP. Furthermore, because AgP onset is during adolescence, it may develop during or after completing an orthodontic treatment.

Therefore, orthodontic treatment is feasible only when the disease is controlled through careful monitoring during all phases of the active therapy. Fixed orthodontic appliance is favored over removable because it acts as splinting and helps in stabilizing anchorage. It also provides light constant forces and controls root movements. The cost for treating AgP is significantly greater than for ChP cases (estimated €882 vs €659, respectively). This reflects the more resource-consuming and demanding intervention required for AgP treatment within the first year. This evidence strengthens the dreadful need for early detection and effective primary prevention of the disease. This review discusses recent findings regarding the different types of enhanced treatments to manage AgP. Novel discoveries concerning etiology and diagnosis tools as well as the pathophysiology of the disease are also highlighted.

DIAGNOSIS

Aggressive periodontitis has various clinical features that include distolabial migration and increased mobility of maxillary incisors and first molars, as well as hypersensitivity of uncovered root surfaces. The absence of local factors such as calculus and plaques, the onset
age from late childhood or adolescence until 30, and the presence of inflammation in deep periodontal pockets are also considered when diagnosing AgP. Conventionally, radiography is used to confirm the incidence of the disease showing vertical bone loss around the incisors and first molars, in addition to bone defects wider than those seen in ChP. Moreover, the arc-shape of alveolar bone, which extends from second premolar distal surface to second molar mesial surface, is lost.7

Recently, cone beam computed tomography (CBCT) was successfully used to diagnose AgP. Using this indispensable imaging tool, detailed examination of each osseous defect around all teeth was carried out. Measurements of surgically exposed osseous defects by a periodontal probe, which could not be achieved by radiography, were identical with those detected by CBCT.8 To better assess alveolar bone loss in CBCT imaging, a six-site measuring method is incorporated such that the distance between cemento–enamel junction and the apical bases of the periodontal bone defect was measured at six different sites, which were the mesiobuccal, midbuccal, and distobuccal, as well as the mesiolingual/palatal, midlingual/palatal, and distolingual/palatal sites. This was proven to be useful in the three-dimensional evaluation of AgP.9 However, the alveolar bone density in periodontally healthy individuals does not differ from that in AgP patients.10

Other robust, noninvasive methods for early AgP detection could include nuclear magnetic resonance (NMR) spectroscopy and mRNA profiling. Because tissue and bone destruction occurs late in the disease progression, metabonomic fingerprints for generalized AgP found in patients’ saliva were successfully identified using NMR spectroscopy to be used for early diagnosis. Most detected metabolites were short-chain fatty acids as butyrate, compared to lactate, methanol, y-amino-butyrate, and threonine, which were present in lower concentrations.11 Similarly, gingival crevicular fluid (GCF) from AgP patients also provided micro-RNAs as diagnostic biomarkers. These that could be implicated in pathogenesis were identified distinctively from those of healthy controls using miRNA profiling.12

Cytokine levels were assessed as risk markers in both saliva and GCF in localized AgP. Six months prior to bone loss, it was found that MIP-1α constantly showed elevated levels as a diagnostic biomarker for site vulnerability to bone loss.13 Using GCF samples only, malondialdehyde (MDA), superoxide dismutase (SOD), and melatonin levels were used as biomarkers for oxidative stress in generalized AgP. Compared to ChP, MDA levels were significantly higher in the generalized AgP group. On the contrary, SOD and melatonin levels were significantly lower. This could serve as useful diagnostic tool in distinguishing ChP and generalized AgP patients.14

Interestingly, using certain levels of immunological parameters such as leukocyte counts in peripheral blood, artificial neural networks (ANNs) were constructed to distinguish AgP from ChP based on their immune response profiles against Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis. The detection and the classification of the two types of periodontal diseases were 90–98% accurate.15

**Microbiological Factors**

Many studies confirmed that there is a correlation between AgP and the presence of *A. actinomycetemcomitans, P. gingivalis, Tannelleria forsythia, Selenomonas sputigena*, and *Treponema denticola*.16,17 These were less frequent in healthy individuals, especially *A. actinomycetemcomitans*, which was proven to produce leukotoxins that are translocated across epithelial membranes and are able to lyse white blood cells like neutrophils. This is achieved through the release of neutrophil extracellular traps (NETs) prior to cell lysis.18 Among studied strains, JP2 clone is a highly leukotoxic strain, also known as *A. actinomycetemcomitans* serotype b, which disables host immune defenses by destroying leukocytes and monocytes. The JP2 sequence has been associated with localized AgP in young African Americans.19,20 Moreover, *A. actinomycetemcomitans* IktA (leukotoxin) genotype showed high prevalence as 71.8% among AgP patients.21

In order to facilitate the transport of endotoxins including leukotoxins and cytolytic distending toxins (CDTs) to host cells, *A. actinomycetemcomitans* secrete membrane vesicles and activate innate immunity via NOD1 and NOD2 molecular pathways.22 However, it has recently discovered that leukotoxins are trafficked to host cells by outer membrane vesicles via a cholesterol- and LFA-1 receptor-independent mechanism, contrary to the mechanism by which free leukotoxins are delivered. Thus, the former secretion type could have provided the toxin with the ability to affect multiple host cell types (Fig. 1). Inhibitors of this toxin’s form can be designed to develop new therapeutic strategies for localized AgP.23

CDT was also reported to impair bone homeostasis and host defense mechanisms in AgP by inhibiting osteoclast differentiation. This was proven by studying altered cytokine profiles and repressed transcription of osteoclastogenesis genes such as rank, nfatc1, and ctpk.24

Another key virulence factor in *A. actinomycetemcomitans* contributing to localized AgP is the pga operon, which was proven to play a role in bone resorption. Among pga genes, PgaB codes for an enzyme that deacetylates poly-N-acetyl glucosamine (PNAG) exopolysaccharide. Using mutant studies, it is reported that N-terminal catalytic domain of PgaB is fundamental for exopolysaccharide export. This is crucial for *A. actinomycetemcomitans* attachment to biotic surfaces in order to start infections.25

In addition, according to immunohistochemistry and polymerase chain reaction (PCR) analysis, both *T. forsythia* and *P. gingivalis* localizations and densities may have contributed to cell and tissue invasiveness. Their presence in the capillary endothelium could explain their possible translocation from inflamed subgingival tissues in periodontal pockets into the systemic circulation. This results in bacteremia in periodontitis patients, which can be considered as an atherogenic stimulus.26

Another study supported that the binding of *P. gingivalis* to red blood cells (RBCs) in circulation protected it from reactive oxygen species (ROS) and phagocytes, as well as it simultaneously enhanced the release of proinflammatory cytokines (IL-6, TNF-α, CXCL8, and CCL2) by neutrophils in localized AgP patients. This provides a selective advantage for *P. gingivalis* viability.27

Herpes viruses such as Epstein–Barr virus (EBV), human cytomegalovirus (CMV), and Herpes simplex 1 (HSV-1) have been researched to play a coinfection role in AgP onset by interacting with periodontitis-associated bacteria, including *A. actinomycetemcomitans, P. gingivalis, T. forsythia*, and *T. denticola*.28

**Etiology**

Considering the multifactorial nature of this periodontal disease, the main risk factors contributing to the etiology consist of oral microbiota, genetics, and less commonly lifestyle.
Genetic Factors

AgP is a polygenic disorder meaning that it results from interactions among lots of gene loci. Autosomal recessive hereditary that has been related to AgP onset and progression leads mostly to nonprotective inflammatory responses, which lead to dysbiotic microbial changes. It is also a heterogeneous genetic disorder that is affected by environmental interactions. Recent study demonstrated that polymorphisms in the IL-6 (-174) and IL-10 (-597) genes have been detected in AgP subjects using PCR-restriction fragment length polymorphism (RFLP) method. The anti-inflammatory cytokine, IL-10, inhibits the synthesis of proinflammatory cytokines such as IL-6, which plays a regulatory role in osteoclast differentiation.

Other studies showed that tumor necrosis factor-α (TNF-α) rs1800629 (-308G/A) polymorphism, which leads to two- to three-fold higher transcriptional activity of TNF-α, might be associated with AgP in Asians, Caucasians, and in eastern Indian population. TNF-α is a proinflammatory cytokine that has been linked with the gingival tissue destruction. It is believed that bacterial pathogens stimulate TNF-α secretion, which leads to osteoclast differentiation and eventually in bone resorption. It also promotes the release of matrix metalloproteinase enzymes (MMPs) that ultimately destroy gingival extracellular matrix.

Similarly, high prevalence of depressed neutrophil chemotaxis in Indian family members (61%) was linked with localized AgP suggesting that these neutrophil defects may also be inherited. However, further studies with a larger sample size are required to elaborate on this topic since neutrophils play a crucial function in the host’s inflammatory response.

In Chinese Han population, AgP is associated with single nucleotide polymorphisms (SNPs) in the 3′-UTR of CTLA4, which prevent binding of miR-105 and resulting in elevated levels of CTLA4. This gene codes for a protein receptor that functions as a checkpoint in downregulating the immune system. However, in Japanese patients, AgP is associated with rs36714306 SNP in the G-protein coupled receptor 126 gene (GPR126). This gene activates the cAMP/PKA signaling pathway as rs36714306 was proven to impair GPR126 signal transactivation using cAMP ELISA analysis. In addition, in vitro transfection of human periodontal ligament (HPDL) cells with mutant GPR126 has resulted in no effect on the expression of calcification-related genes such as bone sialoprotein, osteopontin, and Runx2 genes compared to control. These findings suggest that GPR126 might have a fundamental function in maintaining periodontal ligament tissues homeostasis, which is negatively influenced by rs36714306 SNP.

Other candidate genetic risk factor for AgP includes MPO-463G/A gene polymorphism. Myeloperoxidase (MPO) is a lysosomal enzyme that is mainly found in polymorphonuclear (PMN) leukocytes, azurophilic granules. It also is able to mediate inflammatory tissue destruction in AgP. The level of tissue human telomerase (hTERT), which is a ribonucleoprotein enzyme concerned with telomeric lengthening, has been found to be elevated in AgP subjects as compared to healthy controls. Interestingly, vitamin D-binding protein (DBP) rs17467825 and rs4588 GC gene polymorphisms are associated with lower risk of generalized AgP. This protein plays a significant role in vitamin D transport and metabolism.

Lifestyle Factors

Cigarette smoking is the most significant risk factor in the prevalence and progression of generalized AgP. Smokers affected by this disorder had greater attachment and teeth loss than patients who did not smoke. The myeloid-related protein-8 and myeloid-related
protein-14 levels in GCF of generalized AgP smoking patients were found to be statistically lower than nonsmoking patients. The mechanisms indicate that this decrease in protein levels could have prevented calcium hemostasis, which plays an important role in neutrophils’ migration. This further minimizes the antimicrobial efficiency against microorganisms.

The effects of smoking are related with the alteration of humoral response against P. gingivalis by decreasing total IgG responses as determined by ELISA. Seropositive smokers were also more likely to be infected with P. gingivalis according to 16S RNA analysis. Additionally, smokers with generalized AgP had higher salivary immunoglobulins (sIgA) and lower peroxidase levels than smokers without periodontitis. Smoking alters B-cell differentiation and T-cell immune regulation, generating a decline in immunoglobulins (Igs)’ production, which in turn protect the oral mucosa against periodontal bacteria. Tobacco metabolites restrain neutrophil function and alter the role of PMN chemotaxis and phagocytosis by interfering with Igs production. Bruxism, which is poorly understood, was also significantly associated with higher tooth loss due to periodontal disease (TLPD) rates alongside with smoking and certain features such as abstractions and vertical bone defects.

Pathophysiology

The physiopathology of AgP is not well-documented as that of CbP since there are less numbers of AgP patients. Nevertheless, characteristics such as severe bone loss on first molars, with relatively fast progression to second molars, and abnormal root resorption patterns are common in localized AgP patients with primary dentition. Although these findings represented exceptional cases, they are also frequent in patients with permanent dentition. Histological studies found important alterations of gingival epithelial layer and connective tissue in generalized AgP patients with multiple root curvatures. In addition, disorganization of collagen fibers fascicules and cell inflammatory infiltration in lamina propria were also observed. These events correspond to a fully developed recurrent lesion.

Root abnormalities were documented to have high prevalence and can be evaluated using various methods. A higher incidence of root abnormalities was associated with an increased risk of tooth loss and further periodontal deterioration. Moreover, AgP is characterized by the inability of forming NETs, as they are responsible in evacuating pathogen-associated dental plaque molecular patterns. The formation of gingival pockets boosts periodontitis progress by obstructing this function. The dysregulation of PMN activation was also proven to have a leading role in periodontal pathology.

Since inflammatory mediators play a vital part in the pathomechanism of periodontal tissue destruction, modern research confirms significantly higher concentrations of IL-1β and MMP-8 of both shallow and deep pockets, as well as significantly lower concentrations of IL-17 and IL-23 of in GCF of patients with AgP compared to healthy subjects. Gingival crevicular fluid calprotectin levels were significantly higher in the AgP patients and correlated positively with clinical attachment loss (CAL), probing depth (PD), and bleeding index (BI). Its subunit rhS100A8/A9 was shown to promote cell apoptosis and to augment nuclear factor-kB (NF-kB) activation by promoting p65 nuclear translocation in periodontal ligament cells (PDLCs). Consequently, the expression of proinflammatory cytokines such as TNFα, IL-6, IL-8, and COX2 was induced.

Another pathological phenomenon in AgP is proteolytic periodontal tissue degradation, where several MMPs can be expressed and secreted as a result of fibronectin degradation by HtrA1 (high temperature requirement A 1). This is supported by elevated levels of plasma cell HtrA1 in AgP patients, which could have triggered MMPs overproduction and increased inflammatory mediators IL-1β and TNF-α by inhibiting TGF-b. Also, the phenotypic profile of blood mononuclear cells in generalized AgP patients is distinguished with a significant increase of activated cytotoxic T cells, CD8+ and CD8+ cells, in both defect sites and systemic circulation blood samples. These findings which are linked to inflammation may lead to severe tissue damage.

Nicotinamide phosphoribosyltransferase (NAMPT), also known as visfatin, has been reported as a proinflammatory marker for AgP as it is capable of inducing inflammatory mediators’ production such as IL-6, IL-1β, and TNF-α. Its synthesis in the gingival fibroblast cells and periodontal ligament could be stimulated by common periodontal pathogens such as P. gingivalis and F. nucleatum. In AgP patients, visfatin expression was increased in gingival tissues suggesting it might have a role in etiopathogenesis.

Similarly, macrophages from localized AgP patients had lower Maresin 1 (MaR1) levels (87.8 ± 50 pg/106 cells) compared to healthy controls (239.1 ± 32 pg/106 cells). As a result, phagocytosis against P. gingivalis and A. actinomycetemcomitans was reduced to 40% and neutrophils displayed slower kinetics down to 30%. On the contrary, phagocytes’ impairment was restored by the administration of MaR1 at 1 nM, suggesting its clinical utility in treating AgP.

Treatment

Given the rapid progression of AgP and the difficulty in gaining control over it, diagnosis and treatment of the disease should ideally be carried out by a periodontist. Treatment of AgP starts with patient education and ensuring his/her fulfillment. However, AgP suffers are significantly younger than the average patient with other periodontal diseases. This age aspect can interfere with treatment planning in many ways since losing teeth at such a young age affects their psychological health. As such, investing time in establishing a good relationship between the patient and the clinician is important to reach treatment goals.

Despite better insights into AgP etiology, early treatment is targeted toward the bacterial load of periodontal pockets. Because of its low prevalence, studies assessing the treatment’s effect are limited and often investigate small number of patients. This hampers the implementation of relative clinical trials.

Antibiotics Therapy

The combination of moxifloxacin treatment with scaling and root planning was reported to improve CAL gain and PD reduction at 6 months posttreatment in patients with generalized AgP. Healthy sites were defined to have a PD ≤5 mm. Similarly, nonsurgical treatment combined with chlorhexidine, amoxicillin, and metronidazole has also increased CAL (0.97 mm) and improved PD (2.54 mm), as well as negative bleeding on probing (BOP) and no pathogenic bacteria detected in periodontal pockets.

Mechanical debridement and systemic antibiotics including metronidazole and amoxicillin ameliorated BOP, mean PD (pockets with PD >4 mm), and mean CAL in African-American patients with localized AgP were reported, 12 months after treatment. However, inflammatory response was shown to influence treatment as low responders to Escherichia coli lipopolysaccharides (LPS) presented...
the highest reductions in clinical parameters.\textsuperscript{54} Adjunctive administration of metronidazole and amoxicillin was also proven to be more useful in reducing GCF concentrations of MMP-8 compared to the use of photodynamic therapy (PDT).\textsuperscript{55}

On the contrary, the use of other antibiotics such as azithromycin reduced CAL, PD, and inflammation findings was more effective than metronidazole and amoxicillin. These results were recorded at 3 months post therapy in generalized AgP patients and all tested antibiotics were adjunct to scaling and root planning.\textsuperscript{56} Subjects who received adjunctive azithromycin predicted a 14% reduction in sites with BOP as well as reductions in probing pocket depth (PPD) 0.49 mm higher than placebo subjects during 12 months.\textsuperscript{57}

Since the broad and over usage of antibiotics has led to the emergence of resistant microorganisms, it is ideal to minimize the use of antibiotics. \textit{Lactobacillus brevis} CD2 and/or doxycycline were shown to have long-term positive effects on periodontal health of AgP patients including in gingival index (GI).\textsuperscript{58} Recently, coadministration of synbiotic lozenge with standard therapy was shown to be more effective than doxycycline and nonsurgical treatment alone. Clinical parameters such as pocket depth, gingival bleeding, and CAL were improved. Symbiotics have anti-inflammatory and antimicrobial properties which could have protected against destruction of periodontal tissue and loss of alveolar bone.\textsuperscript{59}

**Nonsurgical Treatment**

Clinical parameters in patients with advanced generalized AgP improved significantly after complete periodontal debridement. Median PD decreased from 7.94 mm to 3.54 mm, whereas for CAL of sites, the median changed from 9.02 mm to 6.45 mm. In all cases, angular bone defects were resolved and inflammation was reduced.\textsuperscript{60}

Nonsurgical therapy consisting of whole-mouth ultrasonic debridement, scaling, and root planning also decreased JP2 clone presence in African-American patients with localized AgP. Using PCR sequencing, JP2 detection was found to be 75% in diseased sites and in 56.67% in healthy sites. At 3, 6, and 12 months post therapy, JP2 detection diminished to 17.5%, 6.45%, and 3.23% in diseased sites and to 2.5%, 3.23%, and 0% in healthy sites, respectively. Additionally, mean PD, CAL, BOP, and plaque index (PI) were reduced after treatment (p < 0001), showing further strong correlations between them and the presence of JP2 clone.\textsuperscript{61}

Similarly, mechanical debridement contributed to successful maintenance of localized AgP for up to 4 years. Percentage of affected sites, CAL, and PD were significantly reduced at all timepoints (mean reductions: 2.80 ± 1.43 mm and 2.18 ± 1.03 mm, respectively). However, noncompliance with appointments has negatively affected the therapy response.\textsuperscript{62}

According to another study, full mouth scaling and root planning influenced the composition of subgingival bacterial community of generalized AgP subjects. \textit{Bacteroides}, \textit{Proteobacteria}, and \textit{Spirochaetes} were dominant during pathogenesis, while \textit{Firmicutes} and \textit{Actinobacteria} were more prevalent after periodontal debridement. The latter findings were recorded at the fourth week of follow-up, where significant enhancements in PD and BOP were observed. The microbial communities were obtained from subgingival plaque samples and were analyzed using high-throughput 16S rDNA sequencing. At phylum level, \textit{P. gingivalis} and \textit{T. forsythia} belong to \textit{Bacteroidetes}, \textit{A. actinomycetemcomitans} belongs to \textit{Proteobacteria}, and \textit{T. denticola} belongs to \textit{Spirochaetes}.\textsuperscript{63}

Scaling and root planning significantly reduced alkaline phosphatase (ALP) levels in GCF of patients with AgP by 17.6%. This enzyme is produced locally in the periodontium and its activity was found to be increased during active phase of disease. This decrease could be attributed to the protective functions of neutrophils in AgP. Changes in ALP levels in GCF were also positively correlated to changes in PPD and PI, although negatively correlated to changes in GI and BI.\textsuperscript{64}

Monocyte chemoattractant protein-1 (MCP-1) polymorphisms were also shown to influence nonsurgical treatment of AgP, which comprise of oral hygiene reinforcement in addition to scaling and root planning. In fact, elevated levels of this protein are related to drastic periodontal destruction. The MCP-1-2518 A/G genotype predicted poor treatment response in GI, BI, and PD improvement, whereas MCP-1-2518 A/A genotype predicted better treatment outcome in BI and PD improvement.\textsuperscript{65}

**Surgical Treatment**

In localized AgP patients with bilateral intrabony defects, open flap debridement has managed to significantly lower mean PD and mean relative attachment level (RAL) in both maxillary and mandibular arches (p < 0.05). Radiographically, more defect fill was achieved in tested group as compared to control group, 12 months post therapy. Combined platelet-rich plasma with hydroxyapatite graft was used during flap surgery to fill defects.\textsuperscript{66}

In a similar way, advanced bone defect in compromised maxillary anterior teeth was successfully reconstructed using papilla preservation technique and flap surgery combined with bone graft. The first treatment was applied to obtain interdental space closure. In the second treatment, intrabony defects were carefully debrided and filled by cerabone bovine graft granules, which were then covered by a resorbable bovine collagen membrane. Moreover, a fixed wire retainer was used to splint upper anterior teeth as well as to stabilize wound healing. At 2 years posttreatment, BOP had declined from 40% to 16% with absence of PPD beyond 4 mm and average CAL increase of 3.07 mm.\textsuperscript{67}

Flap surgery and ridge augmentation have resulted in clinical and microbiological improvements in subjects with generalized AgP. On sites with periodontal pockets having PD of ≥10 mm, modified Widman flap surgery was carried out. For maxillary incisors and molar region bone defects, ridge augmentation using connective tissue graft was performed, which has resulted in enhanced marginal bone levels and reduced PD.\textsuperscript{68}

The administration of 0.3% fibroblast growth factor (FGF-2) as part of flap surgery procedure was also proven effective by standardized radiographs. At 36 weeks post FGF-2 treatment, alveolar bone height increased by 86.9%, CAL decreased from 9 mm to 6 mm, and PPD from 5 mm to 3 mm. Furthermore, significant alveolar bone development was observed by 6-year postoperative radiograph.\textsuperscript{69}

Surgical periodontal therapy was shown to influence serum markers as it has decreased serum C-reactive protein levels from 3.09 ± 1.21 mg/L to 1.43 ± 1.21 mg/L, which are usually elevated in AgP. This corresponded with other clinical findings such as mean attachment loss, PI, and PD. In the surgical procedure, careful debridement was carried out after removing lining pocket epithelium. Using interrupted suture technique, lingual and buccal flaps were approximated and then periodontal dressing was set.\textsuperscript{70}

In a recent study, AgP patients exhibited higher C-reactive protein and neutrophil elastase levels than ChP patients (p < 0.01).
up to 5 years following flap surgery therapy. However, clinical variables such as BOP, PPD, and percentage of affected sites have significantly recovered.\textsuperscript{71} Other essential information on AgP treatment research is summarized in Table 1.

**Psychotherapy**

As mentioned earlier, AgP could have an impact on the mental health of young patients because of changes in esthetics. It was reported that psychological counseling had positive effects on the attitude and behavior of patients with generalized AgP, which contributed to a better periodontal treatment. This was carried out without medication and at three different stages: individual, group, and conjoint-family psychotherapy.\textsuperscript{72} Other case reports suggested that clinical depression could be a systematic manifestation of this disease. This was treated accordingly using psychotherapy along with supportive periodontal therapy. At the 3rd week from initial treatment, there was marked enhancement in the patient’s mental status.\textsuperscript{73}

**Laser Therapy**

PDT is a new noninvasive therapeutic tool that is site- and patient-specific. In combination with scaling and root planning, PDT has enhanced PI, BOP, PPD, and CAL. Periodontal bacteria such as \textit{A. actinomycetemcomitans}, \textit{P. gingivalis}, and \textit{Prevotella intermedia} were also reduced at 3 months posttreatment.\textsuperscript{74}

**Other**

\textit{Boswellia serrata} and \textit{Nigella sativa} are herbal therapies, which were recently assessed to evaluate their antibacterial effect on \textit{A. actinomycetemcomitans}. The calculated minimum inhibitory concentration (MIC) of \textit{N. sativab} and \textit{B. serrata} were 128 μg/mL and 512 μg/mL, respectively. Due to their effectiveness, these herbal plants must be considered as main ingredients of oral hygiene products.\textsuperscript{75}

Moreover, novel \textit{in vitro} studies showed that sonicated bacterial fragments of \textit{A. actinomycetemcomitans} exerted beneficial effects on gingival mesenchymal stem/progenitor cells including proliferation and expression of regenerative genes. This means that power-driven ultrasonic devices can be used to treat localized AgP as they are able to reduce subgingival microbial load, and unlike hand instruments, they can generate \textit{A. actinomycetemcomitans} bacterial fragments, which are cell stimulatory and thus contribute to reparative responses of stem/progenitor cells in gingival tissues.\textsuperscript{76}

**Implants**

When tooth loss occurs at latest stages of AgP, getting dental implants is the only remaining solution for both functional and aesthetic rehabilitation, especially for generalized AgP patients.

Maxillary incisors were restored with minimally invasive implant surgery, which did not require bone augmentation or flap raising. Four short locking-taper implants were placed on which four zirconia crowns were cemented using extraoral cement on the abutments. During 5-year follow-up, there were no functional differences between the patient’s natural teeth and implants as well as stable gingival margins lacking inflammation. This is the first case that reports immediate placement of implants into maxillary alveolar fresh sockets.\textsuperscript{77} However, this was observed in another study after performing extraction and guided tissue regeneration in a single setting. The patient underwent immediate implant surgery to restore lower anterior incisors and upper right molars. During 12-year follow-up, all implants had marginal bone stability and no residual pockets were observed with any inflammatory condition.\textsuperscript{78}

In another less expensive way, cemented implant-supported Toronto Bridge has managed to compensate for tooth and vertical bone loss in right maxilla. During 2-year follow-up, there was no further bone resorption with any signs of instability.\textsuperscript{79} Other cases involving affected upper interior region, mucoperiosteal flap raising was considered necessary before three implant surgeries. In fact, due to deficiency of buccal bone, one of the implants was angulated more palatally. After 8 months of healing period, cementable final denture was placed.\textsuperscript{80}

To correct vertical bone loss in hopeless upper left first premolar, bone regeneration was guided using allograft bone grafts and a resorbable collagen membrane. Six months later, bone regeneration was completed and dental implant was submerged. After 3 months of healing, implants were restored with a crown. This strategy has the possibility to eliminate procedures that are necessary in sinus lift and extensive block graft operations.\textsuperscript{81}

When there is severe bone loss, it is compulsory to extract teeth with hopeless prognosis, especially those with higher grades of mobility. Four conventional and two zygomatic implants were placed for full mouth fixed rehabilitation. During 2-year follow-up, no implant failure occurred although there was peri-implant soft-tissue inflammation. This was easily controlled by proper oral hygiene and maintenance. However, this type of implant surgery requires meticulous training, thorough knowledge, and superior surgical skills.\textsuperscript{82}

Rigorous maintenance program was also shown to ensure the stability of the periodontium, where dental implants were placed in the maxillary and mandibular anterior region. This program consisted of sustaining oral hygiene, scaling, and root planning, and flap surgeries. After planning using CBCT, one implant of size 3.5 and three implants of size 4.3 mm × 13 mm were placed, which exhibited successful osseointegration without any biological complications, after 4 months. Fixed metal–ceramic prosthesis was then cemented.\textsuperscript{83}

In a recent study, although oxide-coated dental implants provided rehabilitation for AgP subjects, the implant survival rate was 96.2% compared to only 38.5% as implant success rate, over a 6-year study. This was explained by the presence of mucositis and peri-implantitis in 28.0% and 32.0% of the implants, respectively, which were more prevalent for implants >10 mm and in the maxilla. Findings also demonstrated that CHP subjects were less susceptible to these complications, which resulted in 97.1% implant survival rate and 77.9% implant success rate.\textsuperscript{84}

**Future Perspectives**

There are several gaps in the literature concerning the factors that adjust host-pathogen relationship, making categorizations of periodontitis a challenge. Different AgP classifications may exhibit varied patterns of periodontal destruction, which might not be distinct pathologically. Within a new definition, the role of microorganisms association, multiplicity of inherited genes, and host response elements in the earliest stages of disease could be assessed. A new definition could present better insights into the involvement of genes in limiting the disease’s extent to its earliest stages. However, validating this hypothesis will necessitate populations with larger sample sizes employing a more restrictive definition.

The fact that AgP could be considered as a silent, orphan disease, meaning that it affects fewer people and presents symptoms unnoticeable by the individual, makes it even more
Table 1: List of different summarized therapies for aggressive periodontitis (AgP)

| Treatment type          | Subjects                                      | Treatment plan                                                                                     | Parameters tested/materials used                                      | Results                                                                                                                                   | Literature cited |
|-------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Antibiotics             | G-AgP/40 patients                             | Moxifloxacin (400 mg ×1/day for 7 days)                                                           | CAL/PD                                                                | PD diminution and CAL increase after 6 months                                                                                           | 52               |
| (adjunctive)            |                                               |                                                                                                   |                                                                        | P. gingivalis, T. denticola, T. forsythia, P. intermedia and A. actinomycetemcomitans                                             |                  |
|                         | G-AgP/10 patients aged 15–35 years            | 0.12% chlorhexidine, 875 mg amoxicillin and 500 mg metronidazole every 12 hours for 10 days       | BP/BOP/PD/CAL/subgingival plaque samples                               | PD decrease, CAL increase, −ve BOP, and no pathogenic bacteria detected after 6 months                                               | 53               |
| Non-surgical treatment  | L-AgP/60 African American aged 5–21 years     | 250 mg of metronidazole and 500 mg of amoxicillin (adjusted for children, <40 kg) ×3/day for 7 days | BOP/PD/CAL/blood was stimulated with LPS from E. coli                   | Low responders to LPS presented the highest reductions ameliorated BOP, mean PD, and mean CAL after 12 months                            | 54               |
|                         | 36 patients (24 females, 12 males) aged 5–21 years | 375 mg of amoxicillin and 250 mg of metronidazole 3 × daily for 7 days                          | MMP-8 and -9 GCF concentrations                                         | Decrease of MMP-8 GCF levels after 3 and 6 months                                                                                       | 55               |
|                         | G-AgP/45 patients                              | 500 mg of azithromycin, ×1/day for 3 days                                                     | PD, CAL, GI, PI, and BOP                                                | Reduction in PD, CA Loss, and clinical inflammation findings after 3 months                                                            | 56               |
|                         | 24 patients aged 13–26 years                  | 500 mg of azithromycin in ×1/day for 3 days                                                      | PL, PPD, gingival recession (GR) and BOP                                 | Improvements in PD, CAL and BoP after 3, 6, 9, and 12 months                                                                              | 57               |
|                         | 18 patients aged 14–35 years                  | L. brevis CD2 lozenges with oral doxycycline 100 mg ×1/day for 14 days                           | PI, GI, PPD, and CAL/microbiological parameters (Lactobacilli and A. actinomycetemcomitans) from saliva samples | All clinical parameters improved at 5 months                                                                                           | 58               |
|                         | 60 patients aged 18–30 years                  | 100 mg of doxycycline ×2/day for the 1st day followed by 100 mg ×1/day for 1 week and synbiotic lozenge ×2/day for 8 weeks | PD, CA loss, oral hygiene index, and BoP                                | Reduction in PD, CA loss, oral hygiene index, and BoP with no adverse drug reactions was noted after 12 months                            | 59               |
|                         | G-AgP/7 patients aged under 30 years          | Complete periodontal debridement                                                                | PD and CAL/ resolution of inflammation and bone fill                   | Resolved inflammation and repaired angular bone defects/ameliorated PD and CAL after 12 months                                          | 60               |
|                         |                                               |                                                                                                   |                                                                        | After 12 months, JP2 detection diminished from 75% to 3.23% in diseased sites and from 56.67% to 0% in healthy sites/mean PD, CAL, BOP and PI were reduced | 61               |
|                         | L-AgP/60 African American aged 5–25 years     | Whole-mouth ultrasonic debridement/scaling and root planning                                   | PD, CAL, BoP and PI/subgingival plaque samples                         | Improved PD and CAL up to 4 years. Reduced % of affected sites. Bacteroidetes, Proteobacteria, and Spirochaetes were found during pathogenesis, while Firmicutes and Actinobacteria were found after treatment. After 4 weeks, enhancements in PD and BOP were observed | 62               |
|                         |                                               |                                                                                                   |                                                                        |                                                                                                                                           |                  |
|                         | L-AgP/141 African American aged 5–25 years    | Mechanical debridement                                                                            | PD, CAL, BoP, visible plaque, and gingival margin position (GMP)       |                                                                                                                                           |                  |
|                         |                                               |                                                                                                   | PD and BOP on six sites per tooth/microbiological sampling (subgingival plaque) |                                                                                                                                           |                  |
|                         | G-AgP/2 females aged 27 and 29 years old      | Full mouth scaling and root planning                                                             |                                                                        |                                                                                                                                           |                  |

Contd...
| Treatment type | Subjects | Treatment plan | Parameters tested/materials used | Results | Literature cited |
|---------------|----------|----------------|---------------------------------|---------|-----------------|
| Surgical treatment | Patients aged 20–60 | Scaling and root planning | PD, PI, GI and bleeding index (BI)/ALP in GCF analysis | Reduced ALP levels in GCF by 17.6% after 8 weeks | 64 |
| Surgical treatment | 40 patients (including ChP) aged: 46.88 ± 11.48 | Oral hygiene reinforcement/scaling and root planning | GI, BI, and PD MCP-1 genotype analysis | MCP-1-2518 A/G genotype predicted poor treatment response in GI, BI, and PD improvement/MCP-1-2518 A/A genotype predicted better treatment outcome in BI and PD improvement | 65 |
| L-AgP/10 patients | Open flap debridement and hydroxyapatite (HA) graft material mixed with platelet-rich plasma (PRP) | Bilateral intra-bony defect (radiographs)/PD, BOP, RAL | After 12 months, PRP/HA group presented better PD reduction, clinical attachment gain and radiographic bone fill than HA group | | 66 |
| L-AgP/Malay female/34 years old | Papilla preservation technique and flap surgery combined with bone graft (cerabone bovine)/fixed wire retainer for splinting | Radiography/BOP, PD, and CAL | Reconstructed bone defect in compromised maxillary anterior teeth. After 2 years, BoP declined from 40% to 16%/absence of PPD beyond 4 mm/average CAL gain of 3.07 mm | | 67 |
| G-AgP/female/39 years old | Modified Widman flap surgery and ridge augmentation (connective tissue graft) | Radiography/PD/microbiological sampling (subgingival plaque) | Clinical and microbiological improvements/enhanced marginal bone levels and reduced probing depth | | 68 |
| G-AgP/Japanese male/32 years | Flap surgery with an administration of 0.3% fibroblast growth factor (FGF-2) | Increase in alveolar bone height (RIBH), CAL, PPD, BOP, GI, PI, tooth mobility, and width of keratinized gingiva | At 36 weeks, alveolar bone height increased by 86.9%, CAL decreased from 9 mm to 6 mm, and PPD from 5 mm to 3 mm/alveolar bone development was observed after 6 years | | 69 |
| Psychotherapy | 50 patients (including ChP) aged 15–50 years | Removal of lining pocket epithelium and debridement/interrupted suture technique | Serum C-reactive protein levels/GI, PI, PPD, and CAL | After 3 months, decreased serum C-reactive protein levels 3.09 ± 1.21 to 1.43 ± 1.21 mg/L/improvements in mean attachment loss, PI, and PD | 70 |
| Psychotherapy | 29 patients aged 16–37 years | Flap surgery | Neutrophil elastase (NE), C-reactive protein (CRP), lipopolysaccharide binding protein, interleukin 6, 8, and leukocyte counts/PPD/BoP | After 5 years, BoP, PPD, and % of affected sites have significantly recovered/higher CRP and NE levels than ChP patients | 71 |
| Psychotherapy | 28-year-old man | Individual, group and conjoint-family psychotherapy | No medication was prescribed during the therapy | Positive effects on patient attitude and behaviour/better periodontal treatment | 72 |
| Psychotherapy | 21-year-old girl | Individual psychotherapy | Diagnosis of mental depression | Treated clinical depression/enhancement in the patient's mental status after 3 weeks | 73 |
| Treatment type | Subjects | Treatment plan | Parameters tested/materials used | Results | Literature cited |
|----------------|----------|----------------|---------------------------------|---------|-----------------|
| Laser therapy (adjunctive) | G-AgP/L-AgP 15 patients aged 18–35 years | Photodynamic therapy | Laser irradiation with 810 nm at 1 W, continuous mode for 30 seconds per tooth | Enhanced PI, BOP, PPD, and CAL/reduced P. gingivalis, A. actinomyctemcomitans, and Prevotella intermedia after 3 months | 74 |
| Others | Lyophilized A.a ATCC 33384 strain Basella serrata and Nigella sativa (Herbal therapies) | Antibacterial effect (MIC) | | Antibacterial effect on A. actinomyctemcomitans with MIC of 128 μg/mL and 512 μg/mL for N. sativab and B. serrata respectively | 75 |
| In vitro | Sonicated bacterial fragments of A. actinomyctemcomitans | Gingival mesenchymal stem/progenitor cells' (G-MSCs) | | Enhanced proliferation and expression of regenerative genes in G-MSCs | 76 |
| Implants | 37-year-old female | Immediate, minimally invasive implant surgery (no bone augmentation or flap raising) | Four zirconia crowns were cemented using extraoral cement on the abutments | Maxillary incisors were restored/stable gingival margins lacking inflammation after 5 years | 77 |
| | 41-year-old male | Immediate implant surgery after extraction and guided tissue regeneration | Four osseospeed Astra implants (4.5 × 11 mm, 4.0 × 11 mm) and (4.0 × 13 mm, 5.0 × 11 mm) | Restored lower anterior incisors and upper right molars/marginal bone stability and no residual pockets and inflammation were observed, after 12 years | 78 |
| | G-AgP/30-year-old female | Implant surgery/sinus elevation of the posterior right maxilla | Bio-Oss® and Bio-Gide® (sinus lift) three implants (4.5 × 13 mm) | Compensated tooth and vertical bone loss in right maxilla/no further bone resorption with any signs of instability, after 2 years | 79 |
| | G-AgP/25-year-old female | Mucoperiosteal flap raising and implant surgery | Three implants of 3.75 mm × 11.5 mm/cemented implant-supported Toronto Bridge | Compensated upper interior region | 80 |
| | G-AgP/30-year-old female | Allograft bone grafts and a resorbable collagen membrane/dental implant after 6 months | Cemented denture/modified 20 × 30 mm collagen membrane | Corrected vertical bone loss in hopeless upper left first premolar | 81 |
| | G-AgP/two patients aged 33 and 44 years | Four conventional and two zygomatic implants/full mouth fixed rehabilitation | Implants were restored with a crown/four 4.3 × 13 implants | No implant failure/peri-implant soft-tissue inflammation (controlled by proper oral hygiene and maintenance) | 82 |
| | G-AgP/24-year-old male | Scaling and root planning/flap surgeries/implants in maxillary and mandibular anterior region | One implant of size 3.5 and three implants of size 4.3 mm × 13 mm/cemented fixed metal–ceramic prosthesis | Successful osseointegration without any biological complications | 83 |
| | G-AgP/5 patients (2 males and 3 females) mean age of 31 years | Implant surgery | Oxide-coated dental implants with a length of 10–15 mm and a diameter of 3.5 or 4 mm/single crowns or removable superstructures | After 6 years, there was 96.2% survival rate compared to only 38.5% implant success rate due to 28.0% mucositis and 32.0% peri-implantitis after 6 years | 84 |
crucial to make vigorous attempt in generating a restrictive definition in order to control it at its earliest stages. Moreover, it is important to develop reproducible and highly sophisticated technologies that use minimal amounts of saliva, plaque, and serum/crevicular fluid. This facilitates simultaneous inspection of many host, microbiologic, and genetic factors. In this manner, diagnostic comparisons can be completed in a relatively unbiased fashion, which aids to identify earliest stages of the disease and helps in preventing further progression.

Since current research generally suggests that there exist defects in immune protective mechanisms, future studies may also consider investigating how expression of host susceptibilities change over time, as well as once the disease is terminated. If certain patterns exist in this regard, then there is another way to understand the nature of this aggressive form of periodontal disease.

**Conclusion**

In conclusion, AgP is a devastating disorder that is characterized by progressive loss of alveolar bone and tooth-supporting tissues. As a result, this leads to less tooth attachment and eventually tooth loss. Although it is infection-induced by several pathogens such as *A. actinomycetemcomitans* and *P. gingivalis*, the pathogenesis of AgP is further complicated by genetic factors, which seem to be linked to host response defects that consequently lead to inability to defend against these destructive pathogens. Radiography and CBCT imaging are widely used to diagnose AgP. However, recent studies showed that certain clinical parameters, obtained from GCF of patients, can assist in early diagnosis of the disease. Moreover, it can be treated using variety of therapies according to the stage of bone loss. Debridement combined with systematic antibiotics and flap surgeries can be used to preserve compromised teeth, whereas costly implants can be carried out to replace hopeless teeth. Since AgP affects face esthetics, psychotherapy is also essential to enhance the patient’s mental status to better engage with treatment. Regardless the polygenic nature of this disease, it is necessary to perform studies concerning the inhibition of periodontal pathogens’ toxins and compensating immunological factors. Finding better treatment options could provide hope for affected young individuals.

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