

Could Sublingual Immunotherapy Affect Oral Health in Children with Asthma and/or Allergic Rhinitis Sensitized to House Dust Mite?

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Keywords

Asthma · Rhinitis · Allergy · House dust mite · Sublingual immunotherapy · Caries · Oral health

Abstract

Background: Sublingual immunotherapy (SLIT) has been successfully employed in IgE-mediated respiratory allergies. However, it is not known whether the modulation of immune responses in the sublingual area during SLIT has any deleterious effect on oral health. We sought to determine the oral health prospectively in children receiving SLIT for house dust mite allergy. **Material and Methods:** Eighteen children with allergic asthma and/or rhinitis and 31 age-matched healthy controls (HC) were included in an open-labeled trial. Oral health was evaluated by scoring the decayed, missing, and filled teeth for primary (dmft) and permanent (DMFT) dentition, and the plaque and gingival indices. Moreover, cariogenic food intake and teeth-brushing habits were also noted at baseline and at 19 months. **Results:** The mean age of the SLIT participants was 9.5 ± 3.1 years and that of the HC was 9.2 ± 3.7 years. The mean duration of SLIT was 19.13 ± 3.81 months. At baseline, the total

dmft and DMFT indices were similar in the SLIT and HC groups ($p > 0.05$), which demonstrated poor hygiene overall. In the within-group comparisons at the examination at 19 months, the SLIT group had a lower number of carious primary teeth and a higher number of filled primary teeth compared to the count at baseline ($p = 0.027$ and $p = 0.058$, respectively). **Conclusion:** Our study showed no detrimental effect of SLIT on oral health during a period of 19 months of follow-up. Parents should be motivated to use dental health services to prevent new caries formation since our cohort had overall poor oral hygiene at the baseline.

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Introduction

Sublingual immunotherapy (SLIT) is accepted worldwide as a safe and well-tolerated treatment for IgE-mediated respiratory allergies [1–3]. Specific allergen immunotherapy has been shown to be capable of preventing new allergen sensitizations, limiting the progression of rhinitis to asthma and thus changing the natural course of the allergic disease [1, 2]. Allergen-specific immuno-

therapy has various effects on the immune system such as reducing specific IgE levels, the induction of blocking IgG antibodies, generating a shift in T cell cytokines (from Th1 to Th2), T cell anergy, and the stimulation of regulatory T lymphocytes [4, 5].

The complex interplay between the normal flora, mucosal elements, and immune system has a critical role in the development of healthy immunity. For example, the gut microbiota has been shown to play a beneficiary role in the modulation of the severity of allergy in infantile atopic dermatitis [6]. As the entry organ of the gastrointestinal tract, the mouth is continuously exposed to a wide spectrum of microbial agents and, optimally, a specialized environment that supports healthy immunity is created here. The oral environment promotes tolerance despite microbial colonization and exposure to foreign antigens [6]. Besides the microbiota, the mapping of the oral immune system contributes to the induction of tolerance [7, 8]. Studies employing sublingual biopsies have revealed that most of the dendritic cells with tolerogenic characteristics are localized in the upper layers of oral tissue, as opposed to the proinflammatory cells which are settled in the muscular tissue. These unique organizational features of the oral mucosa account for the efficacy and safety of the sublingual route during immunotherapy [7, 8].

The development of oral tissues occurs rapidly in early childhood, with the eruption of primary (deciduous) dentition beginning at the age of 6 months. A period of transition to permanent dentition follows, so that the primary dentition will have been replaced by the permanent teeth by the age of 6 years. This transition period is defined as mixed dentition [9]. Diverse microbial communities are the etiological agents for tissue infections, ending with dental caries in the mouth which could also be associated with high carbohydrate intake, impaired salivary factors, or a lack of teeth-brushing and flossing [9–12]. In general, *Streptococcus mutans* and *S. sobrinus* are the bacteria responsible for human dental caries [13]. Sugars, and especially starch, are used by *S. mutans* to produce organic acids which enhance the demineralization of the tooth surface and initiate the dental caries [9, 14]. In addition to dental caries, gingivitis is the other important health problem in patients with poor mouth hygiene; it is caused by microbial plaque accumulation around the teeth [15].

The goal of immunotherapy is to induce a predominantly regulatory type of immune response. Therefore, we hypothesized that the modulation of native immune responses in the sublingual area during SLIT might potentially alter normal immunity to the microbial agents

that form the oral flora, thus having the potential to affect oral health. Here, we examined the impact of SLIT against house dust mite allergy on oral health, using an established method and measuring the indices of dental caries, i.e., decayed, missing, and filled teeth for primary (dmft) and permanent (DMFT) dentition, and of plaque and gingival health.

Material and Methods

Study Population

Eighteen children with a diagnosis of mild-to-moderate allergic asthma and/or rhinitis followed up at Marmara University Pediatric Allergy and Immunology outpatient clinic and 31 age-matched healthy controls (HC) were included in this study. The children receiving SLIT were evaluated for dental health at baseline and 19 months after therapy. Data were collected by clinical examination and a questionnaire regarding nutritional habits and oral hygiene applications. The study protocol was approved by the local ethics committee of Marmara University (IRB number: IRB00009067) and a written informed consent was obtained from all patients/parents of the children. Due to the young age of our patients, a simple oral description of the study was given to participating children in the presence of their parent(s) and a verbal assent was requested.

SLIT Protocol

The diagnosis and severity of asthma and rhinitis were based on medical history, physical examination findings, and postbronchodilator changes in FEV₁, as described in the GINA consensus report [16]. Sublingual immunotherapy (Staloral, Stallergenes Greer™, Antony, France) was given 3 times a week at a fixed dose according to the manufacturer's recommendation. The mean duration between the 2 assessments, i.e., pre- and posttherapy, was 19.13 ± 3.81 months.

Evaluation of Oral Health

The caries experience was evaluated by the dmft and DMFT indices of tooth decay, appropriate for age. Children in the mixed-dentition period were examined for both dmft and DMFT. Patients were examined by the same investigator (A.K.) to evaluate oral health at all assessments since intraobserver differences were not seen in oral examinations ($n = 10$ patients) between the dentist (G.M.) and the pediatrician (A.K.) in a prior pilot study. A final dentition score was obtained for dmft and/or DMFT by calculating the number of teeth that were decayed, missing, or filled [9]. Moreover, we evaluated the children for microbial plaque accumulation around the teeth [17, 18], designated as plaque index (PI) and for gingival-tissue inflammation [18, 19], which we referred to as the gingival index (GI). The children were considered to have good oral care if the sum of the PI and GI scores was zero, and poor oral care for values above zero [9]. Our questionnaire sought to evaluate nutritional habits of children for carbohydrate intake. Carbohydrate-rich nutrition was defined as the consumption of >3 snacks containing starch each day. In addition, the daily frequency of teeth-brushing was noted in all children.

Table 1. The demographic and laboratory findings for SLIT patients

	Total IgE, IU/L	Eosinophils, cells/mm ³	<i>Dermatophagoides pteronyssinus</i> skin-prick test wheal diameter, mm	<i>D. farinae</i> skin-prick test wheal diameter, mm
Mean ± SD	435.4±314.9	553.3±580.4	6.83±1.95	7.11±3.04
Median (range)	414 (64–1,134)	500 (100–2,500)	7 (3.5–12)	6 (3–13.5)

Table 2. Oral health status of patients treated with SLIT and of the healthy controls

	SLIT at baseline (n = 18)	SLIT at 19 months (n = 18)	HC (n = 31)	SLIT at baseline vs. at 19 months ^a , p value	SLIT vs. HC at baseline ^b , p value
Plaque index	0.05±0.16	0.05±0.17	0.11±0.24	0.317	0.556
Gingival index	0.02±0.06	0.02±0.06	0.04±0.14	0.655	0.798
dmft index	1.61±2.54	1.6±2.29	2.03±2.21	0.619	0.362
Decayed primary teeth	1.28±2.44	0.53±1.24	1.81±1.86	0.027	0.144
Filled primary teeth	0.17±0.7	1.07±1.53	0.06±0.35	0.058	0.672
Extracted primary teeth	0.17±0.51	0±0	0.16±0.45	0.317	0.884
DMFT index	0.89±1.45	1.2±1.69	0.83±1.24	0.194	0.794
Decayed permanent teeth	0.61±1.09	0.67±1.44	0.58±1.06	1.000	0.889

Values are expressed as means ± SD. SLIT, sublingual immunotherapy; HC, healthy controls; dmft, decayed, missing, and filled teeth index for primary dentition; DMFT, decayed, missing, and filled teeth index for permanent dentition.

^a Wilcoxon signed-rank test. ^b Mann-Whitney U test.

Statistical Analysis

Data were analyzed by nonparametric tests including the Mann-Whitney U test and the Wilcoxon signed-rank test. The χ^2 test was used for categorical variables. All analyses were performed by SPSS v16.0 (SPSS Inc., Chicago, IL, USA).

Results

Eighteen patients treated with SLIT (9 females and 9 males; mean age 9.5 ± 3.1 years) and 31 age-matched HC (13 females and 18 males; mean age 9.2 ± 3.7 years) were included in the study. In the SLIT group, patients were evaluated at baseline and at 19 months, while the sampling in the HC group was made only at baseline. The demographic features of the patients are presented in Table 1.

The Baseline Characteristics of the SLIT and HC Groups Were Similar in Terms of Oral Care and Carbohydrate Intake

Overall, the children in our study did not have good teeth-brushing habits, with only 55.6% of the SLIT group

and 71% in the HC group brushing their teeth ≥ 1 times/day. The difference between the groups was not statistically significant ($p > 0.05$). The oral health indices for the SLIT group at baseline were similar to those of the controls, regarding the number of carious, filled, and extracted teeth, and the PI and GI scores ($p > 0.05$; Table 2). We also detected no significant differences in terms of carbohydrate-rich nutrition habits between the 2 groups (the consumption of >3 carbohydrate-rich snacks a day was reported by 77.8% of the SLIT group vs. 58.1% of the HC group; $p > 0.05$).

Follow-Up Evaluation of Oral Health

Assessment of Oral Health in the SLIT Group

Overall, we detected no differences in the indices of plaque and gingiva or dmft and DMFT scores between baseline and 19 months of therapy in the within-group analyses ($p > 0.05$; Table 2). The only difference between the pre- and posttherapy examinations was in the number of decayed primary teeth, with less decayed teeth in the 2nd assessment ($p = 0.027$), likely because of decayed

teeth being filled during the follow-up period, evident from the increased number of fillings at the second exam versus at baseline ($p = 0.05$; Table 2). For the permanent teeth, however, there were no such differences between the baseline and follow-up examinations ($p > 0.05$).

When we assessed oral care in terms of teeth-brushing habits and carbohydrate intake during the study period, there were no significant differences between the baseline and follow-up examinations that would account for a change in dmft and DMFT scores (Table 2). In these analyses, carbohydrate-rich nutrition was 66.6% at baseline and 50% at 19 months, respectively ($p = 0.29$). The frequency of teeth-brushing ($\geq 1/\text{day}$) had actually decreased at follow-up (44.8%, $n = 8$) versus baseline (55.6%, $n = 10$) ($p = 0.015$).

Discussion

In this study, we investigated the effect of SLIT on oral health over a period of 19 months. Our study group had similar baseline characteristics to the age-matched HC, with comparable DMFT and dmft scores. We have demonstrated for the first time that SLIT has no detrimental effects on oral health, as there was no increase in any of the indices evaluated at the follow-up. It is known that oral health is affected by numerous factors, including the microbial ecosystem, nutritional habits, oral hygiene practices, the utilization of dental health services [20], the attitude of patients, saliva characteristics, and epigenetics [12, 21–23]. Alterations in salivary properties [24] and an increase in caries risk might be observed in asthmatic children treated with conventional therapies [25]; in asthmatic children, a 2-fold increase is reported in caries in primary teeth compared to children with no asthma [25].

In this study, we observed a decrease in the number of primary carious teeth in patients receiving SLIT over time, due to the filling of some of the decayed teeth by the time of the follow-up examination, likely due to parental motivation towards better oral care for their children. We did not observe any detrimental effect of SLIT on oral health. One of the strengths of our study is that all the participants were evaluated by the same researcher during the follow-up. We believe that a follow-up period of 19 months would be good enough to detect any potential alterations in the oral health indices stemming from SLIT. However, we may have been limited by the relatively wide age range of the subjects, which meant there was only a small sample in each age group; this

potentially decreases the power of our study for detecting any age-specific alterations. Due to the fact that the overall oral health of our study population was not satisfactory, we may have missed small changes possibly caused by SLIT, so similar studies on children with better oral care are warranted. We evaluated the HC group only at baseline, which limited us in observing changes in oral health in normal children.

In conclusion, our study demonstrated the safety of SLIT in children with regard to the potential impact of local immune modulation on oral health. We did not encounter any formation of dental caries attributable to SLIT during a period of 19 months of follow-up. However, minor effects might have been missed due to the overall poor oral hygiene of the study group at the baseline. Further studies could focus on extended bacterial profiling and saliva analyses that would enable a better understanding of the effects of SLIT on oral health.

Acknowledgements

We are grateful to our departed mentor Prof. Isil Barlan for her contribution to our lives and to this paper. We thank Ozlem Yigit and Burak Aksu for their supportive role. This study was supported by The Marmara University Scientific Research Committee (BAPKO No. SAG-A-200611-0188 01/07/11-01/07/12).

Disclosure Statement

The authors declare no conflict of interest directly relevant to this paper.

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