Role of Salivary Nitric Oxice on Caries Status of Children with Down Syndrome

by Nita Naomi

Role of Salivary Nitric Oxide on Caries Status of Children with Down Syndrome

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Abstract

Down Syndrome (DS) is a genetic congenital disorder caused by additional third chromosome 21 (Trisomy 21). Dental manifestation includes malocclusion, delayed eruption, and open mouth posture. Combined with muscular hypotony and decrease of visual and audio vestibular capability, these factors make DS children struggle to maintain oral hygiene. Systemic factor such as hematological abnormalities, heart and immune defect also makes dental treatment plan more complex. Research of caries prevalence (as an infectious disease) in DS compared to healthy children have varied result.

The purpose of this literature review is to describe the role of salivary Nitric Oxide (NO) and its effect on the caries status of children with Down syndrome (DS). Several studies have linked caries prevalence in DS children with saliva composition. Dental and systemic manifestation of DS cause changes in the oral ecosystem of DS, result in physiological changes in salivary flow rate and composition such as Nitric Oxide (NO). NO can be obtained from breathing, diet, and body metabolism. DS children prefer to consume foods rich in carbohydrates and refuse to consume vegetables and fruit. Since salivary NO can inhibit the growth of cariogenic bacteria such as Streptococcus mutans by forming reactive radical hydroxyl, inhibit respiration and DNA synthesis to damage the bacterial cell, this lack of fiber intake habit causes nutritional deficiencies from which NO obtained and may increase caries risk.

This literature review concludes factors influencing the level of salivary Nitric Oxide and their effects on caries status of children with Down syndrome.

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Introduction

Down Syndrome (DS) was first recognized in 1866 by Dr. John Langdon Down from England. This congenital genetic disorder caused by additional third chromosome 21 (Trisomy 21). Prevalence of DS children reaches 1 in every 800-1000 births.[1,2,3] World Health Organization (WHO) estimates there are 8 million DS cases worldwide, while in Indonesia, DS cases tend to increase every year, based on the 2018 Riset Kesehatan Dasar (Riskesdas).[4]

DS often accompanied by medical conditions such as mental retardation, hypotonia, decreased visual and audio-vestibular abilities, respiratory system disorders.[1,5,6] Several studies show that DS children prefer to consume carbohydrates that are easier to chew and swallow, and tend to refuse eating vegetables and fruit. This causes nutritional deficiencies and lack of fiber intake.[7] The typical skeletal and soft tissue forms occur in DS can increase occurrence of angular cheilitis, dry mouth, mouth breathing, macroglossia, fissures on the lower lip and tongue, crowding, and bruxism.[8,9] These conditions make DS patient struggle to maintain oral hygiene independently. Systemic factors such as heart defects, decreased immune system, and hematopoietic disorders also complicate dental treatment plan in DS children.[10]

Caries prevalence in DS children worldwide varies.[1] Some reviews stated that DS children have lower caries prevalence.[11] Different data stated that 60% of children had high

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def/DMF scores.[12-15] Several studies have linked caries prevalence in DS with saliva composition.[11,16] Many components of saliva have direct and indirect roles in the caries process, one of which is Nitric Oxide (NO). NO plays an important role in the immune response, neuro transmission, and vasodilation in various body tissues.[17] Several studies have suggested that salivary NO levels have negative correlation with caries status in DS children, indicating NO ability to fight caries. The group with caries-free status also had high levels of NO in saliva when compared to the group with active caries status.[18,19]

Characteristics of DS children such as immune defects, dental malformations, motoric disorders and modifications of nutritional intake can affect salivary NO level, which will impact oral hygiene and caries status. However, not many studies explain the role of salivary NO and correlation with caries status in DS children. This literature review describes several factors that could affect salivary Nitric Oxide (NO) level and its effect on caries status of DS children.

Review

A systematic review using a meta-analysis conducted by Deps *et al* (2015) stated that children with DS have lower caries prevalence.[11] Several factors often associated with lower caries prevalence are orofacial characteristics of DS such as microdontia, diastema, agenesis, delayed tooth eruption, and bruxism. Diastema and bruxism, reduces the risk of food debris sticking between teeth and cariogenic bacteria colonization.[3,6] Another study stated low caries rate in DS was related to saliva composition (high salivary pH and bicarbonate content) and differences in microbiota composition (amount of *S. mutans*).[10,11]

Another studies state that caries prevalence in DS is more likely the same or higher than general population, which is influenced by risk factors for caries such as cariogenic diet, decreased salivary flow, mouth breathing, and lack of access to dental care.[1] Data reported by the Department of Pediatric Dentistry, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, from 34 DS children stated 14.71% had good oral hygiene, 42.3% in the moderate category and the remaining 43.99% categorized as bad.[12] A study of a high prevalence of caries in DS children mention several factors that caused it including lack of parental attention about the child's dental and oral health, a high-sugar diet, and irregular visits to the dentist.[16] Other studies also mention DS have higher number of cariogenic biofilms than normal children, which can be associated with the caries incidence in DS children.[17]

DS children also show difficulty eating, chewing and swallowing food boluses, and inadequate nutrition. A study stated DS children prefer to consume foods made of simple carbohydrates and foods that are easy to chew and swallow. These make fresh fruit and vegetables are rarely eaten and rejected, leading to various nutritional deficiencies and lack of fiber intake.[7] DS children tend to have lower intake of fiber and several vitamins and minerals (vitamins A, B, C, sodium, potassium, calcium, phosphorus and iron) and excessive intake of carbohydrates, protein and fat. Lack of vitamin and mineral, especially vitamin B group (B1, B2, B6, B12 and folic acid) can aggravate intellectual disability in DS.[7]

Saliva is 99% water, also contains various electrolytes (sodium, potassium, calcium, chloride, magnesium, bicarbonate, phosphate) and proteins (enzymes, immunoglobulins, other antimicrobial factors, mucosal glycoproteins, albumin and some polypeptides and oligopeptides) which is important for oral health. It also contains glucose and nitrogen products, such as urea and ammonia.[20,21] Salivary function (flow, dilution, buffering, and remineralization ability) is also an important factor affecting caries development.[18] Enamel demineralization occurs at pH 5.5 (critical pH). Once demineralization reaches the dentin, the process occurs at a much higher pH, so demineralization occurs more rapidly.[22] Research conducted by Loesche stated that *Streptococcus sobrinus* and *lactobacilli* are odontopathogenic bacteria in humans with *Streptococcus mutans* being the main organism causing dental caries. *S. mutans* ability to produce acid is an important factor in the occurrence of dental caries.[21] Other species such as *S. sobrinus* plays an important role in the occurrence of dental caries on smooth surfaces and rampant caries.[22,23]

Further research on caries proved that the cause of caries is not an absolute organism but a group of microbes inside biofilm that adheres to the tooth surface.[22,23] The biofilm contains exopolysaccharide (EPS), a biopolymer that harbors microorganisms. In the pathogenesis of dental caries, EPS plays an important role by promoting biochemical and physiological changes in the biofilm matrix: (i) increasing bacterial attachment and accumulation, (ii) providing structural and bulk integrity of the biofilm, and (iii) increasing the acidogenicity of the biofilm matrix.[24,25,26] *S. mutans* have unique ability to convert sucrose into insoluble extracellular glucans, which can increase bacterial attachment and form the EPS matrix core.[26] A study revealed new findings that cariogenic species are able to bind free calcium ions from saliva to strengthen their own biofilm core. The reduced free calcium ions can affect the rate of tooth remineralization.[27,28]

Nitric Oxide (NO) is a free radical gas found in the atmosphere. NO in the human body can be obtained from breathing, body metabolic products, and diet.[16] Human body metabolism can produce NO from endothelial cells and neural cells, but macrophages and other inflammatory cells can also induce NO synthesis and release. Most of the NO synthesis is produced from bacterial products. Nitric Oxide Synthase (NOS) consists of three different isoforms, endothelial NOS (eNOS), neural NOS (nNOS), and inducible NOS (iNOS). Each NOS is derived from a different gene.[19,20,29] A recent study revealed NOS activity on the pathophysiology of pathogenic bacteria such as *Bacillus anthracis* and *Staphylococcus aureus*.[29] Inducible NOS (iNOS) derived from macrophages stimulated by inflammatory cytokines such as IL-1 or IFN γ, TNF- α, can produce more stable NO over several hours.[30]

Name	Gen	Location	Function
Neuronal NOS (nNOS/NOS1) NOS1	(Chromosome 12)	Neural tissue, Skeletal muscle	Cell communication type II
Inducible NOS (iNOS/NOS2) NOS 2	(Chromosome 17)	Immune system, Cardiovascular system	Pathogen defense
Endhotelial NOS (eNOS/NOS3/cNOS) NOS3	(Chromosome 7)	Endothelium	Vasodilatation
Bacterial NOS (bNOS)	More than one chromosome	Gram + bacteria	Oxidative stress defense, immune

Table 1. NOS classification.[27]

Respiratory NO in human is concentrated 10 times more in the salivary glands compared to plasma.[14] Enzyme in the nose and paranasal sinuses produce NO, however NO levels are higher in the sinuses than the nose, indicating the main site of NO production is in the paranasal sinuses. This makes mouth breathing will result in human body get less NO.[30]

Salivary NO produced by free nerve endings, salivary gland secretory cells, salivary gland endothelial cells and intraoral bacteria.[29,31,32] Other source of salivary NO is nitrate. About 11-41% of the daily diet contain nitrate.[30,33] Dietary nitrates are absorbed in the duodenum and upper ileum to the blood circulation, and concentrated in the salivary glands through active transport, reaching up to ten times higher concentrations than plasma.[34,35] The recommended daily nitrate intake according to the Scientific Committee on Food (SCF) in 2002 is 0-3.7 mg/kg body weight per day, equivalent to 222 mg nitrate/day for adults weighing 60 kg. According to FAO/WHO (2013), the daily consumption of vegetables is approximately 400 grams, equivalent to nitrate intake of 157 mg/day for adult.[30,36]

Eating more green vegetables which high in nitrates will promoting nitrate-reducing bacteria in the oral cavity. Nitrate-reducing microorganisms also found on the surface of the tongue such as *H. parainfluenza* and *Proteobacteria.*[37] Saliva also contains microorganisms such as *Veillonella* species, *Staphylococcus aureus* and *S. epidermis*, *Nocardia* species, and *Corynebacterium pseudodiptheriticum* that produces nitrates, but in hypoxic condition by nitrate reductase enzyme become nitrite. [38] Nitrite in acidic environment leads to formation of nitrous oxide and a mixture of nitric acid. This acidic oral environment is promoted by *Lactobacillus*, *S. mutans*, *Actinomyces*, *S. Aureus* and *Staphylococcus Epidermidis*. [31,37] Nitric acid is an unstable compound and will spontaneously be converted to NO and Nitric dioxide (NO_2). This acidic oral environment is also found in the caries development process, where the pH value can drop to 3.6. Low pH value allows nitrite conversion into antimicrobial components that can inhibit acidogenic bacteria growth, such as *S. Mutans*.[39]

The human oral cavity is an environment with abundant supply of nitrate and nitrite, which result in NO as a metabolic product.[28] While salivary nitrite can be derived from food and bacterial metabolism product in saliva, concentration of salivary nitrite varies related to dietary nitrate, bacterial nitrate reductase activity, salivary flow, and endogenous nitrate production. Other influencing factors are local parasympathetics, hormones, cytokines, inflammatory activity or endothelial cells. Various genetic and environmental factors also affect the production of salivary NO.[15]

Bactericidal ability of NO has multiple pathways, making NO a potent broad-spectrum antimicrobial agent with a low risk of causing bacterial resistance.[32] Low nitrite concentrations (0.02 mM, which is normal fasting salivary level) can inhibit bacterial growth when compared to negative controls. Other organism such as yeasts (*Candida albicans*) are also sensitive to acidified nitrites. In addition, toothpaste containing nitrite has been shown to inhibit tooth decay, while drugs that inhibit nitrite secretion in saliva can accelerate tooth decay.[14] A study shows the bactericidal and anti-biofilm abilities were obtained from the trial using alkyl modified dendrimers that released NO against the cariogenic bacteria of *S. mutans*. The NO carrier modified dendrimer at pH 7.4 requires large doses to produce a bactericidal effect. When the pH dropped to 6.4, the bactericidal effect was significantly increased and the dose required was also reduced, from 52.5 to 8.7 mol/mL for propyl-modified dendrimers and from 46.6 to 7.8 mol/mL for butyl-modified dendrimers.[32]

Other properties of NO include reducing the inflammatory response; reduces platelet aggregation and vasodilation, bone remodeling, and anticariogenic effects. Odontoblast cells exhibit immune reactivity to 3-nitrotyrosine (a biomarker of peroxynitrite produced by NO) in pulp inflammation indicating that odontoblast cells activated by NOS2 can release NO, these can be an important defense factor against oral pathogens because NO can inhibit the growth of *S. mutans*.[28] NO also has antiviral activity against certain viruses (Herpes Simplex virus -1, Hepatitis virus type 3, and Coxsackie virus group B).[14]

Discussion

Down Syndrome (DS) children have different characteristics than general population, such as intra-oral mouth breathing, macroglossia, and fissures on the lips and tongue. Several studies have shown that abnormal immune response in DS causes them to be more susceptible to oral mucosa diseases. Low oral muscle tonus combined with a smaller jaw tend to promote tongue protrusion which can cause mouth breathing habits.[1] Air from mouth breathing is not converted to Nitric Oxide (NO) by the enzyme Nitric Oxide Synthase (NOS) present in the nose and paranasal sinuses, causing NO levels to decrease.[30] Hypotonus in DS also affects motor/coordination abilities and neurological disorders (vision and hearing) so it makes oral hygiene maintenance in DS independently more difficult, which affects the frequency of teeth and tongue brushing.[10,33] On the dorsum of the tongue there are commensal bacteria such as *H. parainfluenza* and *Proteobacteria* that reduce nitrate to nitrite which will eventually become NO.[33] Reduced frequency of tongue brushing causes the accumulation of debris in the fissure, result in less supportive environment to promote NO formation, this can cause change of NO levels.

Salivary nitrates also derived from high-nitrate food, such as green leafy vegetables.[29] Most DS children have difficulty adapting to food with various textures, so they often need food to be crushed or mashed prior before eating. In addition, DS children also likes to eat snacks.[7] Consumption of soft foods, sweets, and sugary drinks that are higher than green leafy vegetables not only cause nutrition imbalance but also lack of nitrate supply.

Various genetic and environmental factors in DS affect the oral defense mechanisms in individuals can cause changes of salivary NO production. Study comparing oral microbiota in DS and general population shows that DS have significantly lower pH, larger number of periodontal pathogen bacteria (*S. aureus*) and *Candida*. While this does not relate directly towards caries, the combination of poor oral hygiene, lower pH and increase in acidogenic organism may suggest oral environment suitable for caries development in DS.[34] In oral cavity, nitrate (NO_3^-) is produced by facultative anaerobic bacteria microorganisms in saliva such as *Veillonella* species, *S. aureus* and *S. epidermis*, *Nocardia* species, and *Corynebacterium pseudodiptheriticum*. But in hypoxic condition, nitrate (NO_3^-) is reduced by nitrate reductase enzymes become nitrite (NO_2^-).[37] Nitrite in an acidic environment causes formation of nitrous oxide (N_2O) and a mixture of nitric acid. The acidic environment in oral cavity can also formed by acidogenic cariogenic bacteria such as *Lactobacillus, S. mutans*, and *Actinomyces*. Nitric acid is unstable and will spontaneously decompose into NO and nitric dioxide (NO_2).[28,31]

Salivary NO can inhibit the growth of cariogenic bacteria such as *S. mutans* by penetrate cell membranes to inhibiting DNA synthesis and damage cells. NO also react with the iron-sulfur center of mitochondrial respiratory chain enzymes or combine with superoxide to form highly reactive hydroxyl radicals.[31] In normal condition, odontoblast cells in inflamed pulp will stimulate inflammatory cells that induce NOS 2 enzymes to synthesize NO. However, DS have growth disturbance of the embryonic jaw, causing odontoblasts degeneration.[35] It was also found that NOS 2 gene regulation was decreased in DS, causing a decrease in NO levels.[40,41]

As conclusion, salivary NO has antibacterial properties to fight against dental caries. But many factors in DS such as oral and teeth anatomy, mouth breathing, motoric disability, modification of daily food intake, genetics and immune defects could affect salivary NO levels. Altered salivary NO levels can affect caries status in DS children. Future research to improve salivary NO levels and function could be beneficially for reducing caries risk in DS children.

Conclusions

This literature review concludes factors influencing the level of salivary Nitric Oxide and their effects on caries status of children with Down syndrome.

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Declaration of Interest

The authors declare that there are no conflict interest

References

1. Aldossary, M.S. Down Syndrome: A Review for the Dental Professionals. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861. 2017; 16(7): 61-66 www.iosrjournals.org DOI: 10.9790/0853-1607016166 www.iosrjournals.org 61
2. Kazemi, Mohammad; Salehi, Mansoor; Kheirollahi, Majid. Down Syndrome: Current Status, Challenges and Future Perspectives. Int J Mol Cell Med Summer. 2016; 5(3): 126.
3. Renawati, Renawati Darwis, R.S., Wibowo, H., 2017. Interaksi Sosial Anak Down Syndrome Dengan Lingkungan Sosial (Studi Kasus Anak Down Syndome Yang Bersekolah Di Slb Pusppa Suryakanti Bandung). Pros. Penelit. dan Pengabdi. Kpd. Masy. 4, 252–256. https://doi.org/10.24198/jppm.v4i2.14341
4. Kementrian Kesehatan RI Pusat Data dan Informasi. 2019. Pedoman Layanan Kesehatan Anak dengan Disabilitas bagi Keluarga.
5. Huggard, D., Doherty, D. G., & Molloy, E. J. Immune Dysregulation in Children With Down Syndrome. Frontiers in pediatrics. 2020, 8: 73. https://doi.org/10.3389/fped.2020.00073.
6. Gupta, Priya Verma. Pediatric Dentistry for Special Child first edition Bangladesh: Jaypee Brother Medical Publisher 2016
7. Mazurek, D., & Wyka, J. Down syndrome--genetic and nutritional aspects of accompanying disorders. *Roczniki Panstwowego Zakladu Higieny. 2012; 66(3)*: 189-94.
8. Areias, Cristina & Sampaio, Benedita & Macho, Viviana & Norton, Ana & Macedo, Ana & Andrade, David. Oral Health in Down Syndrome. 2015. 10.5772/60652.
9. Anggraini, Luly, Rizal, Mochamad Fahlevi, & Indiarti, Ike Siti. Prevalence of Dental Anomalies in Indonesian Individuals with Down Syndrome. Pesquisa Brasileira em Odontopediatria e Clínica Integrada. 2019; 19: e5332. Epub January 13, 2020. https://dx.doi.org/10.4034/pboci.2019.191.147
10. Ibragim, Salar Amer. 2017. Oral Status Among Down Syndrome Patients. Master Thesis. Lithuanian University of Health Sciences, Medical Academy, Faculty of Odontology, Clinic for Preventive and Paediatric Dentistry.
11. Deps TD, Angelo GL, Martins CC, Paiva SM, Pordeus IA, Borges-Oliveira AC. Association between Dental Caries and Down Syndrome: A Systematic Review and Meta Analysis. PLoS ONE. 2015; 10(6): e0127484. doi:10.1371/journal.pone.0127484
12. Dewi AM, Saskianti T, & Puteri MM. Dental and Oral Care Treatment Needs in Children with Down Syndrome in Surabaya. Indian Journal of Forensic Medicine & Toxicology. 2021; 15(2): 1990-8. https://doi.org/10.37506/ijfmt.v15i2.14656
13. Hamdaoui H, Aouar A, Beikhatir D, Moussouni A, Moqaddem Z, Khater S. Cytogenic Profile and Main Comorbidites of School-Aged Children and Adolescents with Down Syndrome in the Northwester Algeria. Journal of International Dental and Medical Research 2020; 13(1):201-8
14. Isabella C, Suharsini M, Rizal MF. Caries Experience in People with Down Syndrome Aged 14 Years and Older in SLB C Jakarta. Journal of International Dental and Medical Research 2019; 12(4):1468-73
15. Alwafa NM, Herdiyati Y, Eriska R, Risti SP, Soewondo W, Sasmita IS. Frequency Distribution of Missing Teeth in Down Syndrome Children at POTADS Foundation. Journal of International Dental and Medical Research 2019; 12(4):1248-52
16. Brij Kumar, Nilotpol Kashyap, Alok Avinash, Ramakrishna Chevvuri, Mylavarapu Krishna Sagar, Kumar Shrikant, The composition, function and role of saliva in maintaining oral health: A review. Int J Contemp Dent Med Rev. 2017; 2017, Article ID: 011217.doi: 10.15713/ins.ijcdmr.121
17. Assudani, HG; Hugar, SM; Patill, A; Sogi, SHP; Dhariwal, NS; Thakkar, P. Evaluation of salivary nitric oxide levels in caries-free children and children with early childhood caries: An in vivo study. Indian Journal of Health Sciences 2016. Published by Wolters Kluwer – Medknow.

18. Dharmadhikari P, Thosar N, Baliga S, Rathi N. Comparative evaluation of salivary constituents and oral health status in children with Down's syndrome. Eur J Gen Dent 2016; 5: 90-4.
19. Kusuma H, Saptarini R, Sasmita I, Willyanti S, Effendi SH. Correlation Between Flow Rate, Viscosity, Buffering Capacity, pH and Carries in Full and Mozaic Down Syndrome Children: A Study in Trisomy and Mozaic Type Down Syndrome. Journal of International Dental and Medical Research 2017; 10(2):343-9.
20. Ghaith, B., Halabi, M.A., Khamis, A.H., & Kowash, M. Oral Health Status among Children with Down Syndrome in Dubai, United Arab Emirates. *Journal of International Society of Preventive & Community Dentistry.* 2019; 9(3): 232–9.
21. Schwertner, C., Moreira, M. J., Faccini, L. S., & Hashizume, L. N. Biochemical composition of the saliva and dental biofilm of children with Down syndrome. International journal of paediatric dentistry. 2016; 26(2), 134–40. https://doi.org/10.1111/ipd.12168
22. Dawes C, Pedersen AM, Villa A, Ekström J, Proctor GB, Vissink A, Aframian D, McGowan R, Aliko A, Narayana N, Sia YW, Joshi RK, Jensen SB, Kerr AR, Wolff A. The functions of human saliva: A review sponsored by the World Workshop on Oral Medicine VI. Arch Oral Biol. 2015 Jun;60(6):863-74. doi: 10.1016/j.archoralbio.2015.03.004. Epub 2015 Mar 10. PMID: 25841068.
23. Kumar B, Kashyap N, Avinash A, Chevvuri R, Krishna Sagar M, Shrikant K. The composition, function and role of saliva in maintaining oral health: A review. Int J Contemp Dent Med Rev 2017; 2017, Article ID: 011217. doi: 10.15713/ins.ijcdmr.121
24. McDonald RE, Avery DR, Dean JA. McDonald and Avery's Dentistry for the Child and Adolescent, 9 th edition. Missouri: Mosby Inc, 2011
25. Babu A, Malathi L, Karthick R, Sankari S. L. Immunology of Dental Caries. Biomed Pharmacol J. 2016; 9(2). Available from: http://biomedpharmajournal.org/?p=8090
26. Cai JN, Jung JE, Dang MH, Kim MA, Yi HK. Functional Relationship between Sucrose and a Cariogenic Biofilm Formation. PLOS ONE. 2016; 11(6): e0157184. https://doi.org/10.1371/journal.pone.0157184
27. Du, Q., Fu, M., Zhou, Y. et al. Sucrose promotes caries progression by disrupting the microecological balance in oral biofilms: an in vitro study. Sci Rep. 2020; 10: 2961. https://doi.org/10.1038/s41598-020-59733-6
28. Bowen, W., Burne, R., Wu, H., & Koo, H. Oral Biofilms: Pathogens, Matrix, and Polymicrobial Interactions in Microenvironments. Trends in microbiology. 2018; 26(3), 229-42.
29. Astasov-Frauenhoffer M, Varenganayil MM, Decho AW, Waltimo T, Braissant O. Exopolysaccharides regulate calcium flow in cariogenic biofilms. PLOS ONE. 2017; 12(10): e0186256. https://doi.org/10.1371/journal.pone.0186256
30. Saghazadeh A, Mahmoudi M, Dehghani Ashkezari A, Oliaie Rezaie N, Rezaei N. Systematic review and meta-analysis shows a specific micronutrient profile in people with Down Syndrome: Lower blood calcium, selenium and zinc, higher red blood cell copper and zinc, and higher salivary calcium and sodium. PLoS ONE. 2017; 12 (4): e0175437. https://doi.org/10.1371/journal.pone.0175437
31. Borkar SP, Bhutada G, Pandagale S. Nitric Oxide as an Inflammatory Biomarker in Oral and Periodontal Diseases. Int J Oral Health Med Res 2016;3(2):76-80.
32. Poorsattar Bejeh-Mir A, Parsian H, Akbari Khoram M, Ghasemi N, Bijani A, Khosravi-Samani M. Diagnostic Role of Salivary and GCF Nitrite, Nitrate and Nitric Oxide to Distinguish Healthy Periodontium from Gingivitis and Periodontitis. Int J Mol Cell Med. 2014;3(3):138-145.
33. Dickerson, Heidi DDS, LVIM, FIAPA. 2017. Nitric Oxide & Mouth Breathing: Physiology You Want to Understand.
34. Mithra N, Hegde, Nidarsh D, Higde, Aparna, A, Shilpa, S. Salivary Nitric Oxide (NO2+NO3) as Biomarker of Dental Caries in Adults: An In Vivo Study. IRJP 2012, 3(11).
35. Backlund, C; Worley, BV; Schoenfisch, MH. Acta Biomater. Anti-Biofilm Action of Nitric Oxide-Releasing Alkyl-Modified Poly(amidoamine) Dendrimers against *Streptococcus mutans.* Acta Biomater. 2016; 29: 198–205. doi:10.1016/j.actbio.2015.10.021.
36. Brkić, D., Bošnir, J., Bevardi, M., Bošković, A. G., Miloš, S., Lasić, D., … Trstenjak, N. U. Nitrate In Leafy Green Vegetables And Estimated Intake. African journal of traditional, complementary, and alternative medicines: AJTCAM. 2017; 14(3), 31–41. doi:10.21010/ajtcam.v14i3.4
37. Tribble GD, Angelov N, Weltman R, Wang B-Y, Eswaran SV, Gay IC, Parthasarathy K, Dao D-HV, Richardson KN, Ismail NM, Sharina IG, Hyde ER, Ajami NJ, Petrosino JF and Bryan NS. Frequency of Tongue Cleaning Impacts the Human Tongue Microbiome Composition and Enterosalivary Circulation of Nitrate. Front. Cell. Infect. Microbiol. 2019; 9:39.doi: 10.3389/fcimb.2019.00039
38. Willis JR, Iraola-Guzmán S, Saus E, Ksiezopolska E, Cozzuto L, Bejarano LA, Andreu-Somavilla N, Alloza-Trabado M, Puig-Sola A, Blanco A, Broglio E, Carolis C, Hecht J, Ponomarenko J, Gabaldón T. Oral microbiome in down syndrome and its implications on oral health. J Oral Microbiol. 2020 Dec 30;13(1):1865690. doi: 10.1080/20002297.2020.1865690. PMID: 33456723; PMCID: PMC7782466.
39. Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, Smith AJ, Cooper PR. Dental Pulp Defence and Repair Mechanisms in Dental Caries. Mediators Inflamm. 2015;2015:230251. doi: 10.1155/2015/230251. Epub 2015 Oct 11. PMID: 26538821; PMCID: PMC4619960.
40. Zampieri BL, Biselli-Périco JM, de Souza JES, Bürger MC, Silva Júnior WA, *et al.* Altered Expression of Immune-Related Genes in Children with Down Syndrome. PLOS ONE. 2014; 9(9): e107218. https://doi.org/10.1371/journal.pone.0107218
41. Elyassi Gorji N, Shafaroudi A M, Nasiri P, Moosazadeh M, Nahvi A. Relationship Between Salivary Nitric Oxide Concentration and Dental Caries in Children: A Systematic Review and Meta-analysis, Iran J Pediatr. 2021; 31(2):e107050. doi: 10.5812/ijp.107050.

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