



Effect of Inhaled Anti-Asthmatic Medication on Teeth

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Abstract

Objectives: The present study aimed to investigate the adverse consequences of inhaled anti-asthmatic medications on dentition and the mechanism by which it can progress to dental caries.

Material and Methods: PubMed database search from 2003 to 2019, with the subject heading "asthma" and "caries", was done. The subjects were determined based on types of medications administered, the effect on salivary glands, lowering of pH in the oral cavity, proliferation of microflora and prevention of the ill effects in the oral cavity. A total of 26 articles were selected which matched the inclusion criteria.

Results: Among 26 studies reviewed, eight articles revealed no significant effect on caries in comparison to 18 which emphasized caries after the use of anti-asthmatic medications. On the other hand, seven studies including review articles stated increased xerostomic effect in the oral cavity. Accordingly, the acidic values due to the use of inhalers and additive sugars in especially dry powder inhalers can lead to the development of caries. Majorly, studies agreed that caries is a multi-factorial disease and assessment of the disease by taking sole drugs effect is not justified.

Conclusion: Studies based analysis suggests that asthmatic inhalers do increase the risk of cavities in teeth. The risk increases with the severity of asthma, as the adverse effects on salivary glands, changes in pH and proliferation of oral microbes, and ill oral hygiene habits combine.

Keywords: Asthma; Caries; Salivary Flow; Ph; Cariogenic Bacteria

Abbreviations

PH: Pouvoir Hydrogene; WHO: World Health Organisation; MDI: Metered Dose Inhaler; VHC: Valved Holding Chamber; DMFT: Decayed, Missing, Filled Teeth; DPI: Dry Powder Inhaler; IGA: Immunoglobulins A; ICS: Inhaled Corticosteroid; SABA: Short Acting Beta Agonist; LABA: Long Acting Beta Agonist; COPD: Chronic Obstructive Pulmonary Disease; GERD: Gastroesophageal Reflux Disease; Combi2: Beta 2 Agonist Inhalers +Corticosteroid; SFR: Salivary Flow Rate; SM: *Streptococcus mutans*; LB: *Lactobacillus*; NCD: Noncommunicable disease; CRT: Caries Risk Test

Introduction

Asthma has been one of the most prevalent chronic diseases, which is affecting more numbers of children and adults nowadays,

in both developing and developed countries. It is a chronic inflammatory disorder of airways leading to airflow obstruction in the lungs, triggering adverse responses.

Chronic lung diseases are a worldwide problem. Approximately 300 million people around the globe have a respiratory disorder called asthma. It has been observed that the prevalence of asthma has increased in the past two decades [1]. Asthma is characterized by a reduction in beta-adrenergic reactivity and increased sensitivity towards adrenergic and cholinergic agonists. According to Alaki, *et al.* [2], this disease affects approximately 1-18% of people on earth and as per Rezende, *et al.* [3] has ill effects not only in the body systems but also in person's social, behavioral, day to day

life. Paganini, *et al.* [4] stated that there are several predisposing factors for asthma which include respiratory infection, genetic makeup, environmental conditions. It is also added by Alaki, *et al.* [2] that viral infections, exercise, tobacco, allergic reaction to dust mould and pollens can trigger an inflammatory response in the lungs. It has been found that drugs for the treatment of asthma have a strong effect on the overall health of the individual.

These drugs can be delivered in the human system in various ways including oral, parenteral and inhalation route. Inhalers are frequently preferred as the drug is administered directly to the airways, instead of syrup or tablet form. Another major advantage is that one required a lower dose of the drug to be delivered directly to the action site in comparison to other routes (NIH, 2006). The asthmatic medications can be delivered in different ways, like syrup, tablet or inhalers. Different aerosol delivery devices are being used. Metered-dose inhalers (MDI) or breath-actuated MDI are generally used for patients more than five years old with a spacer or valve holding chamber (VHC) masks. Whereas dry powder inhalers are used for any above four years of age. Though nebulizers can be used at any age for those who cannot use MDI or VHC masks. The inhalation therapy has currently become the mainstay for treating asthma and chronic obstructive pulmonary disorder (COPD), as the safest and most effective mode. The indication of antiasthmatic therapy is based on the type of asthma and its frequent attacks on the body. Currently, the guidelines state the inhaled form of anti-inflammatory drugs, either corticosteroid or non-steroidal or combination of both. The aim is to maintain normal respiratory function or restore it to allow normalcy.

Godara, *et al.* [5] stated that it has been frequently pin-pointed that treatment of this systemic disease, has a negative effect on the oral cavity as well, based on their frequency, and prolonged duration of medication. It has also been observed by Chelliah, *et al.* [6] that salivary glands are targeted by these drugs and lead to lesser production of saliva. Tootla, *et al.* [7] found that pumps used for inhalation though may prove very difficult in children, and a major amount of drug gets deposited in the oropharynx [8], leading to further and direct effect on the oral cavity which needs to be studied.

As some authors suggested an association between inhalers and dental caries due to the above said reasons, whereas others have found contradictory results. Possible reasons for such

contradiction may be due to the multifactorial etiology of caries, and also due to incoherent age groups selected, with the difference in the severity of diseases, prevention programs included, or even when small numbers of samples are studies.

As several oral conditions have been found coexisting with asthmatic inhalers in use such as xerostomia, gingivitis, caries, thus understanding the impact of asthma on dental health and enhancement of dental care becomes inevitable.

WHO stated in 2017 [9] that dental caries as a major public health problem globally, and is the most widespread non-communicable disease (NCD) and it is also the most prevalent condition included in the 2015 Global Burden of Disease Study, ranking first for the decay of permanent teeth (2.3 billion people) and 12th for deciduous teeth (560 million children). Severe dental caries affects the general health of both adults and children. WHO also said that it can lead to malnourishment in children, which was reported in some low-middle-income countries, though the cause-effect relationship is yet to be determined. If there is any lesion in the tooth surface where a softened floor can be detected, undermined enamel and walls of the tooth are softened, then the tooth is considered carious. Dental caries and asthma have been co-related and the co-relation been studied often. The severity of dental caries may be measured by using indices such as the DMFT/dmft index (capital letters when referring to permanent dentition and small letters in deciduous dentition), where D stands for 'decayed', M denotes 'missing' and F depicts 'filled' teeth.

There have been limited studies and controversial views regarding the effect of inhaled medications used for asthmatics, on the oral cavity, particularly caries in teeth. Dental caries is a progressive disease and can lead to subsequent complications including pain, and tooth loss. There have been limited studies to prove a correlation between the two diseases "asthma and dental caries". As there is a lack of consensus, regarding the detrimental effect of inhalers on the oral cavity, the aim of this literature review was to find out a link between caries and regular usage of inhalers used for asthma.

Thesis objective

The objective of the study was to assess the cariogenic potential of inhalers, on primary, and permanent dentition, depending on the severity and duration of asthma and its prevention.

Research questions

1. Can the severity of asthma and the duration of inhaled medications affect teeth?
2. How are salivation, pH and microflora in mouth affected?
3. How can we prevent the detrimental effect of the medication?

Material and Methods

The literature search was done in electronic database PubMed, for past 10 - 16 years, i.e. 2003 till 2019 by using multiple search terms, for research articles, reviews, comparative studies, clinical trials, guidelines. Search terms or combinations of search terms were used to collect the numbers of articles for our relevance.

During the electronic PubMed search, a total of 108 hits were found with the keywords 'asthma and caries'. However, narrowing down the MeSH terms more specific matching words gave the following results: "oral steroid inhalers," three articles, eight with inhalers, three with Salbutamol in combination with "asthma and caries". With search terms 'Corticosteroids and caries 33 articles, which were narrowed down to 14 with combination with keyword "asthma". In total ten articles were selected after searching with

the words "inhaler and caries" and the article search was again narrowed down to 8, when it was combined with the word "asthma". 39 articles were found with "bronchodilators and caries", and the search again came down to nine, when combined with "asthma". Also, "Xerostomia and caries" got 469 hits, which came down to six when the word "Asthma " was added.

Table 1 depicts the complete process of the selection of articles. The 49 articles were screened for the relevance of caries, excluding gingival disease, survey-based bone-related pathology, single case reports and the number of articles came down to 41. Out of these 41 articles, the selection was narrowed down to 26 articles after reading and selecting according to their relevant information that can be quantified, like the number of asthmatic patients examined, and excluding those children/adults with other medical co-morbidity. Original studies and literature reviews were taken into consideration including WHO guidelines for caries. Articles in languages other than English like French, Spanish were not taken into account in this review. And those asthmatic treatments which used only tablet or syrup formulations and not inhalation mode for their drug delivery were also excluded from the study.

Asthma and Caries Caries108 Articles	Corticosteroid and Caries 33 Articles	Inhalation Drugs and Caries10 Articles	Bronchodilators and Caries 39 Articles	Xerostomia and 469 Articles
And Inhaler = 8 Salbutamol = 3 Oral Steroid Inhaler = 3	And Asthma	And Asthma	And Asthma	And Asthma
14 Articles	14 Articles	8 Articles	7 Articles	6 Articles
↓ Total = 49 Articles ↓ Screened for focus on caries ↓ Articles 41 ↓ Full-text articles screened exclusion & inclusion criteria ↓ Articles included for analysis=26				

Table 1: Process of selecting articles

Different geographical region's studies like Iran, India, Sweden on any age group starting from a year old child to the adults of any age were included, therefore the study is not limited to a particular region or country, and not focused on any age group. So, finally, 26 articles throwing light on the effect on teeth by the inhalers were taken into account for the literature review.

Results

The initial database search yielded 49 studies, 41 studies passed the first review phase, and 26 studies were finally selected after screening based on the inclusion and exclusion criteria. The included studies were either prospective or retrospective in nature and with an observation period of at least 3-6 month. Two authors have written review articles regarding caries and asthma.

Except in one study by Tootla., *et al.* [10], the number of years of medications administered and studied was more than one year and only in his study, the individuals selected were healthy and did not have any asthmatic ailment. Three studies had less than 20 asthmatic patients, otherwise all had more than 30. More than 370 adults and 2940-children were screened in different geographical areas including India, Iran, England, Russia, Saudi Arabia, Serbia, Denmark, US, Italy, Belgium, Slovenia, Brazil, Sweden, etc.

Cariogenic mechanism of inhalers

Inhalers have direct and indirect effects in the oral cavity. It affects the production of saliva which is a major drawback of an inhaler. Additive sugars in the medication and creation of bacteriogenic environment after being retained in mouth adds to further insult.

Various studies indicated an influence on salivary glands. Seven articles indicated a xerostomic effect due to inhaled medications. Four studies found a significant decrease in pH in asthmatics, whereas two authors did not find any significant pH difference between asthmatic and nonasthmatics. Five studies detected the proliferation of cariogenic *Streptococcus mutans* (SM) in oral cavity and five showed *Lactobacillus* (LB) in addition to SM. Other studies did not have any inference in relation to bacteria.

Only 10 - 20% of inhaled doses reach lungs and thus 80% remains in the oropharynx region. Therefore, anti-asthmatic medications that contain lactose could, along with decreasing salivary flow rate, lead to an increase in cariogenic bacteria.

Also, because of the dry mouth in children occurs due to reduced salivation in mouth, and further development of mouth-breathing habit due to repeated airway obstruction during acute asthmatic attacks, there is an increased tendency to take sugary, acidic drink in asthmatics.

Medication Induced acidic pH

Low pH is a risk factor for enamel demineralization, if it persists longer it encourages aciduric bacteria and continue to metabolize carbohydrate and sets a stage for an uncontrolled carious attack [5]. Resting pH of a mouth is usually seven and chemical dissolution of enamel starts at 5.5 pH. Such pH disturbances were found in an asthmatic patient, which was due to the inhalants used [11]. Majorly, all dry powder inhalers have a pH lower than 5.5.

Lower the pH of medication, as an ill effect of any medication for a prolonged period, results not only in caries but a higher degree of erosion and demineralization of teeth. Arafa., *et al.* [10] found a lower pH score, which is 6.06 as mean value in asthmatics in comparison to control non-asthmatic group with 7.02 pH mean value. He found that the severity of the disease is inversely related to pH. Severe asthmatics had the lowest pH of 5.52 (mean value). Although, Paganini., *et al.* [4] and Stensson., *et al.* [12] could not find any statistical difference between buffer capacity among the studied groups-controls and asthmatics, the low initial pH value of saliva was statistically significant. Mazoleni., *et al.* [13] on the other hand showed only one patient has high buffer capacity and others had medium or low (43.3%), whereas out of 30 healthy individuals, 18 had high capacity.

A study by Tootla., *et al.* [7] showed, no inhaler exhibited an acidic response lower than the critical pH of 5.5. Similarly, Kinc., *et al.* [14] found no statistical significant difference in pH values among controls and asthmatics when observed in different periods in a year. Alaki., *et al.* [2] too found reduced buffer capacity in severe asthmatics, though it was statistically not significant, but when he compared different drug forms, patients taking a combination of beta-agonist and corticosteroid inhalers had the lowest level of buffering capacity in saliva.

Bozejac., *et al.* [15] stated that lactose based powders are more acidic when compared with other inhalers. When lactose based dry powder inhalers and pump with inhalers were used substantial pH reduction was observed which lead to enamel demineralization,

although the use of turbo inhaler (nonlactose carrier) did not affect the pH of plaque present in the tooth surface. According to Tootla, *et al.* [10] there is no effect of lactose content in any inhaler, as it's behavior is equal to twice daily rinse of mouth with a 10% sucrose solution, leading to minimum subsurface demineralization.

The Beta-agonist inhalers can also cause relaxation of smooth muscles which often leads to gastro-esophageal reflux disease (GERD) which further decreases salivary pH. This relaxation and pH reduction simultaneously affects palatal surfaces of central incisors and buccal surfaces of posterior teeth, predominantly, and leads to erosive actions on teeth. According to Godara, *et al.* [5]

following the use of the inhalants, after 30 minutes, the salivary pH drops below the critical value.

Table 2 depicts a significant decrease in pH was found by three studies, whereas one study found a decrease in initial pH and no difference in buffer capacity. Two studies found no difference in pH score between asthmatic and control groups. Two authors specifically mentioned that the significant change in the acidic environment in oral cavity was in severe cases or with a specific group of combination drugs. Various studies took different tests for assessment of pH, which has been mentioned in the table.

Study	Test	Ph/Buffer Capacity	Significance
1. Arafa, <i>et al.</i> (2017)	Pre-calibrated PH meter	Decrease	Significant (severe cases)
2. Klinik, <i>et al.</i> (2016)	Pre-calibrated PH meter	Normal	--
3. Alaki, <i>et al.</i> (2013)	CRT ivoclar vivadent kit	Decrease	Significant (only with 'combi 2' drugs)
4. Paganini, <i>et al.</i> (2011)	PH meter, Ericssons method	Decrease in initial PH	No difference in buffer capacity
5. Mazzoleni, <i>et al.</i> (2008)	CRT buffer test	Decrease	Significant
6. Stenenson, <i>et al.</i> (2011)	Microtouch method	Normal	--

Table 2: Comparison of pH/buffer capacity in various studies.

Table Legend: CRT - Caries Risk Test, Combi2 = Combination of beta 2 agonist and corticosteroid.

Effect on salivary glands

Saliva is composed of water (99%), and organic and inorganic contents. It helps in cleaning endogenous and exogenous microorganisms and products from the bowel. Pathological and physiological changes in salivary characteristics are seen after the prolonged use of inhalers. Paganini, *et al.* [4] found 23.08% normal Salivary Flow Rate (SFR) in asthmatic children 50.77% had a severely low salivary flow rate. There is a negative relationship between asthma severity and salivary flow rate, as even mild asthmatic children had two times higher salivary flow rate than those suffering from severe asthma. Stenenson, *et al.* [12] and Alaki, *et al.* [2] found lower saliva flow in asthmatic patients than controls, but they added that this difference was not statistically significant.

Severe asthmatic cases had lowest SFR ($P = 0.04$), and no significant difference was found between the span of disease and the caries score [2]. Lower salivary flow leads to decreased ability to clear acids from the mouth as well as the remineralization of

damaged teeth. It was found that almost 50 - 77% of asthmatic patients had a very low salivary flow rate. Inhalers containing a combination of drugs- Beta-agonist and Corticosteroids were the most affected. Klinik, *et al.* [14] studied both the control and asthmatics groups thrice in a year 0, 6 and 12 months and found a decrease in the saliva in asthmatics which could be a cause of dryness of mouth if long-term treatment is there. Salbutamol causes the production of saliva with high protein concentration but in low volume, also decreases the resorption of water in salivary ducts. Godara, *et al.* [5] found that there are also changes in saliva, leading to a decrease in the availability of biologically active compounds like amylase, calcium ions, secretory IgA, peroxidase, lysozyme, which leads to an increase in plaque and bacteria.

Godara, *et al.* [5] stated that the beta-agonists decreases the flow rate of parotid saliva by almost 36% and whole saliva by 26%. With this decrease, the protective effects of saliva diminish, leading ultimately to dental caries. Consequently, the pH level decreases and the bacterial level rises. Increased levels of calcium are found

in the saliva of asthmatic patients, thus more calculus formation leading to periodontal issues than normal children [11]. This study detected 0.64 mean value of SFR in severe asthmatic cases, and 1.26 in mild cases. When SFR was compared between controls and asthmatics, it was found higher in the controls. On the contrary Brigic., *et al.* [16] concluded that anti-asthmatic drugs do not cause any hyposalivation and change in oral bacteria.

Table 3 shows comparisons of the salivary flow rate detected by various tests in the studies. Majorly four tests used the same method for assessment for salivary flow rate detection and Stennson., *et al.* [12] took dentobuff strip test to measure saliva flow. All the studies who measured SFR found a decrease in saliva in the asthmatics. Two of the studies, however, found the decrease not significant in comparison to controls.

Study	Age Group (Years)	Test	Salivary Flow Rate	Statistical Significance
1.Stennson., <i>et al.</i> (2011)	18-24	Dentobuff strip chair-side test	↓	NS
2. Paganini., <i>et al.</i> (2011)	3-15	Volume measure after collection	↓	Significant
3. Alaki., <i>et al.</i> (2013)	5-13	Volume measured with calibrated sterile tube	↓	NS
4. Klinic., <i>et al.</i> (2016)	4-16	Volume measured after collection	↓	Significant
5. Arafa., <i>et al.</i> (2017)	4-12	Volume measure after collection	↓	Significant

Table 3: Comparison of Salivary Flow Rate.

Table legend: NS = Not Significant.

Bacteriological effect

Dental caries arises due to the combined effect of a susceptible host, cariogenic microflora, dietary habits. Primary pathogens are *Streptococcus mutans*, *Streptococcus sobrinus*, *Lactobacilli*. Asthmatic medications have been responsible for altering oral flora leading to the development of caries. The sugar-containing drugs such as salbutamol lead to an increase in levels of SM and lactobacilli (LB), which are both cariogenic. Also, Alaki., *et al.* [2] stated that prolonged course of treatment and using medication three times a day decreases the salivary flow and adds to increase microbial proliferation. He found a higher lactobacilli level in asthmatics, especially those taking a combination of beta-agonists and steroids. In contrast, Stennson., *et al.* [12] did not find any statistically significant difference in the salivary flow rate or LB, SM levels between asthmatics and control group in his study.

Ashuja., *et al.* [17] compared bacterial counts in asthmatic's oral cavity at baseline (0 months), post 3 months and 6 months by digital colony counter. Colony-forming unit/ml of SM and LB (mean value) was 62.1 and 78.7 in controls and 246.3 and 191.6 respectively in asthmatics at 6 months. Although he found increased counts of SM

and decreased *Candida albicans*, the results were not statistically significant. Botelho., *et al.* [18] found an increased concentration of cariogenic SM but no significant difference with LB levels between the asthmatics and non-asthmatics group. He found a positive correlation between increased SM levels and caries detected in asthmatics and control group, and as the duration of treatment prolonged, greater was the presence of SM levels in the mouth. Mean LB and SM levels in asthmatics were significantly higher (p, 0. 01) than controls [6].

Other associated bacteria include *Lactobacillus*, *Actinomyces*, *Veillonila*, *Bifidobacterium* species. According to Beighton., *et al.* (2005), species of *Bifidobacterium* and *Actinomyces* can lead to dental caries, besides LB and SM, as mentioned by Sergey., *et al* [19]. Huge number of microorganisms like *Veillonila*, were found in asthmatic children with dental caries when compared with asthmatics with caries-free teeth. The oral cavity of asthmatic children is abundant with opportunistic bacteria with increased pathogenicity such as *Streptococcus*, *Veillonela*, *Provetella*, *Haemophilus*. *Neisseria* was associated with the occurrence of gingivitis and related diseases.

Table 4 shows the bacterial count studied by various authors. Different tests were used to count bacteria like the colony-forming unit, catalase test, mannitol test even DNA analysis was also done in one study. Five studies found an increase in SM count, but two found it not statistically significant. Botelho., *et al.* [18] and Stensson., *et al.* [12] found not statistically significant increase

in lactobacillus count whereas five studies favor LB's significant increase in asthmatics. One study also found an increase in opportunistic bacteria along with SB and LB. Also, there was a decrease in particular bacteria called *Candida albicans* along with the increase in the cariogenic bacteria.

Study	Test	Bacteria		Others
		SM	LB	
1. Stensson., <i>et al.</i> (2011)	CFU counted on agar plate	NS	NS	
2. Sergey., <i>et al.</i> (2019)	DNA sequencing and bioinformatic analysis	Increase	Increase	Veillonila and other opportunistic bacteria.
3. Alaki., <i>et al.</i> (2013)	CRT ivoclar vivadent kit	NS	Increase	
4. Mazzoleni., <i>et al.</i> (2008)	CRT bacteria test	Increase	Increase	
5. Botelho., <i>et al.</i> (2011)	Electronic colony counter	Increase	NS	
6. Ashuja., <i>et al.</i> (2018)	CMD, catalase test, mannitol fermentation test	Increase	Increase	Decrease in CA
7. Chelliah., <i>et al.</i> (2016)	CMD on agar plate	Increase	Increase	

Table 4: Comparison of bacterial count in different studies.

CFU=colony forming unit,CRT=caries risk test,CMD= colony morphology detection,NS= not significant, CA= candida albicans, SM=streptococcus mutans,LB= lactobacillus.

Correlation between severity/Duration of asthma and caries

Asthma has seasonal attributes and its severity fluctuates with time, therefore a dose-response relationship is at times difficult to quantify.

Increase in caries prevalence can be due to an increase in dosage, frequency of drug delivery and the type of drugs used like combination drugs (Beta- agonist + steroid). According to Reddy., *et al.* [20], dental caries increased in children and adults, as the severity of asthma rises. In severe asthma cases, almost 100% of subjects had caries, in comparison to mild and moderate cases. Alaki., *et al.* [2] also had similar findings that patients taking medications 3 times a day had the highest level of cariogenic bacteria than those taking once or twice a day. Arafa., *et al.* [11] talked about deciduous dentition where with severity, dental caries

increased. Another study by Botelho *et al.* [18] found no correlation between the type/frequency/mode of medicines consumed and caries detected, but there was a definite relation between SM levels and length of treatment. Association between severity of the disease and caries was positive in 11-15-year-old children Botelho., *et al.* [18]. Guergolette., *et al.* (2009) had mentioned tooth enamel defect was higher as the severity of asthma increases. Uncontrolled and severe asthmatics are often taking Beta-agonists inhalers as compared to the controlled group of asthmatics. Arafa., *et al.* [11] stated that after the prolonged use of beta-agonist- Salbutamol, the incidence of dry mouth and alterations of tastes were seen. Also, there was an increased mineral content of saliva, which leads to frequent calculus deposition on teeth. Alak., *et al.* [2] proved an association between change in certain salivary characteristics like its flow rate, reduced buffering capacity and increased bacterial

count, as the severity of asthma increases. Children with severe asthma had the lowest salivary flow rate. When SM and Lactobacilli counts were compared by Ashuja., *et al.* [17] after 6 months of medication and beginners (0 - 3 months), there was a significant rise in the microbial count. So, as the duration of medication was increased, so its ill effect.

However, Stensson., *et al.* [12] detected initial proximal cavities in asthmatic patients, but as the duration /severity of the disease increased the DFS (Decayed, filled surface) score did not increase in the cavity significantly. Samec., *et al.* [21], used multilinear regression for assessment of the influence of length, mode and frequency of medication used on dental caries experience in asthmatics. Though there was an increase in DMFS score in the permanent teeth of the subjects with an increase in frequency and length of the application of medicines but was not statistically significant. Though the duration of the disease cannot always be interpreted as one of the precursors of the effect [22].

No correlation was found between the increased span of the disease and the susceptibility of caries in the mouth of these

patients except in two studies. Among the two, Samec., *et al.* [21] reported increased dmfs score and Botelho., *et al.* [18] found an increase in the number of cariogenic bacteria with an increased period of the disease. However, with the increased severity of the disease reduced SFR rates were noted by two studies, namely Alaki., *et al.* [2] and Paganini., *et al.* [4]. Two authors, Reddy., *et al.* [20] and Botelho., *et al.* [18] showed an increase in caries score. Although no sign of any change was found by the other two, Eloot., *et al.* [22] and Boskabady., *et al.* [23].

In table 5 different duration of medications were studied, with a minimum of one year to more than four years. With the increase in the severity of asthma, there was an increase in cavities in the mouth in only two studies and a decrease in salivary flow rate in two different studies. One study also found an increase in the microbial count with an increase in severity. Two studies clearly stated that the caries index was not significantly affected by the severity of the disease. Also, with the increase in the duration of medication, no significant effect was found in dmfs/DMFT scores in seven of the studies.

Study	Duration of Medication (Years)	Effect of Severity	Effect on Duration
1. Alaki., <i>et al.</i> (2013)	1- >4	↓SFR, ↑LB ↑SM	NS on DMFT and SC
2. Samec., <i>et al.</i> (2013)	1-3 and >4	--	↑ DMFS but NS
3. Eloot., <i>et al.</i> (2004)	<2->10	NS on DMFS	NS on DMFS
4. Sergey., <i>et al.</i> (2019)	--	--	NS on caries
5. Boskabady., <i>et al.</i> (2012)	1yr followup	NS	NS on caries
6. Paganini., <i>et al.</i> (2011)	1-4	↓SFR	--
7. Reddy., <i>et al.</i> (2003)	--	↑CARIES	--
8. Botelho., <i>et al.</i> (2011)	2->4	↑CARIES, NS on SFR	↑SM
9. Godara., <i>et al.</i> (2013)	1	--	NS on caries
10. Heidari., <i>et.</i> (2016)	1-2	--	NS on caries

Table 5: Comparison of effect and severity of asthma in oral cavity.

Table Legend: SFR=Salivary Flow Rate, NS= Not Significant, LB= Lactobacilli, SM= Streptococcus Mutans, DMFT=Decayed, Missing, Filled Teeth, DMFS=Decayed, Missing, Filled Surface, SC= Salivary Characteristic.

According to Shahikaran., *et al.* [24], there is a significant rise in caries for those who use Salbutamol inhalers. It showed a higher caries prevalence than beclomethasone inhaler. Asthma severity increases by about 17 times the risk of having a reduced salivary flow leading eventually to caries. Alaki., *et al.* [2] found no relation between the duration of medication taken (1 year, 2 years, 4 years) and the caries score. Heidari., *et al.* [25] stated that there was no relation between no. of medication sprays, duration and type of medications used, whether beta-agonist/antihistamines/steroids or their combinations on caries score in permanent dentition.

Eloot., *et al.* [22] also did not find any correlation between oral health and caries score and duration/severity of asthma with statistical values by multiple logistic regression. Boskabady., *et al.* [23] have similar opinions with his study on different age groups with mild, moderate and severe asthmatics. He found no difference in caries scores affected by the dose of medicaments or technique of inhalers. Though it has been reported that inhalers used for more

than four years showed increased caries indices score. Though the increased risk of caries occurs with increased frequency of Dry powder inhaler (DPI), the duration of treatment was not found to be linked with cavities in the study by Godara., *et al.* [26].

Table 6 shows the effect on inhalers. 16 studies were done on minors and five were made on the adult population. Nine studies showed high caries score in the asthmatic patients. A study by Heidari., *et al.* [25] proved higher caries with tablet form of the drug instead of spray form, and Brigic., *et al.* [16] insisted that he found more caries in the control group rather than asthmatics. Stensson., *et al.* [12] showed an increase in initial caries and increase in only permanent dentition by Botelho., *et al.* [18]. Wogelius., *et al.* [27] found demarcated opacities in the teeth of asthmatic children. In total 13 authors showed high caries score in the subjects, whereas seven studies found no significant cavities in their subjects when compared to the healthy counterparts.

Author	Year of Medication	Size of Population	Age Group (Years)	Geographic Region	Result Interpretation On Caries	Inhalers Used
Alaki., <i>et al.</i> (2013)	-	60 Total 30A, 30C	5-13 Years	Jeddah, Saudi Arabia.	Not significant	B2A and Corticosteroids, Combi 1, Combi 2, Combi 3
Samec., <i>et al.</i> (2013)	1 Year	220 A	2-17 Years	Slovenia	High caries risk	GC (Daily) and Bronchodilators when required.
Rezende., <i>et al.</i> (2019)		228 Total 112A, 116C	6-12 Years	Southern brazil	Increased caries risk.	Salbutamol +beclomethasone or Budesonide +systemic corticosteroid.
Paganini., <i>et al.</i> (2011)	1-4 Years	130 Total 65A, 65C	3-15 Years	Londrina-PR, Brazil	Not significant.	Corticosteroid, Bronchodilator Combi 2
Stensson., <i>et al.</i> (2011)	3-5 Years	114 Total 64A, 50C	3-6 Years	Sweden	Increased incidence if caries	Inhaled long acting B2A, Glucocorticosteroid.
Wogelius., <i>et al.</i> (2010)	0-8 Years	647	6-8 Years	Denmark	Increased risk of demarcated opacities	B2A, Oral beta-agonist, Inhaled corticosteroid.
Lindemeyer., <i>et al.</i> (2011)	-	172 Total 86A, 86C	<71 Months	Philadelphia	Not significant	B2A and inhaled steroids.
Reddy., <i>et al.</i> (2003)	-	205 A	3-18 Years	Mangalore, India	High caries prevalence	B2A Inhalers, syrups, tablets and combination of all three.
Mazzoleni., <i>et al.</i> (2008)	>6 months	60 Total 30 A, 30 C	6-12 Years	Italy	Higher caries susceptibility	Short acting B2A and Corticosteroid.

Eloot., <i>et al.</i> (2004)	<2->10 Years	140A	3-17 Years	Belgium	Not significant	Beta 2 mimetics, corticosteroid (Inhaled and oral)
Tootla., <i>et al.</i> (2005)	4 Months	10 Healthy Individuals	Adult	England	No effect on teeth	Lactose based powders: 1. Biclomethasone dipropionate. 2. Fluticasone + salmeterol
Sergey., <i>et al.</i> (2019)		18??	3-6 Years	Russia	No significant difference.	Corticosteroids, Ipratropium bromide + Fenoterol, and antihistamines
Ashuja., <i>et al.</i> (2018)	3-6 Months	20A 20C	20-45 Years	Karnataka, India	Increased microbial count in asthmatics	B2A, Corticosteroid.
Arafa., <i>et al.</i> (2017)	-	180 Total 60A 60 Healthy Negative C 60 Healthy Positive C	4-12 Years	Saudi arabia	Increased risk of dental caries	Corticosteroid B2A, Bronchodilator
Bozejac., <i>et al.</i> (2017)	>5 Years	80 Total 40A 40C	18-65Years	Serbia	Increased caries risk	Dry powder inhaler / Aerosol inhalers.
Shashikaran., <i>et al.</i> (2011)	1 Year	105A 106C	6-14 Years	Karnataka, India	Significant increase in caries	
Chelliah., <i>et al.</i> (2016)	2 Years	53A 55C	6-14 Years	India	Increased caries and bacterial count.	B2A and Steroids
Boskabady., <i>et al.</i> (2012)	1-16 Years	40 A 40C	20-30 Years		Increased caries	Inhaled .Biclomethasone dipropionate, or 2. Fluticasone , salmeterol and salbutamol
Botelho., <i>et al.</i> (2011)	2->4 Years	80A 80C	3-15 Years	Brazil	Increased caries only in Permanent dentition	Bronchodilators, inhaled and systemic steroids.
Brigic., <i>et al.</i> (2015)	>2 yrs	100A 100C	7-14 Years	Bosnia and herzegovina	Increased caries in control	Inhlaed antiasthmatic drug.
Heidari., <i>et al.</i> (2016)	1-2 Years	85A	3-12 Years	Tehran	Increased severity of caries	Antihistamines, B2A, Cirticosteroid in the form of spray, tablet, syrup.
Godara., <i>et al.</i> (2013)	1 Years	100A 100C	16-45 Years	Rajasthan, India	Not significant	B2A, Corticosteroid.

Table 6: Caries experience in different studies. Tablelegend: A=asthmatic, C-=control group (non-asthmatic), B2A= Beta2 agonist, YS=years, COMBI 1=beta2 agonist, antihistamine, COMBI2=beta2 inhaler+corticosteroid, COMBI3=beta2 agonist+antihistamine+corticosteroid, BD= Biclomethasone dipropionate.

Prevention

Since asthmatic drugs pose a carious threat and their potential harm after long-term life-saving usage cannot be avoided, thus there is a need to shift the care more towards preventive than waiting for curative.

Arafa., *et al.* [10] state there is a need to provide very comprehensive care from a dental point of view, and early cross consultation between respiratory and dental specialists in the need of the hour.

According to Godara., *et al.* [26] oral rinsing just after the use of inhaler can counteract the early drop of pH in the mouth to a certain extent, though not very significantly. It also removes the retained medication from the mouth. In his study, 45% of asthmatics practicing this habit had lower caries score in comparison to those who did not. 82% asthmatics rinsed their mouth after inhaling medicines in the study by Samec., *et al.* [21], but his study did not find any statistical significant dmfs score with rinsing, though the score did come down, and in addition he found high caries in asthmatics (2 - 6 yrs age) of less-educated parents, those who brush their teeth less frequently and the ones (7 -12 years) who take sweetened drinks more than 5 times a day.

Shashikaran., *et al.* [24] stated as there was frequent consumption of sweets by the patients due to the underlying disease and less focus imparted to dental hygiene, there was an increase in cavities. Stensson., *et al.* [12] found that since in his study, as the initial caries were found in the subjects but because of aggressive preventive care, there was a decline in manifest caries lesions. He reported an increase in mouth-breathing habit, at 3yrs and of age ($p < 0.05$) and at 6 years of age ($p < 0.001$) in asthmatics and frequent sugary consumption, which are co-founders of dental caries.

According to Mazzoleni., *et al.* [13], with the continuous repeated medical observation and the following prescribed dental recommendation like adequate tooth brushing, fluoride application and identical dietary intake of sweets and beverages were consumed by both asthmatics and non-asthmatics, but then also high carious activity was seen in the asthmatic group. Mazzoleni., *et al.* [13] found an increase in DMFT score and lower buffer capacity in asthmatics. In his study, he found almost 33% of asthmatics brushed teeth thrice a day in comparison to 6.7% of the control group. Eloit., *et al.* [22] found that 79.9% of asthmatics had good oral hygiene as dental care was intensified. In his study, dietary habits were moderate to good and thus considered to be an

effective modification to prevent cavities. Despite the maintenance of good hygiene habits, Lindermeier., *et al.* [28] found a habit of nursing at will and drinking cariogenic liquids while going to sleep which came out to be statistically significant as potential risk factors for asthmatics. Though other factors studied like snacking in between meals had an insignificant effect on DMFT score.

Paganini., *et al.* [4] said that illness did not have its ill effect on the dentition in his study because of the preventive care imparted to them. The patients had fluoridated water, they were given oral health instructions which were followed and also took part in the yearly preventive program. The most contradictory result was found by Brigic., *et al.* [16] where in spite of the comparable frequency of brushing, between asthmatics and non-asthmatics he found higher caries score in the control group. Later, he stated that this might have occurred due to the possibility of a control group being from a lower socioeconomic status.

Different studies gave different outcomes. While two studies by Stensson., *et al.* [12] and Lindermeier., *et al.* [28] found bad oral hygiene habits like increased sugary drinks and bedtime drinks respectively in addition to asthma cause major effect on teeth, a study by Samec., *et al.* [21] stated that rinsing after medicament does not have any significant effect on preventing caries in contrast to Godara., *et al.* [26] who mentioned benefits of rinsing just after inhaler use. Mazzoleni., *et al.* [13] found no effect of even good oral hygiene as a high caries index was present in asthmatics despite frequent brushing. One study found the contrary result and found high caries in controls rather than asthmatics. But if there is excessive indulgence in hygiene practices like brushing more than thrice a day, then this also can lead to dental erosion, as found by Rezende., *et al.* [3].

Table 7 shows that a positive effect of preventive treatment was found in five studies, where four studies with intensive care had led to a decrease in caries and one study by Godara., *et al.* [5] established that rinsing just after the inhalation helped in lowering down the caries score. However, rinsing habit did not help much in preventing caries in the study of Samec., *et al.* [21] four studies showed an increase in caries, where Shashikaran., *et al.* [24] and Samec., *et al.* [21] proved that these enhanced cavities were due to higher sweets/sweetened drinks intake. Despite good hygiene habits including brushing and fluoride, there was elevated caries score detected by Mazzoleni., *et al.* [13] and in another study by Lindermeier., *et al.* [28] due to the habit of nursing at will, the cavities increased in numbers.

Study	Habits / Prevention	Effect on Caries
1. Godara, <i>et al.</i> (2011)	Rinsing after inhalation	↓
2. Samec, <i>et al.</i> (2013)	a. Rinsing after inhalation	a. No effect
	b. Reduced brushing, increase sweet drinks.	b.↑
3. Shashikaran, <i>et al.</i> (2007)	Increased sweets intake	↑
4. Stennesson, <i>et al.</i> (2011)	Aggressive preventive care	↓
5. Mazzoleni, <i>et al.</i> (2008)	Brushing, Fluoride treatment	↑
6. Eloit, <i>et al.</i> (2004)	Intensified dental care	↓
7. Lindermeier, <i>et al.</i> (2011)	Good hygiene habits	↑
	Nursing at will with Cariogenic liquid	
8. Paganini, <i>et al.</i> (2011)	Preventive care, fluoride.	↓
9. Brigid, <i>et al.</i> (2015)	Frequent brushing	↓ (↑ in non-asthmatic).

Table 7: Comparison of studies depicting effect of preventive care.

Wogelius, *et al.* [27] found an increase in demarcated opacities and Hiedari, *et al.* [25] and Reddy, *et al.* [20] compared the impact of tablet, syrup, and inhaler on the oral cavity of asthmatic. In total 13 studies excluding the reviews found an increased risk of caries in asthmatics and seven found it not statistically significant, where one study only commented on an increase in microbial count and in one study of Brigid, *et al.* [16], the numbers of caries detected in controls were found to be more than the asthmatics.

Discussion

The purpose of this systematic review was to evaluate the direct or indirect effect of inhalers used as a cure of asthmatic attack on caries and its prevention in patients leading to tooth loss or decay, due to xerostomia, increased microbial count or creation of acidic environment in mouth.

Due to the heterogeneity of the studies (different age groups, different inhalers, duration of medication), it was not possible to perform a statistical analysis of the data. The gold standard for systematic reviews is to study randomized clinical assessments, which are the studies with the most robust design. Studies were selected according to the strength of evidence and indicate a higher quality of data.

There is a debate on whether the inhalers per se cause the dental decay in patients or since the caries is an evolutionary process with multifactorial etiology, and inhalers might be depicted as add as an additive factor or co-existing medicine with no significance.

Chelliah, *et al.* [6] stated that subjects using inhaled corticosteroids were 6.26 times more likely to develop dental caries, than those who do not.

This present review analyzed studies from 2003 till 2019 with at least 3-6 months to one year of medication. One study included only healthy individuals in limited numbers who were made to use inhalers and the effects were assessed. Two literature reviews were taken into account. Studies either measured dental caries or xerostomia, pH, bacterial count affecting teeth. Several studies have reported conflicting results regarding the effects of inhalation drugs. The present review was to assess the increased carious susceptibility by these medications. Caries is a diet-related multifactor induced disease and asthmatic medications are seasonally based. It is therefore difficult to conclude.

Saliva plays an important role in the oral cavity by providing cleansing endogenic and exogenic microbes and by-products of the bowel. Reduced stimulated saliva has been noted by all the authors who measured the salivary flow rate namely Stennesson, *et al.* [12] Alaki, *et al.* [2] Paganini, *et al.* [4] Klinik, *et al.* [14] Arafa, *et al.* [11] and two literature reviews from Godara, *et al.* [26] and Maupome, *et al.* [29]. Though Alaki, *et al.* [2] and Stennesson, *et al.* [12] did not find the decrease in SFR, of any significant value. With the increase in xerostomia, a chain reaction begins. After dryness in the mouth, patients especially children tend to increase their sweetened beverages intake. Xerostomia may also occur in asthmatics as due to congestion of airway, a habit of mouth breathing develops as

figured by Stennesson., *et al.* [12] and Rezende., *et al.* [3] Thereby decrease in a salivary bath of the teeth surface which usually cleans away food particles, bacteria away from teeth thus leading to an increase in caries risk Bozejac., *et al.* [15]. Calcium and phosphate in supersaturated saliva in normal individuals and with continual bathing of teeth in saliva, re-mineralization of the tooth occurs.

Keeping in mind the hypothesis that inhaler medicaments which come in direct contact of oral cavity and teeth result in erosion/demineralization of teeth. Acidic pH in the mouth can be created due to the medication, especially dry powder inhaler. Rezende., *et al.* [3] found that if this medication remains for a longer period, as saliva is usually found to be diminished in asthmatics, it can damage teeth especially on lingual or palatal surfaces.

Tootla., *et al.* [7] and Godara., *et al.* [26] found that inhaler can bring down oral pH below the critical value. There is one more theory where Godara., *et al.* [5] says that beta-agonist can also cause Gastroesophageal reflux disease (GERD) symptoms. Subsequently leading to erosion and cavities after that. Again since the major amount of medication may remain in the mouth because of the wrong inhalation technique, it can lead to further damage if the sugars are added to medications. Added lactose sugar in an inhaler can ignite the cavities attack. To make the taste of the medicine acceptable, lactose is generally added as a carrier with the medicaments. Apart from providing bulk and improving taste, lactose also improves handling, dispensing and metering of inhaled dose. Lactose monohydrate (the main excipient used in DPI's in the range of 12.5 - 25mg/dose) is commonly added. It is the least cariogenic sugar but does not nullify the caries risk. It has the potential of enamel and root dentin demineralization, also because of reduced pH of saliva. Lactose is a commonly used carrier for salbutamol inhaler. It is suspected that these lactose-containing inhalers can cause inter-dental caries, as it lodges itself between teeth and generally remains undetected unless a symptom arises or bitewing x-rays are taken. Bozejac., *et al.* [15] states that it is one of the least cariogenic sugar, still its potential cannot be ignored. Mouth rinsing just after inhaler usage has been found beneficial by Godara., *et al.* [26] though Samec., *et al.* [21] studies did not find it useful. Inter-dental brushes to clean the inter-proximal areas where the drugs get deposited and use of spacer instead of direct inhalers/syrups have been encouraged as lesser deposition of the drug occurs in between teeth and other parts if used correctly. This

mouth rinsing habit has proven helpful in bringing down the caries score in a study when compared with a nonrinsing asthmatic group Godara., *et al.* [26] But other additional factors cannot be weaned off like reduced salivary flow, change in microflora, etc. thus cumulatively the susceptibility for caries remains on the higher side.

Additive sugars reduced SFR and pH. This may combine and give way to another pathogenicity to occur, which is a proliferation of cariogenic bacteria. Botelho., *et al.* [18] found significant LB count in contrast to SM, and Alaki., *et al.* [2] found the opposite, that is, increased SM. While others namely, Ashuja., *et al.* [17] Mazolenni., *et al.* [13] and Chelliah., *et al.* [6] proved the increase in both the type of bacteria and one also added the proliferation of other opportunistic bacteria. Therefore, asthma should be considered as a risk factor for oral proliferation of bacteria after initiation of medication.

Ashuja., *et al.* [17] showed that children using medication > 3 times a day and using combi2 drugs in inhalers have been found with an increase in bacteria in the oral cavity of asthmatics. As the disease's severity increased so it's ill effects. It leads to increased microbial count as found by Alaki., *et al.* [2] increased caries as detected by Reddy., *et al.* [20] and Botelto., *et al.* [18] whereas other studies found it insignificant. But as the duration of medication was taken into account, with its increase, increased caries score was noted by Samec., *et al.* [21] whereas Alaki., *et al.* [2] Eloit., *et al.* [22] Sergey., *et al.* [19] Boskabady., *et al.* [23] Godara., *et al.* [26] Heidari., *et al.* [25] observed contrary to it. Thus, it is the severity of the disease leading to corresponding medication increase and not the length of the disease that is cariogenic in the oral cavity.

It has been found that people from educated and higher socio-economic backgrounds have better oral hygiene. On the other hand, who has been over-enthusiastically been involved with the brushing, like > 3 times a day has also lost their tooth surface due to dental erosions, instead of prevention. Fluoride can be a major help in preventing dental caries. Nutritional counseling has to be implemented and facilitate awareness in training activities. Low patient awareness and lower socio-economic groups that had less access to preventive measures had increased caries incidences. Pre-existing enamel defects bottle feeding at night are the known additional risk factors for caries, to be taken care of. Rinsing the mouth with neutral pH or basic mouth rinses (milk, water, sodium

fluoride 0.5% mouth rinse) after the use of an inhaler, can diminish the acidic pH of the medication. More fiber-enriched food should be added to the meals. Food like cheese, peanuts, fruits, vegetables has a low cariogenic effect. They should be added in the daily diets. For people who have a high craving for sweets, sugar substitutes are also available which will have a lesser adverse effect on teeth, like xylitol, saccharin, sorbitol can be added as sweeteners. Immediate brushing after the use of inhalers should be strictly avoided. The pH in mouth becomes acidic and if such abrasive forces are drawn on the tooth, surface enamel will be damaged. Hence, caries attack by the asthmatic medication may be prevented by dietary, habits modifications, and by taking preventive measures.

Caries has multifactorial etiology, like good oral hygiene practices, spacer and inhalation technique which decreases the caries score. Inhalers surely do put asthmatics in high caries risk zone via xerostomia, increase in the microbial count and creating an acidogenic environment, but there have been many contradicting results, thus it becomes difficult to assess the growth of an effect called "caries", as it is not limited to one cause. Mere inhalants aren't the sole factor in caries induction, cumulative effects of preventive measures, hygiene habits, environmental, socio-demographic, behavioral, microbiological factors, play a decisive role in the genesis of caries. There is a need to study and further evaluation, as the cariogenic potential of inhalers in a controlled environment taking into account all possible reasons for cavity build-up in mouth, with some medication, severity of disease, same age group, similar prevention protocols followed, dietary habits, methods of delivery of medication, habits, etc.

Conclusion

Dental caries risk increases with the use of asthmatic inhalers and a rise in cariogenic bacteria besides a drop in pH in the mouth and flow of saliva. These changes are amplified with the severity of the disease and may be reduced by taking oral health measures and preventive care. The duration of medication has hardly any effect in the oral cavity.

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