Original Article

Journal of Iranian Medical Council, Volume 7, Issue no 4
http://dx.doi.org/10.18502/jimc.v7i4.16632

Oral Manifestations in Asthmatic Patients Using Metered Dose Inhaler and Dry Powder Inhaler

Hedieh Amin Moghadassi[1], Masoumeh Mehdipour[2], Atefeh Fakharian[3]*, Saranaz Azari-Marhabi[4], Alireza Eslaminejad[1] and Niloofar Koushki[4]

1. Chronic Respiratory Diseases Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Department of Oral Medicine, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Pulmonary Rehabilitation Research Center (PRRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*** Corresponding author**
Atefeh Fakharian, MD
Pulmonary Rehabilitation Research Center (PRRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel: +98 9121551615
Email: fakharian_2005@yahoo.com

Received: 19 Nov 2023
Accepted: 31 Jan 2024

Citation to this article
Amin Moghadassi H, Mehdipour M, Fakharian A, Azari-Marhabi S, Eslaminejad A, Koushki N. Oral Manifestations in Asthmatic Patients Using Metered Dose Inhaler and Dry Powder Inhaler. *Iran Med Counc.* 2024;7(4):702-10.

Abstract

Background: The prevalence of asthma indicates the importance of studying oral manifestations of inhalers as one of the indications of asthma. This study compares two methods of using inhalers, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) in asthmatic patients.

Methods: 100 asthmatic patients (50 MDI-treated, 50 DPI-treated) and 50 healthy individuals were selected by convincing sampling. The three sampled groups were gender- and age-matched. We performed a clinical examination, recorded the information, and analyzed the data by SPSS21 software using a t-test and one-way ANOVA for quantitative and Pearson's chi-square test for qualitative indicators.

Results: DMFT index (p-value 0.001), fissured tongue (p-value 0.005), xerostomia (p-value 0.001), and dental erosion (p-value: 0.011) in MDI-treated patients were significantly higher than the other two groups, while the geographic tongue (p-value 0.008) was significantly higher in DPI-treated patients than in the other two groups. It showed that periodontal disease and median rhomboid glossitis had no significant difference between the three groups.

Conclusion: Due to the higher incidence of manifestations in MDI, it is expected that physicians give more attention to prescribing inhalers and give them the necessary training to maintain oral and dental hygiene.

Keywords: Asthma, Dry powder inhalers, Oral hygiene, Metered dose inhalers

Introduction

Asthma is a heterogeneous and common disease that appears as chronic airway inflammation. This disease affects 1-18% of the population in different countries and the prevalence of this disease in the Iranian population is 8.2% (1). A significant increase in the incidence of the disease depends on many variables such as genetics, age, or air pollution (2,3). Asthmatic patients exhibit variable symptoms like wheezing, shortness of breath, chest tightness, and coughing, which vary in severity. These symptoms are managed with self-care or medication, and their occurrence may be intermittent, with some experiencing exacerbation episodes. Asthma is typically linked to respiratory responses to various stimuli and chronic inflammation. These features manifest when symptoms persist or lung function remains unaffected despite standard treatment (4). Asthma medications are categorized into relievers and preventers. Relievers, like bronchodilators, swiftly alleviate worsening symptoms and are effective during physical activities. Preventers, or control drugs, manage long-term symptoms for sustained disease control (5). Treatment of this disease is performed with Long-Acting β2-Agonists (LABA), Short-Acting β2-Agonist (SABA), Leukotriene Receptor Agonist (LTRA), Oral Corticosteroids (OCS), and Inhaled Corticosteroids (ICS). Inhaled drugs are in the form of Metered Dose Inhaler (MDI), Dry Powder Inhaler (DPI), and Nebulizer (4,6,7). Calverley *et al* have demonstrated that inhaled drugs for the treatment of asthma have adverse effects based on the dose, frequency, and duration of use on the oral cavity (8). Asthma treatment is adapted to the type and severity of the disease. Inhaled anti-inflammatory drugs (such as ICS and LTRA) serve as the first line of treatment. Long-term control involves β-adrenergic agonists and combination therapies to enhance lung function. ICS, particularly when combined with LABA (formoterol, salmeterol), is highly effective for primary asthma control by reducing inflammation and adhering to cytokine molecules (9). The long-term use of β2 agonist drugs is associated with an increase in oral caries because this group of drugs affects the secretion and production of saliva (10).

Effects on the mouth include xerostomia, dental caries, candidiasis, ulcers, gingivitis, periodontitis and taste changes, oral mucosal changes, and dental erosion (11,12). Dental erosion in these patients is increased due to reduced salivary pH (1,12,13). One of the most common side effects of oral medications is dry mouth, caused by hyposalivation, β2 agonists, and corticosteroids oral inhalers (14). Dental caries is a microbial infectious disease that affects dental calcification tissues. The risk of dental caries in asthmatic patients using inhalers is higher in the period of mixed and permanent dentition (10). Oral candidiasis (an acute type with pseudomembranous membrane) is observed in approximately 50% of patients with long-term, high doses or frequent inhalation of steroids (9). Using corticosteroid inhalers can stimulate the pharynx, dysphonia, cough, dry mouth, periodontal disease, and macroglossia (12,13). Corticosteroid inhalers elevate periodontal disease risk, with oral breathing contributing to increased gingivitis due to alveolar mucosa dehydration. Saliva plays a crucial role in limiting periodontal disease (10).

In a comparison of DPI and MDI in terms of the spacer need and how to use an inhaler, DPI is preferred over MDI, since it is easier to use and no spacer is required (15). According to Patel *et al*, compared to the MDI and DPI budesonide-formoterol, the DPI form is preferable to the patient, because this form can be used for a different medicinal diet (16).

In a recent study conducted by Sharma *et al* (17), the role of saliva in the oral cavity, dental caries, dental erosion, periodontal diseases, and candidiasis was investigated. Asthma patients showed more symptoms than healthy ones in all of these factors. According to the research of Virchow *et al* (11), treatment of asthma symptoms with ICS in both MDI and DPI was performed on 605 asthmatic patients over 12 years old. The study represented a similar recovery in two groups, in which, people preferred MDI. One case of discontinuation of DPI due to nasopharyngitis and oropharyngeal pain has been observed in the study.

Many studies have been performed on the oral manifestations of asthma and drugs used, but the method of using drugs can also affect the side effects, which is investigated in this study. In this study, the aim is to compare the differences between oral manifestations induced by MDI and DPI, on which few studies have been conducted.

Methods and Materials

This study was descriptive cross-sectional and was conducted at the 31st session of the ethics committee of Shahid Beheshti Dental School, dated 2/18/2017 and registered with the code IR.SBMU.RIDS.REC.1395.419. In this study, no specific intervention was performed on individuals, and only an oral examination was carried out. However, the study conditions were explained to them and a written informed consent obtained from the participants. In the current descriptive cross-sectional study, 100 asthmatic patients (50 MDI-treated, 50 DPI-treated) and 50 control individuals (gender-matched and age-matched) were selected by convincing sampling by referring patients to the clinic of Masih Daneshvari Hospital and Shahid Beheshti dental clinic. According to Ghapanchi's study (18), the sample size was chosen. The Inclusion criteria in this study were that all of the cases were well-controlled, using their inhalers for at least 6 months, and had their permanent teeth and the exclusion criteria were history of smoking and tobacco, history of other systemic diseases and other drug use. All the asthmatic patients are trained in the correct use of an inhaler by a doctor and a representative of the pharmaceutical company since the onset of diagnosis.

Furthermore, 50 asthmatic patients who used MDI Seroflo®125 *mg*; Cipla, Mumbai, India, 50 asthmatic patients who took DPI Symbicort®160 *mg*; AstraZeneca, Cambridge, United Kingdom, and 50 healthy individuals were examined. Seroflo consisted of fluticasone (corticosteroid) and salmeterol (long-acting βagonist), prescribed in the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD), used with a spacer. Symbicort is comprised budesonide (corticosteroid) and formoterol (long-acting βagonist), prescribed in the treatment of asthma and COPD, and it needs no spacer. The pulmonologists examined 100 patients with a clinical examination, clinical signs, and spirometry test, and FEV1 less than 80% and FEV1/FVC less than 0.7%, indicating asthma.

A graduate dental student recorded the demographic information of the cases in the questionnaire, including name, date of birth, gender, type of drug use, duration of drug intake, and how to use the drug. The graduate dental student performed the oral examination with a disposable mirror, a disposable explorer, and a periodontal stainless-steel probe of the University of Michigan under dental unit light and examined all teeth surfaces for Dental caries, Missing teeth, and Fillings (DMFT) were documented in the corresponding table, and the DMFT index was subsequently calculated.

To assess the Bleeding on Probing Index (BOP), a probing walking technique was applied to all the teeth, and observations were made 30-60 seconds afterward. A positive BOP was recorded for instances of bleeding, while a negative BOP was assigned when no bleeding occurred. In the presence of Clinical Attachment Loss (CAL), CAL was measured with the periodontal probe and the results recorded in the questionnaire. The result of a gingival examination was diagnosed and recorded as a periodontal disease in the questionnaire. The oral cavity and tongue were examined in all regions for the presence of candidiasis, median rhomboid glossitis, hairy tongue, geographic tongue, and fissured tongue with sandwich technique. Xerostomia and dry mouth were also evaluated in the form of subjective and asked about symptoms such as dry mouth, burning of the tongue, and the need for frequent water intake during the day. In addition to the patient's subjective report, a tongue blade and lipstick was used.

The collected data was analyzed using IBM® Statistical Package for Social Sciences (SPSS®), version 21. In the experiments, normality was initially determined through the Kolmogorov-Smirnov test. Following confirmation of normality, an independent samples t-test and one-way ANOVA were conducted. In cases where normality was not observed, non-parametric alternatives, the Mann-Whitney and Kruskal-Wallis tests, were utilized. For the analysis of qualitative variables, both the Pearson Chi-square test and Fisher's exact test were performed (p-value <0.05 was considered statistically significant).

Results

The mean D-index in MDI-treated patients, DPI-treated patients, and healthy individuals was 3.18, 2.68, and 3.88, respectively, in which the difference was not statistically significant (p-value=0.136). Furthermore, the mean M-index in MDI-treated patients, DPI-treated patients, and healthy individuals

were 12.74, 9.16, and 4.92, respectively, in which their difference was statistically significant (p-value =0.001). Lastly, the F-index in MDI-treated patients, DPI-treated patients, and healthy individuals were 4.30, 5.00, and 5.00, in which their difference was not statistically significant (p-value=0.553). A detailed report of this experiment is shown in table 1.

Due to the significant difference between the three groups, One-way-Anova was used for the M index. The variance was not homogeneous in the three groups; thus, it was evaluated by Robust Weich test. In the Robust Weich test, the difference between the two groups was significant (p-value <0.001), hence the Games-Howell test was utilized. Table 2 reports the details of this experiment.

In this study, the Pearson Chi-square test was used for

Table 1. Age and Decay, Missing, Filling Teeth (DMFT index) in the patients and healthy individuals

	MDI-treated patients		DPI-treated patients		Healthy individuals		
Clinical index	Median (interquartile range)	Mean (standard deviation)	Median (interquartile range)	Mean (standard deviation)	Median (interquartile range)	Mean (standard deviation)	p-value
Age	49.98 (13.5)	50 (11.823)	44.62 (22.75)	41 (13.769)	45 (20.75)	46 (13.920)	0.080
D	3.18 (3.75)	3 (2.833)	2.68 (3)	2 (2.729)	3.88 (5)	3 (3.342)	0.136
M	12.74 (9.5)	10 (9.404)	9.16 (7.75)	5.50 (8.660)	4.92 (2)	4 (4.7030)	0.001
F	4.30 (7)	3 (5.250)	4 (7.75)	3 (4.209)	5 (7.75)	3.5 (4.598)	0.553
DMFT	20.22 (12.25)	17.5 (7.52)	15.84 (9)	14.5 (6.95)	13.80 (5.75)	13 (5.55)	0.001

Table 2. Games-Howell Test Results for the Missing Teeth in DMFT Index

Multiple Comparisons Dependent Variable: M Games-Howell						
Group 1	Group 2	Mean	Standard error	p-value	95% Confidence interval	
					Lower bound	Upper bound
MDI	DPI	3.580	1.808	0.123	-0.72	7.88
	Control	7.820*	1.487	< 0.001	4.26	11.38
DPI	MDI	-3.580	1.808	0.123	-7.88	0.72
	Control	4.240*	1.394	0.009	0.91	7.57
Control	MDI	-7.820*	1.487	< 0.001	-11.38	-4.26
	DPI	-4.240*	1.394	0.009	-7.57	-0.91

Table 3. Pearson-Chi-square test results

Variables	Groups			
	MDI-treated	DPI-treated	Healthy individuals	p-value
Candidiasis	6%	8%	2%	0.397
Fissured tongue	50%	30%	20%	0.005
Geographic tongue	10%	18%	0%	0.008
Hairy tongue	0%	0%	0%	
Median rhomboid glossitis	4%	2%	0%	0.360
Periodontal disease	36%	42%	48%	0.499
Xerostomia, Dry mouth	62%	40%	12%	0.001
Dental erosion	8%	0%	0%	0.011

qualitative variables. Table 3 shows the results of the experiment and more detailed results of the study are presented in the discussion section.

Discussion

Drug side effects are common in the oral cavity and become more and more common with new drugs entering the market every day. Healthcare providers should be familiar with these common and unusual reactions. Detection of lesions is based on a history of systemic disease, drug use, and lesion creation. Most mucosal changes and lesions resulting from using drugs occur after weeks and months, but some lesions, such as lichenoid reactions, can initially be developed without signs and become symptomatic after several years (14). Oral manifestations of drugs affect the function, comfort, and patient quality of life (19). Therefore, according to the current study aims, the two groups of asthmatic patients, MDI, DPI, and gender-matched controls of 17 to 87 years of age evaluated and compared for the DMFT index and oral manifestations such as candidiasis, fissured tongue, geographic tongue, hairy tongue, median rhomboid glossitis, periodontal disease, xerostomia, dry mouth and dental erosion. DMFT index, fissured tongue, xerostomia, and dental erosion in MDI-treated patients were significantly higher than the other two groups, while the geographic tongue was significantly higher in DPI-treated patients than the other two groups. It showed that periodontal disease and median rhomboid glossitis had no significant difference between the three groups. According to previous studies (19), 60% of injecting spray particles remain in the oropharynx by the DPI method and do not reach the lungs, while the amount in the inhaler spray reaches 80% by the MDI method. However, there was no significant difference in treatment performance in the two groups of patients with DPI and MDI.

According to this study, the mean DMFT index in the patients using MDI was 22.20, patients using DPI was 15.84 and in the healthy individuals, it was 13.8, in which in patients using inhaler spray MDI, was significantly higher than the other two groups (p-value<0.05). According to Gapanchi *et al* (18), DMFT did not differ significantly between asthmatic patients and the control group. The study which was performed on 18 different inhalers, demonstrated a decrease in salivary pH and it was 5.06 in DPI-used patients and 6.45 in MDI-treated patients. Therefore, the enamel demineralization and DMFT index were higher in MDI-treated patients (20). In a recent study, it was shown that asthma treatment drugs had no effect on the density, and pH of the saliva and consequently did not affect the DMFT index (21). Moreover, according to Heidari *et al* (22), there was

no difference in DMFT/dmft among different drug groups, including antihistamines, β2 agonists, and steroids, but patients who used the pill form had higher dental caries than inhalers. Recent studies suggested that corticosteroid inhalers increase the risk of dental caries and missing teeth in asthmatic patients due to prolonged use of inhaled corticosteroids (23-25). According to a study conducted by Khalilzadeh *et al* (26), a significant difference was found between the patients and the control group in the study, which contrasts with what has been observed in previous research. This difference may be linked to specific factors, such as the use of beclomethasone and salbutamol inhalers. Additionally, a significant difference exists in the dental aspects studied, as this research focused on mixed dentition and primary teeth. Several studies indicated a higher DMFT index in the patient group compared to the control group, with asthmatic patients showing significantly elevated rates of missing and filled teeth (27). In this study, we just found a significant difference in the missing index in the three groups. The duration of using inhalers was similar in the two groups of patients, therefore, the duration of the drug usage did not affect the amount of dental caries. Some studies such as Eloot *et al* (28), Ghapanchi *et al* (18), and Boskabady *et al* (1), confirm the present study results. Some studies suggested that the duration of drug intake was associated with dental caries in asthmatic patients (21,29,30). According to Ersin *et al* (21), there was a negative relationship between the duration of using the inhaler and the salivary pH, and if the duration was longer, the symptoms of reduced saliva levels and increasing dental caries were higher. The rate of dental caries was more in the asthmatic patients who suffered from severe asthma (31). These differences can be due to the types of inhalers, fluoride amount, lifestyle, the amount of sugar used, and the preventive caries methods (7,32).

In our study, erythematous candidiasis was observed in the patient's palates, which is more common in asthmatic patients than in the control group. On the other hand, patients who used corticosteroid inhalers had a significantly high prevalence of candidiasis (33,34). A possible explanation of this difference can be due to the type of inhaler which was used.

Additionally, in the current study, it was observed that the geographic tongue is significantly higher in the asthmatic patients than in the control group. In particular, geographic tongue in the MDI-treated patients is 10%, and in the DPI-treated patients, it is 18%. Geographic tongue mean in studies performed by Honarmand *et al* (35) and Shulman *et al* (36) reported 11.9 and 12.7%, respectively. In a study performed by Ghapanchi *et al* (18), the geographic tongue of the asthmatic patient's group was 10% and the geographic tongue of the control group was 2%. Based on the above studies and our experiments, there is a significant relationship between this disease and the occurrence of a geographic tongue, and the reported geographic tongue mean is close to the result of the present study. According to Miloglu *et al* (37), Yarom *et al* (38), Shulman *et al* (36), and Voros-Balog *et al* (39), there is no significant relationship between systemic disease and geographic tongue. A possible explanation for this difference is due to racial and geographical differences.

In this study, fissured tongue was the most common manifestation, which was significantly higher in the asthmatic patients than in the control group. Specifically, fissured tongue was 50% in the MDI-treated, 30% in the DPI-treated, and 20% in the control group.

According to studies conducted by Yarom *et al* (38) and Voros-Balog *et al* (39), the mean of fissured tongue were reported 30.5% and 29.2%, respectively, which are close to the result of the current study. However, in Yarom *et al* (38) and Voros-Balog *et al* (39) studies, there was no significant relationship between systemic disease and fissured tongue. According to a study performed by Gapanchi *et al* (18), the mean of fissured tongue in asthmatic patients was 13%, and in the control group, it was 11% which is less than the results of this study.

In this study, the median rhomboid glossitis differences between the three groups were not significant. Specifically, the median rhomboid glossitis was 4% in MDI, 2% in DPI, and 0% in the control group, which advocates other studies' results (18,38).

The present study revealed that periodontal disease is not significantly different between the three groups and the prevalence of periodontal disease in the control group is higher than in the MDI-treated and DPI-treated patients. According to McDerra *et*

al (40), Shashikiran *et al* (24), and Stensson *et al* (41) studies, asthmatic patients are more likely to experience periodontal disease than the control group. Eloot *et al* (28) did not find any significant difference between the patients and the control groups and also believed that the relationship between asthma and periodontal disease was due to pathologic, immune, and inflammatory responses. Some researchers believed that asthmatic patients had more calculus and plaque than the control group, due to the greater volume of calcium and phosphorus in the parotid and submandibular glands of these patients (40). According to a study conducted by Shulman *et al* (36), asthma and asthmatic drugs did not affect periodontal disease. The results of the related studies mentioned above advocate the results of the current study.

In this study, significant differences were observed between the three groups. In particular, dental erosion of the MDI group is 8%, but it is 0% for the other two groups. Some research showed that the asthmatic patients were more risk-averse than the control group in dental erosion (42,43). On the other hand, Dugmore-Rock *et al* (44) reported that there was no significant difference in dental erosion between asthmatic patients and healthy ones. Asthma drugs can cause dental erosion with a decrease in saliva levels. Furthermore, the effect of bronchodilators and oral breathing in asthmatic patients raises the symptoms of dry mouth (42). It has also been shown by O'Sullivan *et al* (45) that inhaler contains fluticasone (pH=7.73) and budesonide (pH=6.47), in which DPI inhaled drugs can increase dental erosion by changing the chemical status of the oral cavity. However, according to Tootla *et al* (20), there was no difference in dental erosion between the two groups of patients using DPI and MDI.

The experiments indicate that xerostomia and dry mouth are significantly higher in the MDI group (62%) than the DPI (40%) and the control group (12%), which is consistent with the results of Yuan *et al* (14), in which they measured salivation rate in 232 asthmatic patients. According to their study, dry mouth was more common in patients using Seroflo® (MDI) than ones using Symbicort® (DPI). Furthermore, other research which evaluated 57 asthmatic patients using corticosteroid inhalers, demonstrated that there was no significant difference between the two groups of patients and the control (46).

Conclusion

To the best of our knowledge, this study is the first research in comparison and evaluation of oral manifestations of the two methods of using inhalers (DPI and MDI) in asthma disease. The study results could help various physicians who treat asthmatic patients every day. However, there were some limitations faced during the study, such as low sample size, lack of measuring Unstimulated Whole Salivary (UWS) flow rate for dry mouth, pathological culture for candidiasis, and accurate salivary pH test that reduced the accuracy of the study. To acquire a more accurate result from this study, large-scale research on different types of asthma medications and evaluate oral manifestations in other respiratory diseases and drugs is recommended.

As a general conclusion, the increased prevalence of manifestations in MDI patients, including an elevated DMFT index, fissured tongue, xerostomia, and dental erosion, underscores the importance of physicians paying more attention to both prescribing inhalers and providing necessary training for maintaining patient's oral and dental hygiene.

Conflict of Interest

Authors declare no coflict of interest.

References

1. Boskabady M, Nematollahi H, Boskabady MH. Effect of inhaled medication and inhalation technique on dental caries in asthmatic patients. Iran Red Crescent Med J 2012;14(12):816.

2. Sharifi H, Ghanei M, Sadr M, Emami H, Fakharian A, Hessami Z, *et al*. Prevalence and geographic distribution pattern of asthma in Tehran by ECRHS. Tanaffos 2016;15(4):236.

3. Song WJ, Lee SH, Kang MG, Kim JY, Kim MY, Jo EJ, *et al*. Validation of the Korean version of the European Community Respiratory Health Survey screening questionnaire for use in epidemiologic studies for adult asthma. Asia Pac Allergy 2015;5(1):25-31.

4. Asthma GIf. Global strategy for asthma management and prevention 2018.

5. El Sony A, Chiang C, Malik E, Hassanain S, Hussien H, Khamis A, *et al*. Standard case management of asthma in Sudan: a pilot project. Public Health Action 2013;3(3):247-52.

6. Pinto CR, Almeida NR, Marques TS, Yamamura LLL, Costa LA, Souza-Machado A. Local adverse effects associated with the use of inhaled corticosteroids in patients with moderate or severe asthma. J Bras Pneumol 2013;39(4):409-17.

7. Thomas MS, Parolia A, Kundabala M, Vikram M. Asthma and oral health: a review. Aust Dent J 2010;55(2):128-33.

8. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, *et al*. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;361(9356):449-56.

9. Little J, Falace D, Miller C, Rhodus N. Dental Management of the medically compromised patient. 9th ed. Elsevier; 2018. 675 p.

10. Godara N, Godara R, Khullar M. Impact of inhalation therapy on oral health. Lung India 2011;28(4):272.

11. Virchow JC, Rodriguez-Roisin R, Papi A, Shah TP, Gopalan G. A randomized, double-blinded, double-dummy efficacy and safety study of budesonide–formoterol Spiromax® compared to budesonide–formoterol Turbuhaler® in adults and adolescents with persistent asthma. BMC Pulm Med 2016;16(1):42.

12. Ektah K, Arun R, Elza T. Oral findings in asthmatic children. Amrita Journal of Medicine. 2014;10(1.1-44).

13. Brigic A, Kobaslija S, Zukanovic A. Cariogenic potential of inhaled antiasthmatic drugs. Med Arch 2015;69(4):247.

14. Yuan A, Woo S-B. Adverse drug events in the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119(1):35-47.

15. Geller DE. Comparing clinical features of the nebulizer, metered-dose inhaler, and dry powder inhaler. Respir Care 2005;50(10):1313-22.

16. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, *et al*. Efficacy and safety of maintenance and reliever combination budesonide–formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. Lancet Respir Med 2013;1(1):32-42.

17. Sharma S, Gaur P, Gupta S, Kant S. Impact of asthma on oral health: a review. Int J Recent Sci Res 2018 Mar;9(5):26512-4.

18. Ghapanchi J, Rezazadeh F, Kamali F, Rezaee M, Ghodrati M, Amanpour S. Oral manifestations of asthmatic patients. J Pak Med Assoc 2015;65(11):1226-7.

19. Miyahara H, Korematsu S, Nagakura T, Izumi T. Efficacy of fluticasone metered-dose inhaler and dry powder inhaler for pediatric asthma. Pediatr Int 2008;50(1):103-8.

20. Tootla R, Toumba K, Duggal M. An evaluation of the acidogenic potential of asthma inhalers. Arch Oral Biol 2004;49(4):275-83.

21. Ersin NK, GÜlen F, Eronat N, Cogulu D, Demir E, TanaÇ R, *et al*. Oral and dental manifestations of young asthmatics related to medication, severity and duration of condition. Pediatr Int 2006;48(6):549-54.

22. Heidari A, Seraj B, Shahrabi M, Maghsoodi H, Kharazifard MJ, Zarabian T. Relationship between different types and forms of anti-asthmatic medications and dental caries in three to 12 year olds. J Dent (Tehran) 2016;13(4):238.

23. Santos N, Jamelli S, Costa L, Baracho Filho C, Medeiros D, Rizzo J, *et al*. Assessing caries, dental plaque and salivary flow in asthmatic adolescents using inhaled corticosteroids. Allergol Immunopathol (Madr) 2012;40(4):220-4.

24. Shashikiran N, Reddy V, Raju PK. Effect of antiasthmatic medication on dental disease: dental caries and periodontal disease. J Indian Soc Pedod Prev Dent 2007;25(2):65.

25. Han ER, Choi IS, Kim HK, Kang YW, Park JG, Lim JR, et al. Inhaled corticosteroid-related tooth problems in asthmatics. J Asthma 2009;46(2):160-4.

26. Khalilzadeh S, Salamzadeh J, Salem F, Salem K, HAKEMI VM. Dental caries-associated microorganisms in asthmatic children. Tanaffos 2007;6(4):42-6.

27. Bozejac BV, Stojsin I, Ethuric M, Zvezdin B, Brkanic T, Budisin E, *et al*. Impact of inhalation therapy on the incidence of carious lesions in patients with asthma and COPD. J Appl Oral Sci 2017;25(5):506-14.

28. Eloot AK, Vanobbergen JN, De Baets F, Martens LC. Oral health and habits in children with asthma related to severity and duration of condition. Eur J Paediatr Dent 2004;5(4):210-5.

29. Milano M, Lee JY, Donovan K, Chen JW. A cross-sectional study of medication-related factors and caries experience in asthmatic children. Pediatr Dent 2006;28(5):415-9.

30. Botelho M, Maciel S, Neto AC, Dezan C, Fernandes K, De Andrade F. Cariogenic microorganisms and oral conditions in asthmatic children. Caries Res 2011;45(4):386-92.

31. Bălăcel I, Lăcătuşu Ş, Topoliceanu C, Stoleriu S, Bălăcel E, Andrian S, *et al*. Influence of salivary factor on rampant caries to patients with athma. Roman J Oral Rehabil 2011;3(3):22.

32. Chellaih P, Sivadas G, Chintu S, Vedam VV, Arunachalam R, Sarsu M. Effect of anti-asthmatic drugs on dental health: a comparative study. J Pharm Bioallied Sci 2016;8(Suppl 1):S77-S80.

33. Fukushima C, Matsuse H, Tomari S, Obase Y, Miyazaki Y, Shimoda T, *et al*. Oral candidiasis associated with inhaled corticosteroid use: comparison of fluticasone and beclomethasone. Ann Allergy Asthma Immunol 2003;90(6):646-51.

34. Dubus J, Marguet C, Deschildre A, Mely L, Le Roux P, Brouard J, *et al*. Local side-effects of inhaled corticosteroids in asthmatic children: influence of drug, dose, age, and device. Allergy 2001;56(10):944-8.

35. Honarmand M, Mollashahi LF, Shirzaiy M, Sehhatpour M. Geographic tongue and associated risk factors among Iranian dental patients. Iran J Public Health 2013;42(2):215.

36. Shulman JD, Carpenter WM. Prevalence and risk factors associated with geographic tongue among US adults. Oral Dis 2006;12(4):381-6.

37. Miloglu O, Goregen M, Akgul HM, Acemoglu H. The prevalence and risk factors associated with benign migratory glossitis lesions in 7619 Turkish dental outpatients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107(2):e29-33.

38. Yarom N, Cantony U, Gorsky M. Prevalence of fissured tongue, geographic tongue and median rhomboid glossitis among Israeli adults of different ethnic origins. Dermatology 2004;209(2):88-94.

39. Vörös-Balog T, Vincze N, Banoczy J. Prevalence of tongue lesions in Hungarian children. Oral Dis 2003;9(2):84-7.

40. McDerra E, Pollard M, Curzon M. The dental status of asthmatic British school children. Pediatr Dent 1998;20(4):281-7.

41. Stensson M, WENDT LK, Koch G, Oldaeus G, Birkhed D. Oral health in preschool children with asthma. Int J Paediatr Dent 2008;18(4):243-50.

42. Al-Dlaigan Y, Shaw L, Smith A. Is there a relationship between asthma and dental erosion? A case control study. Int J Paediatr Dent 2002;12(3):189-200.

43. Sivasitamparam K, Young W, Jirattanasopa V, Priest J, Khan F, Harbrow D, *et al*. Dental erosion in asthma: a case-control study from south east Queensland. Aust Dent J 2002;47(4):298-303.

44. Dugmore CR, Rock WP. Asthma and tooth erosion. Is there an association? Int J Paediatr Dent 2003;13(6):417-24.

45. O'sullivan EA, Curzon ME. Drug treatments for asthma may cause erosive tooth damage. BMJ 1998;317(7161):820.

46. Spolarich AE. Risk management strategies for reducing oral adverse drug events. J Evid Based Dent Pract 2014;14:87-94. e1.