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Literature Reviews

# The relation between salivary sIgA level and caries incidence in Down syndrome children

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***ABSTRACT***

***Background:*** *Down syndrome or Trisomy 21 is a genetic disorder caused by extra chromosome on chromosome 21. Down syndrome child, however, has good resistance against caries, and some of them even are caries-free. It is because the level of salivary sIgA in Down syndrome children is equal or even higher than that in normal children.* ***Purpose:*** *This review was aimed to review the relation between salivary sIgA level and caries incidence in Down syndrome children.* ***Reviews:*** *Down syndrome is a collection of symptoms caused by chromosomal abnormality that has a number of physical and mental disorders. Down syndrome children, nevertheless, have significantly lower incidence of caries than normal children. These conditions are thought to relate to characteristics of oral cavity and the level of salivary sIgA in Down syndrome children. Caries is a disease of dental hard tissues caused by the fermentation of sucrose into glucans by glucosyltransferase enzymes (GTF) of Streptococcus mutans (S. mutans). One of proteins in saliva that acts as a defense mechanism is imunoglubulin. Secretory immunoglobulin A (sIgA) inhibits the activity of S. mutans as bacteria causing caries forming glucan. This immunoglobulin, sIgA, is the most abundant immunoglobulin in saliva. The level of salivary sIgA in Down syndrome children is significantly higher than that in normal children.* ***Conclusion:*** *Besides factors of tooth eruption delays, wide spaces among teeth, microdontia, pH, and high saliva contents (calcium, sodium, bicarbonate), the low incidence of caries in Down syndrome children is also related with the higher level of salivary sIgA in Down syndrome children than that in normal children.*

***Key words:*** *Down syndrome, sIgA, caries*

***ABSTRAK***

***Latar belakang:*** *Sindroma Down atau Trisomi 21 merupakan kelainan genetik yaitu adanya kromosom ekstra pada kromosom 21. Anak sindroma Down memiliki resistensi yang baik terhadap karies dan sebagian dari mereka bebas karies. Kadar sIgA saliva anak sindroma Down sama atau bahkan lebih tingi dari anak normal.* ***Tujuan:*** *Tujuan dari tulisan ini adalah mencari hubungan antara kadar sIgA di dalam saliva dengan kejadian karies pada anak sindroma Down.* ***Tinjauan pustaka:*** *Sindroma Down adalah suatu kumpulan gejala akibat abnormalitas kromosom yang memiliki sejumlah kelainan fisik dan mental. Anak sindroma Down secara signifikan memiliki prevalensi karies yang lebih rendah jika dibandingkan anak normal. Kondisi ini diduga berhubungan dengan karakteristik rongga mulut dan kadar sIgA saliva anak sindroma Down. Karies merupakan penyakit jaringan keras gigi yang disebabkan oleh fermentasi sukrosa menjadi glukan oleh enzim glucosyltransferase (GTF) dari Streptococcus mutans (S. mutans). Salah satu protein di dalam saliva yang berperan sebagai mekanisme pertahanan adalah imunoglubulin. Imunoglobulin A sekretori (sIgA) berperan menghambat aktivitas S. mutans sebagai kuman penyebab karies membentuk glukan. sIgA adalah imunoglobulin yang paling banyak terdapat pada saliva. Kadar sIgA saliva sindroma Down signifikan lebih tinggi dibandingkan anak normal.* ***Kesimpulan:*** *Rendahnya insiden karies anak sindroma Down berhubungan dengan kadar sIgA di dalam saliva anak sindroma Down yang lebih tinggi dibandingkan anak normal selain faktor keterlambatan erupsi gigi geligi, ruang antar gigi yang lebar, mikrodonsi, pH dan kandungan saliva (kalsium, sodium, bikarbonat) yang tinggi.*

***Kata kunci:*** *Sindroma Down, sIgA, karies*

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## INTRODUCTION

Down syndrome or Trisomy 21 is a collection of symptoms caused by abnormality of chromosome 21.[1] In some reports, this disorder is closely related to mother's age during her pregnancy.[1,2] Down syndrome children have abnormality characteristics which are delayed growth and development, both physically and mental.[1,2] The incidence of Down syndrome children in the world is about one of 800-10000 births.[3]

Down syndrome children, however, have a good resistance against caries, and some of them even are caries-free. Some studies said that the incidence of caries in those Down syndrome children is low.[4–6] Previous research even reported that 44% of Down syndrome children are free of caries.[3] These conditions are related to delay in eruption of permanent and deciduous teeth, hypodontia, microdontia, wide interdental space, and high concentration (pH) of saliva.[5]

Saliva has protective function against microorganisms in oral. One of proteins in saliva that acts as a defense mechanism is imunoglubulin. The most abundant immunoglobulin in saliva is secretory immunoglobulin A (sIgA). As the most important specific defense, sIgA protect oral cavity from bacterial pathogens. The main function of the antibody, sIg A is to limit penetration of microorganisms into oral. Specifically, the role of sIgA is to inhibit adhesion of *S. mutans* adhesin on tooth surface.[7]

Thus, several previous researches have been conducted to find the relation between the level of sIgA in the saliva and the incidence of caries in Down syndrome children.[5,6,8] The low incidence of caries is associated with the higher level of sIgA than that in normal children.[6] Therefore, this research is aimed to review the relation between salivary sIgA and caries incidence in Down syndrome children.

### Characteristics of systemic Down syndrome

Down syndrome was first described by Langdon Down in 1865 based on physical findings in patients with Down syndrome.[5] Down syndrome babies can be born from mothers with all ages, but the risk of Down syndrome births increases as the increasing of maternal age during pregnancy.[2] Based on cytogenetic examination, Down syndrome is generally divided into three types: trisomy 21, translocation, and mosaic. Type of Trisomy 21 occurs when there is an extra chromosome on chromosome 21 it has 47 chromosomes.[9] Type of translocation occurs when there is a segment of chromosome 21 attaching to another chromosome (usually chromosome 14), but the number of chromosomes is still 46.[2] Meanwhile, type of mosaic occurs when some cells have normal complement of 46 chromosomes and others have 47 chromosomes (an extra chromosome on chromosome 21).[3]

A number of physical abnormalities that can be found in Down syndrome children are body with short and fat hand, round face with a flat profile, brachycefalics, pleated epicanthus, strabismus (crossed eyes), small maxilla, short hands and fingers, muscle hypotonus, and distance between the first and second fingers.[1,2,10,11] Moreover, bottom face of Down syndrome children is more dominant, with slanted eyes and significant protruding forehead.[9]

The degree of retardation is determined by Intelligence Quotient (IQ) and Social Quotient (SQ). According to American Association of Mental Deficiency (AAMD), mental retardation is divided into four categories: mild retardation with a score of 55-69, moderate retardation with a score of 40-54, severe mental retardation with a score of 25-39, and profound mental retardation with score of less than 25.[12] Although there are some people with Down syndrome have an IQ above 69, but almost all people with Down syndrome get mental retardation that varies from mild to profound.[13]

It can be found physical examination of Down syndrome patients, leukemia, infections especially on respiratory track, hepatitis B, Alzheimer, and congenital cardiac abnormalities can be found.[1–3] Gene expression of trisomy 21 in Down syndrome, furthermore, causes various abnormalities of immune system.[1] Down syndrome also has systemic immune system disorders, including immunodeficiency of mucosa humoral immune response.[1,14] Some researches even have found that high rate of infection in Down syndrome patients is caused by immune system disorders.[1,14] This can be shown by a defect in neutrophil chemotaxis of PMN leukocytes, antibody response damage against specific pathogens, decreasing number of T lymphocyte cells and immaturity of lymphocyte cells T.[14]

### Caries in Down syndrome children

Down syndrome children have significantly lower prevalence of caries than normal children.[4,5,15] Caries lesion in Down syndrome children is limited to the occlusal surface, while in smooth and proximal surface are rarely occurs.[5] Down syndrome children have good resistance against caries, and some of them are even free of caries.[4] These conditions were related to delay in eruption of primary and permanent teeth, less contamination of cariogenic foods, hypodontia, microdontia, the interdental space, and high salivary pH.[1,5] Previous studies have reported that 29.4–53% of Down syndrome children are free of caries, whereas only 0.5% of normal children are free of caries.[4,6]

Microorganism that plays role in the caries process is *S. mutans*.[1,12,16,17] Previous studies have reported that the number of *S. mutans* in Down syndrome children is lower than that in control group of normal children with caries.

This is associated with a low prevalence of caries in Down syndrome children.[5,18]

Balance of pH and salivary buffering capacity is influenced by quantitative and qualitative of electrolytes in saliva. Buffering capacity of saliva is an ability to maintain and neutralize low pH of saliva, its ability due to clusters of bicarbonate, phosphate, urea, protein, and mainly determined by the content of phosphate and bicarbonate. The composition of calcium, sodium, bicarbonate, pH and buffering capacity of saliva in Down syndrome children was higher than that in normal children, so it can inhibit demineralization.[8,14,18,19]

**The protective role of salivary sIgA in caries process**

Saliva plays a role in oral health by both maintaining integrity of soft and hard tissues as well as protecting soft tissues of oral bacterial infections, fungi and viruses. Saliva has a role to create a balance in oral cavity.[7,20] A variety of compounds that plays a role in defense mechanisms found in saliva, one of which is sIgA.[11]

Immunoglobulin is actually a substance classified as soluble proteins. Immunoglobulin (Ig) formed by plasma cells is derived from proliferation of cell B due to contact with antigen. Immunoglobulin classified into five, namely IgG, IgA, IgM, IgD and IgE based on antigenic differences in constant region of chain H. Immunoglobulin A consists of two types, namely serum IgA and mucosal IgA. The amounts of IgA in serum is small, whereas the higher level of IgA is in the form of secretory IgA (sIgA).[21]

Moreover, sIgA is a dominant isotip antibody in human external secretions. Secretory IgA is mostly found in mucosal secretions, saliva, tracheobronchial, colostrum, breast milk, and urogenital.[21] Immunoglobulin A molecules secreted by plasma cells are found in salivary glands, whereas other protein components are produced in outer epithelial layer that covers the glands. [7]

Components of sIgA actually consist of four dimers consisted of two monomer molecules, a secretory, and a chain J. Secretory components are produced by epithelial cells and connected to immunoglobulin A of crystallizable (fc) fragment by dimer chain J possibly passing mucosal epithelial cells.[7] Immunoglobulin A molecules are secreted by plasma cells found in the salivary glands, while other protein components are produced in outer epithelial layer that covers the glans. Furthermore, sIgA is considered as the first defense mechanism at mucosal areas by inhibiting the development of local antigen, and it has also been known that it can inhibit virus to penetrate into mucosa.[7,23–25] Thus, sIgA is a product of mucosa immune system (MIS) consisted of lymphocytes T and B. [20]

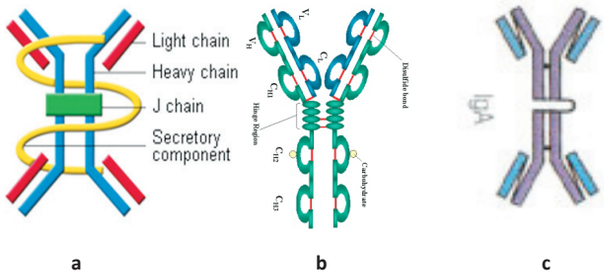


**Figure 1.** a) Structure of sIgA; b, c) Structure of IgA.[21,22]

In addition, sIgA in saliva is a sign of humoral immune response has been activated in oral cavity.[19] Humoral immune response in oral cavity actually has a relation to dental caries.[7] Dental caries infection can trigger salivary sIgA secretion.[20] The level of salivary sIgA in caries-resistant group, therefore, is higher than that in caries-vulnerable group.[5] The level of salivary sIgA in caries-resistant group is 17.88 ± 5.8 mg $dL^{-1}$, whereas that in caries-vulnerable group is 11.78 ± 4.8 mg $dL^{-1}$.[7]

## DISCUSSION

Immune deficiency that occurs in Down syndrome children is generally caused by excessive expression of superoxide dismutase (SOD1) genes and low level of serum zinc.[26] As a results, the number of T and B lymphocytes in Down syndrome children become less.[13] Thus, the levels of IgA, IgG, and IgM in Down syndrome children have a tendency to be lower than those in normal children. Previous research stated that the levels of IgA and IgG in the serum of Down syndrome children who have lower respiratory tract infection are higher than those in normal ones, whereas the level of IgM is lower than that in normal ones.[26] These increasing levels of IgA and IgG are affected by slower elimination of infectious agents in Down syndrome children caused by excessive stimulation of the immune system and increasing production of antibodies. Meanwhile, the low level of IgM is possibly affected by lower ability of anti-infection in Down syndrome children. [26]

The immunodeficiency in Down syndrome children has caused the decreasing number of T cells, and if in immaturity condition, it can make the incidence of periodontal disease in those children increased, but not the incidence of dental caries.[1,5,14] It is because the components of immune system in oral cavity in periodontal disorders include neutrophils, antibodies, lymphocytes, macrophages, lymphokine, secretory immune system. However, the level of sIgA in periodontal disorders is not increased since unlike dental caries process, in periodontal disease sIgA is considered as the most responsible immune component.[7]

Though immunodeficiency occurs in Down syndrome children, but the level of sIgA is higher than that in normal ones. There are unspecified causes for the higher level of sIgA in Down syndrome children sIgA levels than normal children, but the levels of salivary sIgA itself is influenced by many factors, and salivary sIgA is also considered as the local mucosal immune system that does not really need to work together with other systemic immunities.[14] Factors that affect the production and concentration of salivary sIgA are antigen exposure, level of stress or emotional conditions, nutrition, history of consumption, power flow

of saliva, saliva stimulation, age, intensity of activity, hormonal and genetic background. [27,28]

Moreover, previous research has been conducted to find the cause of the low incidence of dental caries in Down syndrome children.[6] Several previous researches have been conducted to assess the relationship between the overall levels of salivary sIgA and the incidence of dental caries in Down syndrome children.[6,29] It is known that the level of salivary sIgA in Down syndrome is significantly higher compared to in normal children, as a result, this condition can protect their teeth from dental caries. [6,10,13]

*S. mutans*, furthermore, is considered as the first bacteria colonizing to the tooth surface and initiating the formation of plague.[1,29] *S. mutans* is also considered as a major pathogen microorganism involved in dental caries because it has virulence factors, such as abilities to produce adhesin, glucosyltransferase GTF, *glucan-binding protein*, acid, and tolerance to high concentration of acid.[30,31] *S. mutans* secretes GTF enzyme that synthesize sucrose into soluble or non-soluble glucans (extracellular polysaccharide). Extracellular polysaccharides produced then cause bacterial colonization and plaque formation on tooth surface.[32,33]

The roles of extracellular polysaccharides, mainly glucans, are strengthen the adhesion and accumulation of *S. mutans* and other *Streptococcus* on tooth surface, strengthen the stability of the extracellular matrix that can increase the density of biofilm, protect microorganisms from microbial or other environmental influences, and to become a source of reservoir energy.[34] The adhesin plays role in early colonization of *S. mutans* to pellicle on tooth surface through salivary receptor cells, and in co-aggregation with other bacteria.[35,36] Glukan-binding protein is a virulence factor of *S. mutans* that generate or glucan binding which produced by GTF.[37]

*S. mutans* is an antigen which will evoke an immune response in oral cavity. As the most important specific defense, sIgA plays a role to protect oral cavity from bacteria causing caries (*S. mutans*).[7] Secretory IgA is able to control the colonization of *S. mutans* by reducing the initial adhesion of bacteria to tooth surface as well as neutralizing extracellular enzyme.[34] The inhibition of *S. mutans* colonization by sIgA in vitro is presumably because sIgA can inhibit GTF work, so glucan is not formed, as a result, the attachment of bacteria does not occur on the mechanism of plaque formation.[37] Secretory IgA has an ability not only to interfere either sucrose-dependent or sucrose-independent adhesion to the surface of hydroxyapatite, but also to inhibit the activity of metabolic adhesion.[38]

The inhibition of sIgA towards the sucrose-dependent adhesion of *S. mutans* is because sIgA can bind to bacteria and cover hydrophilic layer causing bacteria trapped in salivary causes mucus and eliminated from oral cavity.[38,39] It is also known that the inhibition of sIgA towards the sucrose-dependent adhesion of *S. mutans* is because sIgA can inhibit the synthesis of glucan by GTF, principally caused by the ability of antibodies to bind to catalytic domain or glucan-binding domain which then would directly inhibit the function of enzymes.[37,40] Thus, it is known that glucosyltransferase GTF secreted by *S. mutans* play a role in the sucrose-dependent accumulation of streptococci. [40]

In conclusion, children with Down syndrome have a low incidence of caries. Interaction of sIgA, a component of humoral immune system, against *S. mutans,* bacterial cariogenic antigens, in oral cavity possibly causes reduction in the incidence of dental caries. The higher level of sIgA in young Down syndrome children than that of the normal ones makes the incidence of dental caries in those Down syndrome children lower. The other reasons that make lower incidence of dental caries are delayed dental eruption, wide space among teeth, microdontia and higher level of pH and saliva contents (calcium, sodium, bicarbonate).

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