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REVIEW

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Etiological considerations for the heightened incidence and intensity of periodontal disease in Down syndrome: a narrative review

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Abstract

Cross-sectional and longitudinal studies have consistently reported a heightened prevalence and severity of periodontitis in individuals with Down Syndrome (DS), a phenomenon not solely attributable to poor oral hygiene. Much focus has been placed on the altered immune response and we revisiting immune system abnormalities from an immune cell perspective. Notably, recent studies have investigated the involvement of multiple metabolic pathways in the pathogenesis of DS periodontitis, including phosphoinositide 3-kinase-Akt (PI3K-Akt) signaling pathway, which regulates cell proliferation and inflammatory responses, and we have synthesized these for the first time. Both local and systemic factors predispose patients with DS. This article summarizes the latest contemporary knowledge on periodontal disease in individuals with Down syndrome, which can be used to monitor the oral health status of children with Down syndrome for early intervention.

Keywords

Down syndrome; Periodontitis; Etiological factors; Immunological disorders; Developmental defects

1. Introduction

1.1 Down syndrome

Down Syndrome is a neurodevelopmental disorder with a known genetic cause that affects approximately one in 700 individuals at birth [1, 2]. It is characterized by the presence of all or part of an extra 21st chromosome. The syndrome was first identified in 1866 by Langdon-Down. Trisomy 21 has a well-documented distinctive phenotype that includes systemic abnormalities in immune, haemopoietic, metabolic and endocrine pathways [3].

Since Jones's report in 1889 [4], there has been growing attention to the distinct oral health challenges faced by individuals with Down syndrome. Their heightened susceptibility to dental diseases [5], particularly periodontal diseases, has prompted efforts to understand the underlying reasons. Additionally, people with Down syndrome commonly display specific oral-facial characteristics, which can further increase their risk of oral health issues. These characteristics involve various structural and functional aspects of dental health [6].

The overall health care for individuals with DS must be comprehensive, addressing both general and specific health needs. This includes regular check-ups, preventive care, and addressing any comorbid conditions that are commonly associated with DS. Ongoing research and the development of specific health care guidelines are crucial for improving the quality of life for individuals with DS. These guidelines should include studies focusing on the efficacy of different health care approaches and interventions tailored to their needs [7].

1.2 Periodontitis

Periodontitis is a multifaceted inflammatory disease affecting the tooth-supporting tissues, with complex etiologies and varied clinical manifestations. It typically progresses from gingivitis to a chronic, destructive state that can lead to tooth loss and affect overall health [8, 9]. This condition is primarily driven by pathogenic biofilms formed on the teeth, which induce an inflammatory response in the gingival tissues. When these responses become chronic, they can lead to significant periodontal destruction [10].

The disease's pathogenesis involves a dynamic interplay between oral microbiota and the host's immune system. In periodontitis, the balance between health-associated commensals and pathogenic microorganisms is disturbed, leading to dysbiosis. Periodontitis-associated pathogens have been linked to various systemic diseases, including cardiovascular diseases, diabetes, rheumatoid arthritis, and even certain types of cancer. This association is often mediated by systemic inflammatory responses and bacterial translocation into the bloodstream. The immune response in periodontitis is complex, involving various cells like neutrophils, macrophages, dendritic cells, and lymphocytes. These cells not only defend against bacterial invasion but also contribute to the disease's progression through the secretion of pro-inflammatory cytokines, chemokines, and

enzymes [10].

In 2018, a number of international scientific societies and experts updated and revised the classification of periodontal diseases [11]. The new categorization of periodontal diseases allows for the identification and differentiation of a number of periodontal diseases and conditions, arranged as follows:

(a) Necrotizing Periodontal Diseases.

(b) Periodontitis.

(c) Periodontitis as a Manifestation of Systemic Disease.

This classification highlights the importance of considering systemic factors when addressing periodontal issues in individuals with Down syndrome. Periodontal disease in individuals with Down syndrome is recognized as more than just a localized oral issue. Due to its close association with systemic factors, periodontal disease in individuals with Down syndrome is classified under periodontitis as a manifestation of systemic disease. The systemic nature of Down syndrome contributes to the increased susceptibility and severity of periodontitis in these individuals.

1.3 Prevalence and severity of periodontal disease

Studies have shown that periodontal disease is a common issue among people with DS, with prevalence estimates for those under 35 years of age ranging between 58% and 96% [12, 13]. Additionally, both cross-sectional and longitudinal studies have shown a significant prevalence of periodontal disease among DS individuals under 30 years old [14].

Individuals with Down syndrome presented a high prevalence of periodontitis, mainly related to age. In subjects with Down syndrome, periodontal destruction increases with age and increasingly appears as total attachment loss rather than increased pocket depth [12]. Periodontal disease in DS is characterized by severe gingival inflammation, rapid progression, and an early onset, which makes dental care and regular periodontal treatment crucial for individuals with Down syndrome [13]. Due to their increased susceptibility to periodontitis and early symptom onset, individuals with Down syndrome require prioritized preventive dental care, especially from pediatricians.

2. Etiologic factors of susceptibility to periodontitis in patients with Down syndrome (Fig. 1)

2.1 Local factors

2.1.1 Developmental defects

Individuals with Down syndrome often have oral developmental defects that increase their vulnerability to periodontal diseases. One key issue is the abnormal morphology of teeth and gums; for instance, they have shorter tooth roots, which can lead to reduced periodontal attachment and stability. Additionally, short tooth roots are believed to contribute to tooth mobility and subsequent loss [15]. Furthermore, gingival tissues in individuals with Down syndrome exhibit atypical histological features, including compromised fibroblast migration, crucial for maintaining healthy gingival tissue [16]. Moreover, *Porphyromonas gingivalis* rapidly invades DS gingival fibroblasts (DGFs) and degrades paxillin, inhibiting cell motility and potentially impeding wound healing and periodontal tissue regeneration. This inhibits cell motility and may prevent wound healing and the regeneration of periodontal tissue [17]. High frenum insertion and advanced tongue position, distinctive oral features in individuals with DS, have been identified as contributing to an elevated risk of periodontitis [18].

A recent study involving 23 male and female DS patients aged 16 to 33 of any race found that myalgia and associated myofascial pain were more prevalent in males, while females suffered more from arthralgias. Temporal and occlusal myalgia may affect the severity of masticatory muscle hypotonia (MMH) in men [19]. The reduced muscle tone in individuals with Down syndrome leads to difficulties in effectively chewing food [20]. Chewing naturally cleanses teeth by stimulating saliva production and mechanically removing food particles. Inefficiency in chewing can lead to less effective natural teeth cleaning. Consequently, this can contribute to dental health issues in individuals with Down syndrome, as proper oral hygiene becomes more challenging to maintain.

Enlarged tongue (macroglossia) in individuals with Down syndrome can lead to occlusal issues or tongue thrusting, resulting in malocclusion. Malocclusion, the misalignment of teeth when the jaws are closed, can be aggravated by other common oral manifestations in Down syndrome, such as mouth breathing and improper chewing. These factors combined can make it difficult to maintain proper oral hygiene [5].

Additionally, individuals with Down syndrome have an underdeveloped circulatory system. This underdevelopment can lead to reduced blood flow to tissues (tissue hypoxia), which in turn exacerbates the risk of developing oral diseases. Tissue hypoxia affects the body's ability to fight infections and heal, making oral hygiene maintenance challenging and increasing vulnerability to various oral health issues [21].

2.1.2 Oral microbiologic features

Individuals with Down syndrome exhibit a distinct oral microbial profile (Table 1). In children and adolescents with DS, there is a higher prevalence of *Corynebacterium* [22] and *Tannerella* [23], while *Cardiobacterium*, *Rothia*, *Actinobacillus* and *Prevotella* might have a higher detection rate across a wide age range from 1 to 55 years [18]. Additionally, *Porphyromonas gingivalis*, *Treponema denticola* and *Campylobacter rectus* also show increased abundance in the oral microbiota of DS patients [24]. Conversely, genera such as *Saccharibacteria* (*TM7*) [22], *Abiotrophia*, *Lautropia* [25], *Filifactor*, *Fretibacterium*, *Desulfobulbus* [26], *Alloprevotella*, *Atopobium*, *Candidatus* and *Saccharimonas* [18] may exhibit decreased abundance. *Porphyromonas gingivalis*, as a gram-negative anaerobic bacterium, is significantly involved in the destruction of periodontal tissues through the expression of a number of potentially virulent factors involved in the pathogenesis of periodontitis [27]. And it has been demonstrated that *Porphyromonas gingivalis* with type II fibers is more likely to invade DS gingival fibroblasts compared to human gingival fibroblasts [16, 28].

However, it is worth pointing out that there are contradic-

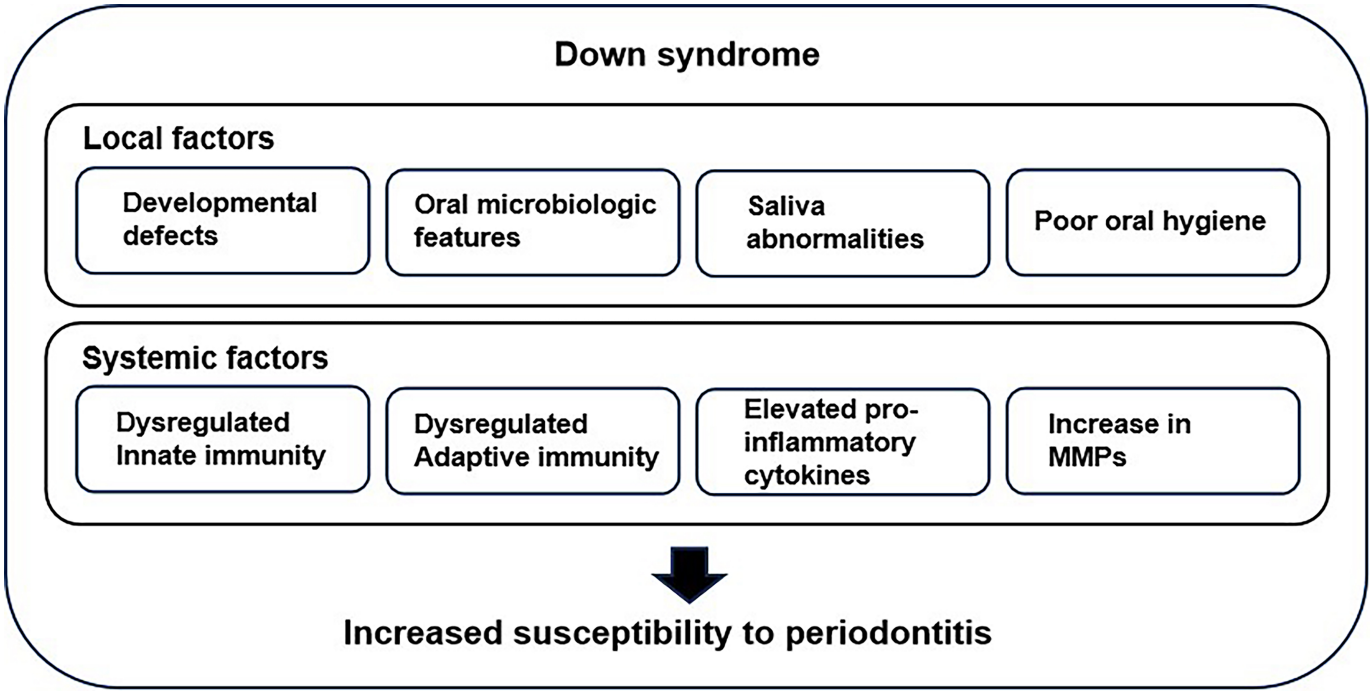

FIGURE 1. The etiological factors of periodontitis susceptibility in individuals with Down Syndrome. Top column: local factors; Bottom column: systemic factors. All these elements collectively contribute to an increased susceptibility of individuals with Down Syndrome to periodontitis. MMPs, Matrix Metallopeptidase.

tory results for certain bacteria, such as Seiji Morishima *et al*. [22] who stated that they were unable to detect *Porphyromonas gingivalis* in the oral cavity of children with Down syndrome, arguing that periodontopathogenic bacteria with high pathogenicity colonize the oral cavity of individuals with Down syndrome in adulthood and participate in the deterioration of periodontal disease [22]. However, Camila Faria Carrada *et al*. [24] showed that higher levels of *Porphyromonas gingivalis* could be detected in the oral cavity of Down syndrome subjects aged 3–12 years. Another example, C Vocale *et al*. [23] showed that *Tannerella* were significantly more prevalent in Down syndrome children (respectively 8 and 9 times) than in controls, but Chieko A study done by Mitsuhata *et al*. [25] showed that *Tannerella* were not detectable in children with Down syndrome.

Notably, despite plaque alone might not fully explaining the severity of periodontal disease in DS patients [34], the undeniable correlation between periodontitis and plaque exists [35]. The reasons for this feature may include the impaired systemic immune status, which is conducive to the early subgingival colonization and growth of periodontal pathogenic bacteria [36], leaving DS patients poorly protected against pathogen invasion [37]. Acquired factor, such as oral cleaning and care, also have an impact on oral microbial community [38], thus affecting the process of periodontitis [39].

The results of a recent bioinformatics study [40] that looked into potential crosstalk genes—genes that are deregulated in both periodontitis and Down syndrome revealed an interaction between tumor protein p53 (TP53), insulin-like growth factor II (IGF2), and insulin (INS), leading to dysregulation of the PI3K-Akt signaling pathway (Fig. 2). The PI3K-Akt signaling pathway plays a crucial role in some infectious diseases. It is involved in many cellular processes, such as glucose metabolism and cell survival. *Porphyromonas gingivalis* produces gingival protease, a toxic enzyme that kills gingival cells and contributes to chronic periodontitis. Studies have shown that *Porphyromonas gingivalis* reduces PI3K activity, promoting periodontal tissue destruction mediated by *Porphyromonas gingivalis* in periodontal disease. Increased PI3K signaling negatively affects neutrophil chemotaxis and polarization. Lipopolysaccharides derived from *Porphyromonas gingivalis* proteins significantly influence autophagy in gingival fibroblasts by inhibiting the PI3K-Akt-mammalian target of the rapamycin (mTOR) signaling pathway, which regulates polymorphonuclear leukocyte activity [41].

2.1.3 Salivary factors

2.1.3.1 Salivary flow

Salivary flow rate was significantly decreased in DS children compared to healthy controls ($p < 0.0001$) [42]. Other scholars' findings support this conclusion [43, 44]. A reduced salivary flow rate can exacerbate conditions such as dry mouth (xerostomia), dental erosive wear, and oral imbalance. Available research does not definitively answer whether the decrease in saliva flow in patients with Down syndrome worsens with age. It's important to note that saliva production can be influenced by various factors, including overall health, medication use, and hydration status, which can vary widely among individuals [45]. While it is established that individuals with Down syndrome may have reduced salivary flow, further research may be needed to conclusively understand the progression of this condition with age.

TABLE 1. Main characteristics of oral microbiology studies in patients with DS.

Author (date) and country	Study design (follow up)	Sample size (cases and controls)	Age of subjects (in years) or (mean ± standard deviation in years)	Main results
T Morinush [29] (1997) Japan	Comparative Study	75 DS	Males (n = 47), 7.0 years Females (n = 28), 6.7 years All children (n = 75), 6.9 years	Colonization by *Actinobacillus actinomycetemcomitans* and *Fusobacterium nucleatum* are associated with the onset of gingival inflammation in DS patients under 5 years old. Colonization by *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Selenomonas sputigena* and *Streptococcus mitis* in DS appears to be associated with gingivitis at puberty.
A Amano [30] (2000) Japan	Research	60 DS 60 NDS	2–13 years old	All pathogens were more frequently in children with DS. *Bacteroides forsythus*, *Treponema denticola*, *Prevotella nigrescens* and *Campyrobacter rectus* were significantly prevalent in DS group. The occurrence of *Porphyromonas gingivalis* was significant in the DS subjects over 5 years old.
A Amano [31] (2001) Japan	Comparative Study	67 DS 41 MD	DS 25.40 ± 4.88 MD 27.00 ± 5.05	Early-onset periodontitis in DS is mainly due to the more susceptible host for the causative microbial agents including *Porphyromonas gingivalis* with type II fimA.
A Khocht [32] (2012) USA	Research	44 DS, 66 non-DS mentally retarded, 83 mentally normal adults	DS 35.81 (1.83) N-DS Mentally Retarded 46.15 (1.40) Mentally Normal 40.93 (1.33)	DS yielded higher proportions of *Selenomonas noxia*, *Propionibacterium acnes*, *Streptococcus gordonii*, *Streptococcus mitis* and *Streptococcus oralis* as compared to NDS.
R E Martinez-Martinez [33] (2013) Mexico	Comparative Study	75 DS patients, 45 with and 30 without periodontitis	PDS 24.7 ± 7.7 DS 21 ± 4.3	The composition of oral biofilm is fundamental for the development of periodontal disease. The frequency of detection of *Actinobacillus actinomycetemcomitans* reported in the literature has a wide range.
Camila Faria Carrada [24] (2016) Brazil	Research	30 G-DS 30 G-ND	3–12 years old	G-DS group has higher densities of *Campyrobacter rectus*, *Porphyromonas gingivalis*, *Treponema denticola*, *Fusobacterium nucleatum*, *Prevotella intermedia* and *Prevotella nigrescens*. Bacterial densities from orange complex were higher in the age group 3–7 years for Fusobacterium nucleatum, Prevotella intermedi and Prevotella nigrescens, Campyrobacter rectus was higher in the age group 8–12 years.
Jesse R Willis [18] (2020) Spain	Research	27 oral rinse samples 20 relatives	27 DS persons (age range 7–55)	DS has less diverse oral microbiomes, which have lower levels of *Alloprevotella*, *Atopobium*, *Candidatus Saccharimonas*, and higher amounts of *Kingella*, *Staphylococcus*, *Gemella*, *Cardiobacterium*, *Rothia*, *Actinobacillus* and greater prevalence of *Candida*.

TABLE 1. Continued.

Author (date) and country	Study design (follow up)	Sample size (cases and controls)	Age of subjects (in years) or (mean ± standard deviation in years)	Main results
Lourdes Nóvoa [26] (2020) Spain	Research	25 PDS 25 HDS	Full sample 26.8 (6.56) PDS 25.1 (6.18) HDS 28.6 (6.61)	*Porphyromonas*, *Treponema*, *Tannerella* and *Aggregatibacter* were higher in the PDS group, as were the less commonly studied *Filifactor*, *Fretibacterium* and *Desulfobulbus* genera.
C Vocale *et al*. [23] (2021) Italy	Case-control study	30 DS 46 ND	DS 5.5 years (SD ± 1.2) ND 4.5 years (SD ± 0.5)	*Actinobacillus actinomycetemcomitans* and *Tannerella forsythia* were significantly more prevalent in Down syndrome children (respectively 8 and 9 times) than in controls. Support the hypothesis of an intrinsic predisposing condition.
Chieko Mitsuhata *et al*. [25] (2022) Japan	Research	40 DS 40 ND	DS Male 18 (10.13 ± 4.45) Female 22 (10.20 ± 4.45) ND Male 18 (8.92 ± 4.15) Female 22 (9.71 ± 4.56)	*Corynebacterium* and *Rothia mucilaginosa* showed higher rates of relative abundance in the DS group. *Abiotrophia* and *Lautropia* showed higher relative abundance in the control group.
Seiji Morishima [22] (2022) Japan	Research	27 DS 27 NDS	PD: DS 2.6 (1.3–4.3) ND 2.4 (1.3–4.4) MD: DS 10.0 (8.0–13.5) ND 9.6 (7.8–11.5)	DS Children had a higher relative abundance of *Corynebacterium* and *Cardiobacterium*, and lower relative abundance of *TM7*.

ND, non-Down syndrome subjects; MD, systemically healthy individuals with mental disabilities; NDS, subjects with non-Down syndrome, but mentally retarded; HDS, periodontally healthy subjects with Down syndrome; PDS, Down syndrome subjects with periodontitis; G-DS, Down syndrome subjects with gingivitis; G-ND, non-Down syndrome subjects with gingivitis; TM7, Bacteria from the Saccharibacteria phylum.

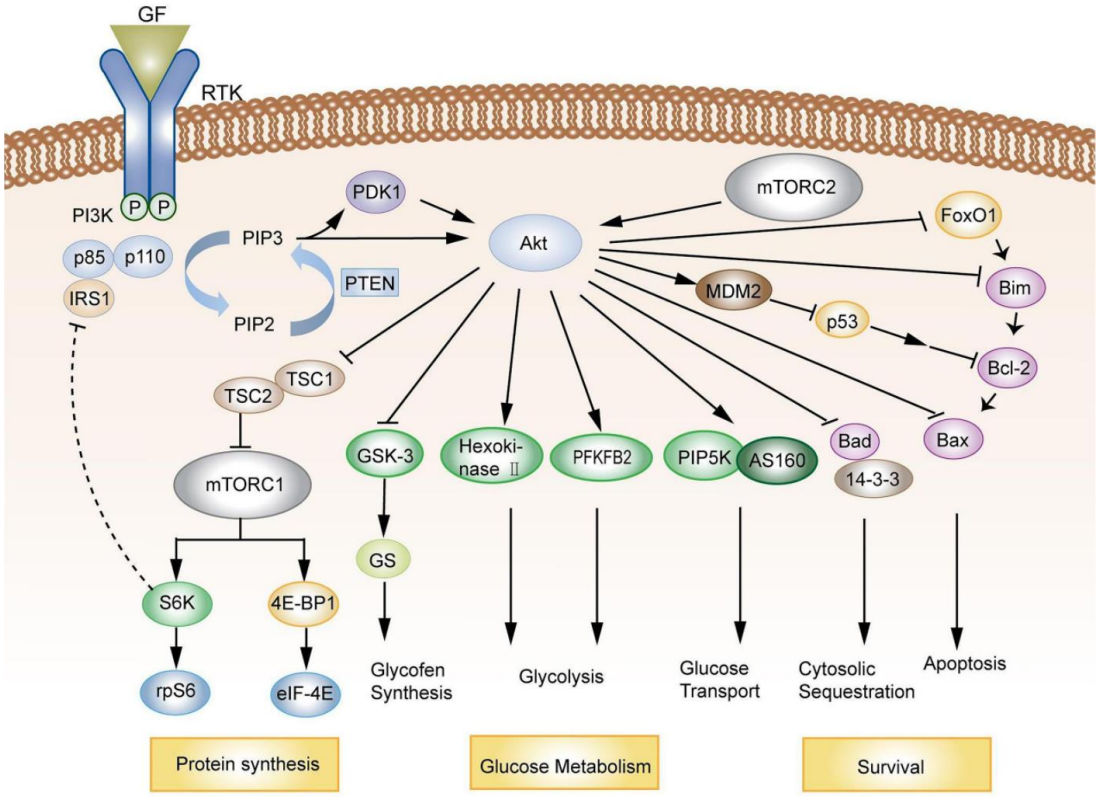

FIGURE 2. Schematic of the PI3K-Akt signaling pathway. RTK recruits PI3K following activation and phosphorylation, and phosphorylates PIP2 to PIP3, which activates Akt by recruiting PDK1 to the PH domain of Akt, thereby activating the entire pathway and regulating protein synthesis, glucose metabolism and survival. PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; GF, growth factor; RTK, receptor tyrosine kinase; PDK1, 3-phosphoinositol-dependent protein kinase-1; PTEN, phosphatase and tensin homolog; PIP2, phosphatidylinositol(4,5)bisphosphate; PIP3, Phosphoinositide 3-kinase; p85, Regulate subunit; p110, catalytic subunit; IRS1, insulin receptor substrate 1; TSC1, TSC complex subunit 1 Gene; TSC2, TSC complex subunit 2; mTORC1, Mechanistic target of rapamycin complex 1; mTORC2, Mechanistic target of rapamycin complex 2; MDM2, Mouse doubleminute 2 homolog; S6K, Ribosomal protein S6 kinase beta; rpS6, ribosomal protein S6; 4E-BP1, 4E-binding protein 1; elF-4E, eukaryotic initiation factor 4E; GSK-3, glycogen synthase kinase-3; PFKFB2, 6-phosphofructo-2-kinase; AS160, RabGAP protein containing multifunctional domain; Bad, Bcl-2asociated death promoter; Bcl-2, B-cell lymphoma-2; FoxO1, forkhead box O1; Bim, Bcl-2 interacting mediator of cell death [41].

A statistically significant increase in Malondialdehyde (MDA), superoxide dismutase activity, and total protein dose was noted in the DS group (all p values < 0.0001) [42]. The elevated levels of superoxide dismutase (SOD) and MDA in saliva demonstrate the important role of oxidative stress and early-onset periodontal disease in individuals with Down syndrome.

2.1.3.2 Antimicrobial peptide

In both DS patients and control groups aged 10–17 years, histatins 3 and 5 (antimicrobial peptides with high activity) showed similar salivary levels. However, while there was a non-significant increase in their concentration with age in DS patients, this led to a notable difference from controls in older age groups, reaching statistical significance (p value 0.02 for both histatins) [46]. A reduction in histatin 5 levels in elderly patients might contribute to the formation of oral *Candida* colonies, which suggests that histatin 5 plays a significant role in preventing fungal colonization in the mouth, particularly in populations such as elderly individuals with Down syndrome [44]. A study that measured levels of leucine leucine-37 (LL-37) (a cationic antimicrobial peptide) and its human cationic antimicrobial protein (hCAP18) precursor in saliva samples from young people with Down Syndrome showed that the secretion rate of the LL-37 component was comparable to that of normal people. However, in cases of oral mucosal acquired immunity (IgA) and systemic immunodeficiency in patients with Down syndrome, normal levels of salivary LL-37 may not be sufficient to prevent periodontitis [47]. Notably, α-Defensins 1, 2 and 3 also exhibited a trend of increasing levels with age in DS subjects, particularly significant for α-defensins 1 and 2 (p value 0.03), but this pattern was not observed in healthy subjects. As a result, α-defensins 1–3 levels were higher in the 18–50 years old DS group compared to controls [46].

2.1.3.3 sIgA

A Comparative Study showed that despite heterogeneity, the results indicated higher average concentrations of IgA in the saliva of people with Down syndrome. Furthermore, while the levels of IgA in the saliva of the sibling group were positively correlated with age, there was no such correlation observed in

people with Down syndrome [48]. Another study involving DS children aged 6 to 14 also corroborated this finding [49].

2.1.3.4 aPRPs (acidic proline-rich proteins), P-B peptide, cystatins and S100A family proteins

In healthy individuals, the concentration of aPRPs increases with age, a trend less evident in DS subjects, resulting in lower aPRPs levels in the 18–50 years old DS group. The DS age group exhibits significantly lower levels of salivary cystatins S, S1, S2 and SN compared to healthy individuals. Across all ages, DS patients consistently showed lower levels of Cystatin SA. In older DS subjects, cystatin B (dimeric form) levels were particularly low, whereas cystatin C levels increased in older healthy subjects but not in DS subjects, possibly due to an increase in its oxidized form in DS individuals. Moreover, P-B peptide concentrations increased with age in healthy subjects, while being more concentrated in the saliva of younger patients. In the saliva of DS subjects, several S100A family proteins were detected, including Psoriasin (S100A7), S100 calcium binding protein A8 Gene (S100A8), S100 calcium binding protein A9 Gene (S100A9), and S100 calcium binding protein A12 Gene (S100A12). S100A7 was more common in younger DS patients (ages 10–17) than in those aged 18–50 years. Salivary S100A8 could serve as a valuable screening tool and potential diagnostic marker for established periodontitis [50]. S100A9 was present in various isoforms, with its short form undergoing age-related oxidation in DS subjects and showing significant differences in phosphorylated and nonphosphorylated levels in older DS subjects compared to controls. S100A9 may control the generation of reactive oxygen species (ROS) and stimulate the mitogen activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) pathways to raise interleukin- 6 (IL-6) and interleukin-8 (IL-8) expression in HGFs [51]. Long glutathionylated S100A9 levels remained constant regardless of age. While less common in younger DS patients and controls, both S100A8 and S100A12 were significantly more prevalent in the 18–50 years old DS group [46].

2.1.3.5 Salivary electrolyte and pH

Saliva in individuals with DS showed increased concentrations of Cl, Ca, Na and K compared to healthy children [52]. Additionally, the concentration of Phosphorous in the saliva of children with Down syndrome was higher than that of normal individuals [53]. Children with Down syndrome aged 2–60 months exhibited a relatively lower saliva pH and higher buffering capacity compared to control children [54]. Nonetheless, the specific impact of alterations in ion concentration, pH, and buffer capacity on early onset periodontitis remains unreported.

2.1.3.6 Oxidative stress biomarkers

The DNA oxidation byproduct 8-hydroxy-20-deoxyguanosine (8-OHdG) is an important biomarker for evaluating oxidative stress. Patients with Down syndrome experience increased production of ROS in GF, resulting in elevated oxidative stress. Both young (1–12 years) and adult (30–62 years) patients with DS exhibited significantly elevated levels of 8-OHdG in their saliva compared to age-matched healthy individuals [44]. This oxidative stress exacerbates the progressive periodontitis characteristic of early aging in patients with DS [55]. An imbalance between the pro-oxidation and antioxidant systems may further increase the risk of periodontal disease. ROS interacts with lipoproteins on cell membranes, leading to lipid peroxidation. The resulting product, MDA, serves as a crucial indicator of oxidative damage detectable in saliva and plasma. These oxidation processes can directly contribute to tissue damage and inflammation, thus exacerbating the progression of periodontal disease [56, 57].

2.1.4 Oral health and hygiene

Children with Down Syndrome generally have poor oral hygiene, influenced by factors such as their ability to perform oral hygiene practices and the level of care and supervision they receive [5]. Another study confirmed that children with Down Syndrome had poor oral hygiene and gingival health. Tartar, plaque, and gingival index values were higher in children with Down Syndrome compared to typical children of the same age [58]. Moreover, children with Down Syndrome had significantly higher calculus levels than healthy children, as reported by a study conducted in Dubai [59]. Older children with Down Syndrome, such as those aged 12 to 16, exhibit significantly higher tartar index, gingival index, and plaque index compared to younger counterparts [5]. This suggests that parents of older children with Down Syndrome should closely monitor them to help maintain oral hygiene habits. A significant and strong inverse relationship was reported between the oral hygiene practices of children with Down Syndrome and those of their parents [60]. The Oral Hygiene Index-Simplified (OHI-S) score decreased to 7.377 with a 1% increase in parents' knowledge, according to the regression analysis's findings.

2.2 Systemic factors (Table 2, Ref. [61, 62])

2.2.1 Systemic immunodeficiency

The development of periodontal disease is significantly influenced by the interactions between the host's immune system and periodontopathogens. Patients with Down syndrome experience premature aging of the immune system, making them prone to infection and immune imbalance [63]. Patients with Down syndrome exhibited decreased levels of interleukin 10 (IL-10), suppressor of cytokine signaling-3 (SOCS3), interferon-inducible protein-10 (IP-10), and intracellular adhesion molecule 1 (ICAM1) mRNA, coupled with elevated expressions of interleukin 10 receptor subunit beta Gene (IL-10RB) and signal transducer and activator of transcription 3 (STAT3) mRNA [64]. This altered expression pattern, particularly the reduction in IL-10 and the potential rise in STAT3 activation, indicates a significant shift in immune response. The transcription factor STAT3 is triggered by a variety of cytokines and growth factors [65]. Involvement of STAT3 in cluster difference (CD)4 T cells in DS may contribute to immunological pathology [2]. This shift is characterized by a reduction in anti-inflammatory agents and an increase in pro-inflammatory mediators. These alterations in the dynamics of the immune system may contribute to the increased frequency and severity of periodontitis in patients

TABLE 2. Major immune system disorders in individuals with Down syndrome [61, 62].

Innate immunity	Adaptive immunity
Decreased neutrophil chemotaxis	Decreased number of B cells
Decreased natural killer cell activity	Smaller-than-normal thymus size
Pro-inflammatory phenotypes of monocyte subsets	Decreased number of T cells (especially naive T cells)

with Down syndrome.

Marcia H. Tanaka *et al*. [66] explored the effects of DS on the regulation of interferon (IFNs) signaling pathways during periodontal disease. The conclusion drawn from this study is that the reduced expression of signal transducer and activator of transcription 1 (STAT1) and interferon regulatory factor 1 (IRF1) genes indicates an impaired activation of IFNs signaling in individuals with DS and PD. The fact that the expression of interferon-alpha (IFN-α), interferon-gamma (IFN-γ), and IFN receptors was not altered in DS patients suggests that indirect mechanisms are involved in the reduced activation of IFN signaling.

2.2.1.1 T Lymphocytes

It has been revealed recently revealed a notable reduction in T lymphocyte numbers in DS individuals. This reduction was evident in both CD4 and CD8 cells. Intriguingly, these cells in DS subjects displayed a distinctive skew towards a memory phenotype [2]. Thymic abnormalities in DS include smaller organ sizes, even in infants and young children [62, 67]. T cell compartments are also compromised by developmental defects of thymocytes and naive T cells, and expansion of memory T cells [68].

2.2.1.2 B Lymphocytes

B lymphocyte dysfunction in children with DS is actually a primary immunodeficiency disease characterized by a fundamental deficiency in B cell differentiation, leading to a significant reduction in the number of switched memory B cells. Children with DS experience alterations in all steps of peripheral B cell development, with more severe defects manifesting in the later stages of B cell development. The number of transitional and mature immature B cells decreased by approximately 50% [69]. Research have revealed low B cell counts in DS patients [2], and more recent studies have found higher apoptosis and decreased proliferation in this population [70].

2.2.1.3 Neutrophils

The high reactivity of DS neutrophils to endotoxins may lead to harmful inflammatory consequences [71]. It cannot be ignored that the main pathogenic bacteria of periodontitis, including *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Actinobacterium semiactinomycetes*, can release endotoxins.

The rate of periodontal damage in DS patients appears to correlate with the degree of neutrophil chemotaxis deficiency. The incidence of bone loss in periodontitis significantly correlates with the patient's age and chemotaxis index [72]. The increased oxidative burst capacity of neutrophils and monocytes is related to clinical evidence of chronic inflammation and periodontitis [73].

2.2.1.4 Monocytes

A significant decrease in monocyte chemotaxis was found [74]. DS children had significantly higher Toll Like Receptor 2 (TLR2) expression on neutrophils, total monocytes, and intermediate and nonclassical monocytes compared to controls [75]. This finding epitomized the pro-inflammatory phenotype of monocyte subpopulations in DS.

2.2.1.5 Natural killer cells

Natural killer (NK) cell cytotoxic activity was reported to be lower in DS patients in a study involving 28 children with the disease and 13 nonmatched controls [76]. In every age group, children with DS had greater absolute NK cell counts than controls; however, the percentage of NK cells in the DS group was only substantially higher than in the controls in children under two years old [77].

2.2.2 Inflammatory mediators and proteolytic enzymes

In people with Down syndrome, elevated levels of proteolytic enzymes and inflammatory factors result in the degradation of periodontal tissue [62]. A. actinomycetemcomitans lipopolysaccharides-induced cyclooxygenase-2 (COX-2) overexpression enhances the ability of gingival fibroblasts to produce Prostaglandin E2 (PGE2) in patients with Down syndrome [21]. According to a meta-analysis of circulating cytokines in children and adults with DS, pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and (IFN-γ) are significantly elevated, with a total sample size of 957 [78]. Louise Malle *et al*. [2] found that people with DS have persistent, stable disruptions in their cytokine levels, similar to those seen in acute COVID-19, leading to the conclusion that DS qualifies as a cytokinopathy.

There is increasing evidence that MMPs play a major role in mediating tissue destruction associated with various periodontal diseases, including the progression from gingivitis to periodontitis [79, 80]. Matrix Metallopeptidase 2 (MMP-2), Matrix Metallopeptidase 3 (MMP-3), Matrix Metallopeptidase 8 (MMP-8), and Matrix Metallopeptidase 9 (MMP-9) levels were higher in GCF in DS patients compared with controls [81, 82], a 2023 comparative study [14] and a study involving 53 subjects [83] also confirmed this. MMPs with collagen-degrading properties, such as collagenases (MMP-1, -8, -13 and -14) and gelatinase (MMP-2 and -9), play a key role in the loss of periodontal support [84]. Furthermore, there exists a distinct relationship between MMP-8 and tissue inhibitor of metal protease 2 (TIMP-2), potentially hindering the turnover of periodontal tissue [85]. Specifically, MMP-8 can facilitate the migration of leukocytes, particularly neutrophils, from the circulation into the gingival sulcus by cleaving collagen and other extracellular matrix components [86]. Research

suggests a positive relationship between serum Matrix Metalloproteinases (MMP-3, -8 and -9) and immune cells in children with Down syndrome, potentially facilitating the migration of CD8 T cells and neural cell adhesion molecule (CD56) NK cells to periodontal tissue [87]. Elevated MMP levels may contribute to an increased migration of T cells, implicating a potential role in the immune response within the periodontal context.

3. Summary and prospects

Local factors like developmental defects, oral microbiological features, saliva abnormalities, and poor oral hygiene, as well as systemic factors such as dysregulated immunity, elevated pro-inflammatory cytokines, and increased MMPs, predispose individuals with Down Syndrome to periodontal disease. To our knowledge, this review is the first to classify salivary antimicrobial peptides as etiological factors contributing to periodontitis in DS individuals. Reduction in histatin 5 levels in elderly DS patients might contribute to oral *Candida* colonization, indicating its role in preventing fungal colonization in the mouth [44]. Furthermore, PI3K-Akt Signaling Pathway is involved in the pathogenesis of periodontitis in DS, which regulates cell proliferation and inflammatory response. Future rigorous observational studies with expanded sample sizes and fine control of confounding factors such as medications and dietary patterns should be conducted and are essential to elucidate the etiology of DS periodontitis. Longitudinal investigations are essential to measure the effectiveness of interventions, with a focus on early preventive measures. Previous oral microbiology studies related to DS have focused primarily on bacteria, with insufficient attention paid to fungi and viruses; therefore, future studies must include these organisms and scrutinize their interactions. Comprehensive investigations encompassing alterations in gingival cell metabolism, changes in glandular secretion, variations in microbial flora, and abnormalities in oral immunity, among other factors, is required to derive valuable outcomes.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

LYS—designed the research study. LYS and LFT—wrote the manuscript. XXT and SFZ—helped with the manuscript and drafted and/or critically revised the work. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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