# Gingivitis in Children with Down Syndrome: Review of Local and Systemic Factors

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## ABSTRACT

**Background.** When compared to healthy children, children with Down Syndrome (DS) have a higher prevalence of gingivitis (46.7%). Individuals with DS have anatomical abnormalities, and mental and orofacial problems. They also have a weakened immune system, resulting in a decrease in the number of T lymphocyte cells, making children with DS more susceptible to infection. This includes an increased prevalence of periodontal diseases, one of which is gingivitis. This systematic review discusses the existing local and systemic factors that may become the etiology of gingivitis in children with DS.

**Objective.** To describe various local and systemic factors as the cause of gingivitis and to find out the main etiological factors of gingivitis in children with DS

**Methods.** We searched PubMed and Google Scholar for Indonesian and English references either in the form of textbook, research results, reviews, and internet articles on the topic. We screened and selected the relevant articles for inclusion into the review.

**Results.** In children with DS, apart from poor oral hygiene, the increasing incidence of gingivitis is caused by changes in other local factors related to systemic factors, such as oral dysfunction, dental and gingival abnormalities, changes in the oral microbial profile, and salivary characteristics. Furthermore, systemic immunodeficiency, changes in inflammatory mediators and proteolytic enzymes, and intellectual subnormality are considered as systemic factors.

**Conclusion.** There is no main etiological factor of gingivitis in children with DS since various local and systemic factors are interrelated with each other causing gingivitis. The severity of gingivitis in children with DS presumably were caused by the systemic factors. Furthermore, good oral hygiene habits and the dentist's intervention in periodontal health can significantly reduce gingivitis in DS patients.

*Keywords: children, Down syndrome, gingivitis, oral health, good health and well-being*



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## INTRODUCTION

Down syndrome (DS) is a condition of retarded physical and mental development of children caused by chromosomal developmental abnormalities. This chromosomal developmental abnormality is due to the failure of a pair of chromosomes to separate from each other during division, which should be two chromosomes; in DS, it becomes three chromosomes.[1,2]

Individuals with DS have anatomical abnormalities, mental and orofacial problems, a weakened immune system, resulting in a decrease in the number of T lymphocyte cells, making children with DS more susceptible to infection including an increased prevalence of periodontal diseases.[3,4] Mouth breathing, delayed eruption, dental malformations, bruxism, fissured tongue and lips, tooth loss, malocclusion,

and macroglossia are several findings found in the oral cavity of patients with DS.[5] The condition of the oral cavity coupled with motor and cognitive developmental barriers in children with DS makes it difficult for them to maintain oral hygiene which has an impact on increasing prevalence of periodontal disease.[2,6]

Gingivitis is defined as inflammation of the gingival tissues caused by accumulation of dental plaque and is characterized clinically by redness, swelling, and bleeding of the tissues. As the periodontal ligament and alveolar bone are not involved in this event, the attachment of the teeth is not affected.[7] There have been many efforts to educate oral hygiene on children and parents of children with DS, but the incidence of gingivitis remained high. In a study in Jakarta, Indonesia, in 174 children with DS aged less than 14 years, 3.4% of them did not have gingivitis, 47.2% had mild gingivitis, 40.8% had moderate gingivitis, and 8.6% had severe gingivitis.[6] Furthermore in all sextants of the mouth, children with DS had significantly higher rates of gingivitis (46.9%) than controls (34%).[8]

Gingivitis can manifest differently in DS children than in healthy children. An experimental gingivitis study discovered that DS children developed more rapid and extensive gingivitis around deciduous teeth than normal control children.[9] Gingivitis in children with DS is influenced by two major factors: local factors and systemic factors. Oral hygiene, impaired oral function, dental and gingival abnormalities, salivary characteristics, and changes in the oral microbial profile are examples of local factors. Systemic immunodeficiency, inflammatory mediators, and proteolytic enzymes, low intellectual level, impaired circulation leading to tissue hypoxia, and propensity to infections, as well as systemic endocrine dysfunction are examples of systemic factors.[10,11] Some of these factors are thought to contribute to the high prevalence of gingivitis in children with DS. This paper discusses the etiology of gingivitis in children with DS based on various related local and systemic factors.

## METHODS

The inclusion criteria were: 1) studies published in English and Indonesian. 2) studies accepted and published in the last 20 years (2000–2020); 3) textbook articles, original articles, research reports, and reviews on the topic; 4) studies that evaluated gingivitis in Down syndrome and healthy children.

We performed electronic searches in PubMed and Google Scholar using the following keywords "children", "Down syndrome", "gingivitis", "oral health", "good health and well-being".

We screened the titles and abstracts from the searches for potentially relevant articles and applied inclusion criteria to retrieved full reports to determine which articles fulfilled our criteria for the review.

We collected the following data from each article: author/year, type of article, sample size, and results. We categorized the factors contributing to gingivitis in patients with DS as local and systemic. We summarized the characteristics of each study and relevant factors.

## RESULTS

We identified 250 titles and abstracts from the databases. After screening and full report assessment for eligibility, a total of 26 articles were included in the review (Table 1).

**Table 1.** List of included studies in review

| Author and Year | Type of Article | Sample Size | Results |
|---|---|---|---|
| ***Dean et al. (2016)*** | Textbook chapter | — | • The definition of DS is a condition of retarded physical and mental development of children caused by chromosomal developmental abnormalities |
| ***Rosida et al. (2006)*** | Clinical Study | 24 | • In DS, chromosomal developmental abnormality is formed due to the failure of a pair of chromosomes to separate from each other during division, it becomes three chromosomes |
| ***Ghaith et al. (2017)*** | Review Article | — | • Individuals with DS have anatomical abnormalities, mental and orofacial problems, also a weakened immune system, resulting increased prevalence of periodontal diseases |
| ***Shyama et al. (2003)*** | Original Article | 106 | |
| ***Asokan et al. (2008)*** | Comparative Study | 130 | • Oral manifestations in children with DS consist of mouth breathing, delayed eruption, dental malformations, among others. |
| ***Amira et al. (2019)*** | Clinical Study | 174 | • In individual with DS: 3.4% had no gingivitis, 47.2% had mild gingivitis, 40.8% had moderate gingivitis, and 8.6% had severe gingivitis. |
| ***AlSarheed (2015)*** | Original Article | 93 children with DS 99 healthy children | • Children with DS have a higher prevalence of gingivitis than healthy children. |
| ***How et al. (2016)*** | Review Article | — | • Gingivitis is defined as inflammation of the gingival tissues caused by accumulation of dental plaque and is characterized clinically by redness, swelling, and bleeding of the tissues. |

**Table 1.** List of included studies in review *(continued)*

| Author and Year | Type of Article | Sample Size | Results |
|---|---|---|---|
| ***Ghaith et al. (2019)*** | Clinical Study | 106 | • The prevalence of periodontal disease in DS patients is reported to be significantly higher than the normal population. The compromised immune system with a decrease in the number of T cells increases the liability of DS individuals to infections including periodontal disease |
| ***Amano et al. (2008)*** | Review Article | — | • Down syndrome related periodontitis is caused by such factors as immunological deficiency, poor oral hygiene, fragile periodontal tissue, early senescence, salivary deficiency, and poor masticatory function. |
| ***Ziętek et al. (2019)*** | Clinical Study | 150 | • Patients with DS exhibited a positive correlation between the values of OHI-S and API, and the values of mSBI and GI |
| ***Hastin et al. (2014)*** | Cross sectional study | 14 | • In Down syndrome, patients have a high level of gingivitis severity.<br>• There is a link between gingivitis severity and oral hygiene in patients with Down syndrome; gingivitis severity was significantly associated with a positive relationship with plaque. |
| ***Gupta (2016)*** | Textbook chapter | — | • The root of the teeth is much shorter in children with DS, resulting in a decrease in periodontal attachment area<br>• The habit of breathing through the mouth causes the gingiva to dry, increasing the occurrence of gingivitis<br>• Children with DS and children with lower-than-average mental abilities have significantly more total aerobic bacterial colonies in their plaques than normal individuals<br>• Connective tissue changes, may be responsible for the progressive periodontal disease seen in people with DS |
| ***Macho et al. (2014)*** | Review Article | — | • Malocclusion is common in most Down Syndrome patients, which can lead to tooth irregularities and increased periodontal disease. |
| ***Arerias et al. (2015)*** | Review Article | — | • Reduced saliva flow in DS patients may be due to changes in the secretory function of the salivary glands of people with trisomy 21 and/or hypotonic muscle. |
| ***Rosdiana and Rizal (2012)*** | Literature Review | — | • In periodontal disease, sIgA is considered to be the most responsible immune component.<br>• In children with DS, it was reported that salivary sIgA levels were significantly higher |
| ***Corthésy (2013)*** | Review Article | — | • sIgA consists of IgA1 isotype which shows reactivity against *S. mutans*, while IgA2 isotype has reactivity to lipoteichoic acid produced by *S. pyogenes* and to lipopolysaccharides produced by *Porphyromonas gingivalis*, *B. fragilis* and *E. coli* |
| ***Pietrzak et al. (2020)*** | Review Article | — | |
| ***Salman (2015)*** | Original Research | 60 | • Mechanism antibacterial of sIgA consist of binding, reduce the negative surface charge and hydrophobicity of bacteria, limiting the potential for ionic and hydrophobic interactions between bacteria and host receptors, sterically block the binding of adhesins to complementary surface receptors on the surface of host cells, and neutralization |
| ***Brandtzaeg (2013)*** | Review Article | — | |
| ***Bachrach et al. (2006)*** | Research Article | — | • Saliva LL-37, a cationic antimicrobial peptide, is commonly found to be secreted in people with Down syndrome. |
| ***Marcovecchio et al. (2019)*** | Clinical Study | — | • Expression of membrane types MMP-1 and MMP-2 by gingival fibroblasts in DS patients was found to be higher than in healthy controls. |
| ***Zhou et al. (2006)*** | Research Article | | • Neutrophil and monocyte chemotaxis disorders, as well as a reduction in cell number and shape Mature T has been well documented in DS patients<br>• SOD activity is increased in various tissues in people with DS |
| ***Tsiligaradis et al. (2003)*** | Comparative Study | | • The Dscam gene causes an increase in thymocyte deletion and a decrease in the proportion of mature T cells in the thymus |
| ***Anders et al. (2010)*** | Systematic Review | — | • Impaired physical coordination and cognitive skills limit the ability of DS patients |
| ***Lopez-Perez et al. (2008)*** | Clinical Study | 44 | • There is a link between dental plaque and the severity of gingivitis in persons with DS |
| ***Jokić et al, (2007)*** | Clinical Study | 160 | • Parents should be encouraged to help their children achieve acceptable oral hygiene measures. |
| ***Ferreira et al. (2016)*** | Systematic Review | — | • Professional intervention and periodontal maintenance significantly reduced plaque and gingival indices in DS patients. |

*DS, Down Syndrome; OHI-S, Oral Hygiene Index-Simplified; API, Approximal Plaque Index; mSBI, modified Sulcus Bleeding Index; GI, Gingival Index; SOD, Superoxide Dismutase*

## DISCUSSION

### Local Factors in the Etiology of Gingivitis in Children with DS

#### *Oral Hygiene*

Oral hygiene plays a key role in the occurrence of gingivitis in children with DS, this is confirmed by several research results. There is a significant correlation between oral hygiene and periodontal conditions in children with DS. Poor oral hygiene will increase plaque score and calculus formation. The level of plaque scores in children with DS is higher than in normal children, which leads to a higher prevalence of gingivitis. An investigation found a positive correlation between the values of OHI-S (Oral Hygiene Index-Simplified) and API (Approximal Plaque Index) and the values of mSBI (modified Sulcus Bleeding Index) and GI (Gingival Index) in patients with DS. Only OHI-S and API were found to have a positive relationship with mSBI in healthy controls (Table 1).[8,10-12]

#### *Abnormalities in Teeth and Gingival Tissues*

Gingivitis is also caused by abnormalities in the teeth and gingival tissues in children with DS. Tooth abnormalities that occur in relational aspects take the form of malocclusion. The presence of malocclusion makes it difficult to clean the teeth, resulting in an increase in plaque accumulation. Malocclusion is common in most patients with DS due to delayed tooth eruption and maxillary development. Smaller maxillary can result in open bites, which can lead to tooth irregularities and increased periodontal disease. A longitudinal study of tooth spacing, crowding, and frenum attachment position discovered a clear correlation between dental crowding and areas of periodontal disease. Malocclusion can also result in traumatic occlusion, which contributes to periodontal breakdown. High frenum attachment is associated with higher rates of severe periodontal disease.[10,13] Anatomical tooth abnormalities in children with DS may be the cause of premature tooth loss due to periodontal disease. The root of the teeth is much shorter in children with DS, resulting in a decrease in periodontal attachment area, which can contribute to the onset of periodontal disease (Table 1).[14]

Gingivitis is known to be exacerbated by histological changes in the gingival tissue. Histological examination revealed the presence of severe gingival inflammation in patients with DS due to hyperinnervation of the gingiva's sensory component. This hyperinnervation may be caused by the inflammatory reaction's growth of afferent nerves, and it may also contribute to gingival inflammation. Furthermore, chemical transmitters released by nerves are responsible for the occurrence of inflammatory reactions; as gingival sensory components are hyper innervated, the chemical transmitter components of inflammatory reactions will increase in number. Gingival biopsies from children with DS were examined in a study, and the results revealed various stages of chronic periodontal disease, as well as striking features of increased vascularity and atrophic epithelium. This condition reduces tissue resistance to local irritation, resulting in gingival damage.[10]

Cellular migration of gingival fibroblasts is an important function for wound healing and regeneration of periodontal tissue that was destroyed during the inflammatory process. The migration of cultured gingival fibroblasts in people with DS was significantly hampered by the periodontal pathogen *Porphyromonas gingivalis* (*P. gingivalis*), compared to gingival fibroblasts in healthy people. Because *P. gingivalis* and intracellular pathogens have infiltrated fibroblasts, they interfere with cellular adhesion, which is required for fibroblast migration.[10]

#### *Oral Function Disorder*

Oral function disorder occurs in children with DS as a result of poor neuromotor control and deformity of the oral structures. It happens because of hypotonicity of the tongue and perioral muscles. The habit of sticking out the tongue and opening the lips is caused by hypotonic tongue and perioral muscles. There are also oral structural deformities in children with DS, such as macroglossia and microstomia, in which the tongue is large, but the oral cavity is small, resulting in the habit of breathing through the mouth. The habit of breathing through the mouth, compounded by the habit of sticking out the tongue and opening the lips, causes the gingiva to dry, increasing the occurrence of gingivitis (Table 1).[10,14]

#### *Characteristics of Saliva*

Saliva flow rate and secretion, levels of sIgA, and levels of antimicrobial peptides are all factors that influence periodontal disease in children with DS. A study found that children with DS had a lower salivary flow rate when they were 6 to 10 years old. Salivary secretion is thought to be about half that of normal children in cases of DS. Reduced saliva flow in patients with DS may be due to changes in the secretory function of the salivary glands of people with trisomy 21 and/or hypotonic muscle. Many other studies have found that people with DS have an age-dependent decrease in salivary secretion. Reduced salivary flow and secretion in children with DS reduces cleaning power in the oral cavity, making plaque retention more likely.[10,15]

In periodontal disease, sIgA is the most responsible immune component. Bacterial colonization was shown to be inhibited by salivary sIgA. In children with DS, it was reported that salivary sIgA levels were significantly higher and the prevalence of dental caries was lower. Salivary sIgA is considered a local mucosal immune system that does not really need to cooperate with other systemic immunity. This event is called the immune exclusion mechanism. When there is an antigen in the oral cavity, the T-shaped Fab fragment will capture the antigen, and this is where the binding process occurs. Secretory Immunoglobulin A

(sIgA) interferes with the attachment of bacteria to the host cell surface by preventing non-specific and stereochemical interactions (Table 1).[16-18]

The binding of sIgA to adhesins can reduce the negative surface charge and hydrophobicity of bacteria, thereby limiting the potential for ionic and hydrophobic interactions between bacteria and host receptors. The reduction in bacterial hydrophobicity may be due to the heavy glycosylation of the Fc and SC components which impart hydrophilicity to the sIgA molecule. The results of a study also suggested that sIgA can sterically block the binding of adhesins to complementary surface receptors on the surface of host cells. After that, the bacteria will undergo a neutralization process that aims to remove enzymes and toxin products from the bacteria. After neutralization, sIgA impairs bacterial adhesion by means of agglutination, thereby facilitating clearance by secretion. Thus, the penetration of antigen into the oral mucosa can be prevented by the mechanism of action of sIgA.[17-20] About 60% of sIgA consists of IgA1 isotype which shows reactivity against S. mutans, while IgA2 isotype has reactivity to lipoteichoic acid produced by S. pyogenes and to lipopolysaccharides produced by *Porphyromonas gingivalis, B. fragilis* and *E. coli* (Table 1).[20]

Antimicrobial peptides, in addition to sIgA, are thought to play an important role in the first line of defense in the oral cavity. These molecules have direct bactericidal activity as well as indirect immune system stimulation through chemotactic activity and cytokine induction. Saliva LL-37, a cationic antimicrobial peptide, is commonly found to be secreted in people with DS. Although the sIgA level in children with DS is high and the LL-37 salivary secretion level is normal, it is insufficient to prevent periodontal disease, both gingivitis and periodontitis, because it is accompanied by a systemic immune deficiency found in children with DS (Table 1).[10,21]

### *Changes in Oral Microbial Profile*

Periodontal disease is also influenced by the oral microbial profile of people with DS. Bacterial-neutrophil interactions may play a role in periodontal disease virulence. The pathogenicity and effect of the black pigmented Bacteroides subspecies on polymorphonuclear leukocytes are well known. Bacteroides with black pigmentation was isolated from the gingival sulcus in 71% of children with DS and 10% of non-gingivitis controls. This statistically significant difference supports the link between the presence of black pigmented Bacteroides and the prevalence of periodontal disease. It has been reported that children with DS and children with lower-than-average mental abilities have significantly more total aerobic bacterial colonies in their plaques than normal individuals.[14] *P. gingivalis, Treponema denticola, and Tannerella forsythensis* were found in greater numbers in children with DS than in the control group at the same age, indicating that periodontal pathogens colonize at an early age and then mature into pathogenic microflora in the oral cavity. *P. gingivalis, A. actinomycetemcomitans, and T. forsythensis* were found in significantly higher numbers in 70 DS subjects aged 8–28 years when compared to healthy people and cerebral palsy patients. These findings suggest that periodontal pathogens can colonize and survive in the oral cavity of people with DS from an early age (Table 1).[10,11]

## Systemic Factors in the Etiology of Gingivitis in Children with DS

### *Inflammatory Mediators and Proteolytic Enzymes*

Changes in inflammatory mediators and proteolytic enzymes in children with DS will result in a different response than in normal individuals. Periodontal pathogens such as *P. gingivalis* induce the production of inflammatory mediators such as prostaglandin E2 (PGE2), matrix metalloproteinases (MMPs), and proinflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-8 in periodontal cells. These mediators activate host cells to bind the exaggerated inflammatory response of the host. People with DS have an exaggerated inflammatory response to periodontal infection. In patients with DS, the lipopolysaccharide *A. actinomycetemcomitans* significantly increased PGE2 production by inducing COX-2 (PGE2-producing enzyme) mRNA expression by gingival fibroblasts. Furthermore, *P. gingivalis* infection significantly increased COX-2 and IL-6 mRNA expression by gingival fibroblasts in these patients with DS. The periodontal breakdown is caused by MMP overexpression. Furthermore, the expression of membrane types MMP-1 and MMP-2 by gingival fibroblasts in DS patients was found to be higher than in healthy controls. TIMP-2's inhibitory capacity against MMP-2 is also suppressed and functionally diminished. Several processes that occur in all of the above may be involved in periodontal destruction in people with this syndrome (Table 1).[10,22,23]

### *Systemic Immunodeficiency*

Other subfactors in systemic immunodeficiency factors include phagocytic and chemotactic responses, changes in oxidative metabolism associated with genes on chromosome 21, and Dscam (Down syndrome cell adhesion molecule) genes on chromosome 21. Neutrophil and monocyte chemotaxis disorders, as well as a reduction in cell number and shape Mature T has been well documented in DS patients. The initial discovery of the neutrophil anomaly in DS shows a poorly segmented nucleus with normal numbers of neutrophils and leukocytes, implying a younger cell shape. In DS patients, this phenomenon is regarded as a trend toward a shorter neutrophil life cycle half-life. Furthermore, a significant decrease in the number of neutrophils in DS children, accompanied by the occurrence of chemotaxis defects, is thought to be significantly correlated with the development of gingivitis and periodontitis in DS patients, including bone loss. The phagocytic ability of neutrophils in people with DS has also been shown to be reduced, with in vitro phagocytosis against *Candida albicans* being

significantly inefficient. Furthermore, peripheral T cells (lymphocytes) have been reported to be reduced in children with DS, both quantitatively and qualitatively, which is qualitatively related to T cells' ability to recognize and respond to specific antigens (Table 1).[10,24]

Cellular immune disorders characterized by functional defects in polymorphonuclear leukocytes and monocytes could explain the increased susceptibility to periodontal disease. The immature immune system is under stress, as the antigenic stimulus is so strong that the immune system becomes overburdened. As a result, most studies indicate that an atypical pattern of T cell immunodeficiency, combined with functional defects and decreased activity of polymorphonuclear leukocytes and monocytes, may result in inadequate responses to bacterial attack. This, along with connective tissue changes, may be responsible for the progressive periodontal disease seen in people with DS.[14]

Changes in oxidative metabolism are linked to genes on chromosome 21 in children with DS. The superoxide dismutase (SOD) gene, which is located on trisomic chromosome 21q.16, was found to be overexpressed in T-lymphocytes from two patients with DS. SOD is a key enzyme in the conversion of superoxide-derived oxygen ($O_2$) to hydrogen peroxide ($H_2O_2$), and SOD activity is increased in various tissues in people with DS. The increase in $H_2O_2$ produced by abundant SOD can react with transition metals such as iron to form hydroxyl radicals, which can initiate lipid peroxidation and cause cell membrane damage. Thus, increased SOD activity theoretically reduces immunity in people with DS. First, increasing SOD activity raises $H_2O_2$, which can harm immune cells and interfere with cellular signal transduction processes involved in phagocytosis. Second, it will lower the concentration of $O_2$, resulting in a reduction in phagocytic bactericidal activity. Another study found that neutrophils from people with DS produce less oxygen than normal people. The presence of the Dscam gene (cell adhesion molecule in DS) in individuals with DS, which was isolated from chromosome 21q22.2-22.3, proved to be a new member of the immunoglobulin superfamily and belongs to the nerve cell adhesion molecule relevant to nerve fibers. The Dscam gene causes an increase in thymocyte deletion and a decrease in the proportion of mature T cells in the thymus. This situation alters thymic epithelial cells (TEC) and impairs T cell function, increasing susceptibility to infection (Table 1).[10,24]

### *Low Intellectual Level*

Children with DS are characterized by low intellectual levels. Which also contributes to the occurrence of periodontal disease. Children with DS have a low intellectual level that limits their ability to learn, communicate, and adapt to the environment, in addition to that resulting in limited manual dexterity. Impaired physical coordination and cognitive skills limit the ability of DS patients to independently perform sequential tasks such as daily tooth brushing, it plays a role in the occurrence of poor oral hygiene, resulting in the accumulation of plaque and debris. The accumulation of plaque and debris is an important local factor in the occurrence of gingivitis (Table 1).[11,25,26] Parents should be encouraged to help their children achieve acceptable oral hygiene measures. As a result, as part of the prevention plan for DS children's oral health, the dentist should educate the parents.[27] Furthermore, professional intervention and periodontal maintenance significantly reduced plaque and gingival indices in DS patients, regardless of treatment performed. The use of CHX also reduced these parameters.[28]

## CONCLUSION

There is no main etiological factor of gingivitis in children with DS since various local and systemic factors are interrelated with each other causing gingivitis. The severity of gingivitis children with DS presumably were caused by the systemic factors. Furthermore, good oral hygiene habits and the dentist's intervention in periodontal health can significantly reduce gingivitis in DS patients.

### Statement of Authorship

AO, TS and SW contributed in the conceptualization of work, acquisition and analysis of data, and drafting of the manuscript. AN and DS contributed in the translation and proofreading of the manuscript. AO, TS, SW and UT critically revised the manuscript. All authors approved the final version submitted.

### Author Disclosure

All authors declared no conflicts of interest.

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