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Formerly part of: The Dental Journal of Malaysia & Singapore

Scopus coverage years: 1974, from 1976 to 1977, from 1979 to 1990, from 1993 to 1997, from 2000 to 2001, from 2004 to 2007, from 2010 to 2015, 2017, 2019

Publisher: Elsevier

ISSN: 0377-5291 E-ISSN: 2214-6075

Subject area: Medicine: General Medicine

Source type: *Journal*

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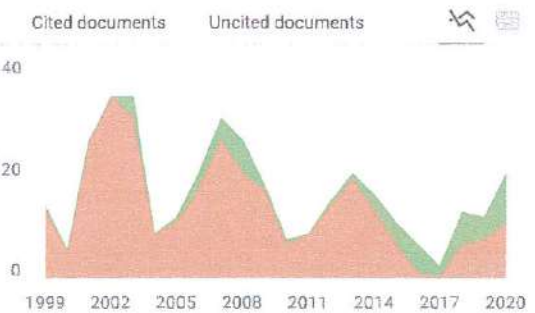
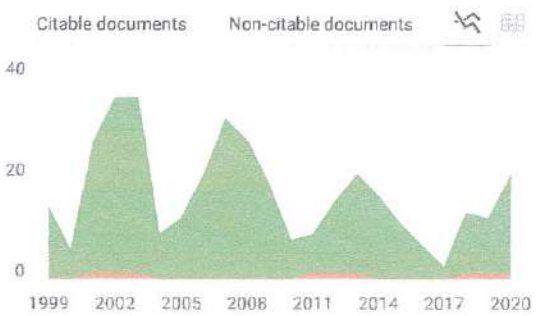
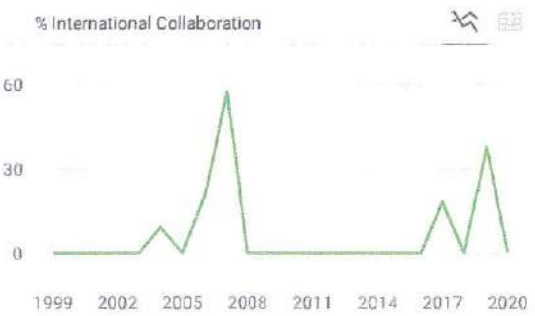
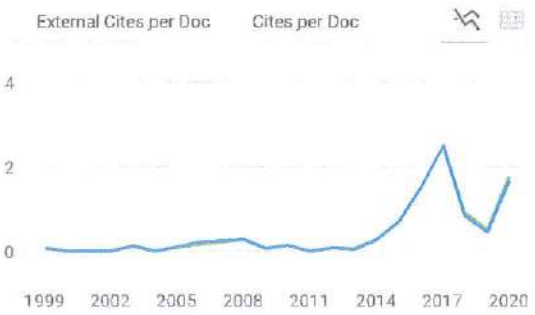
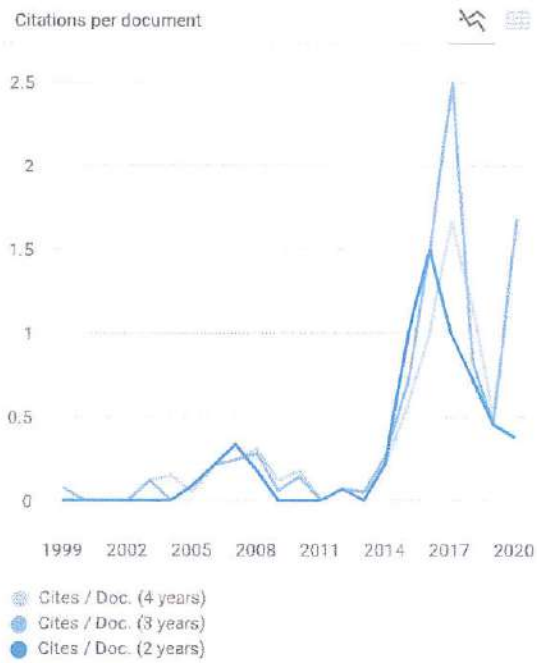
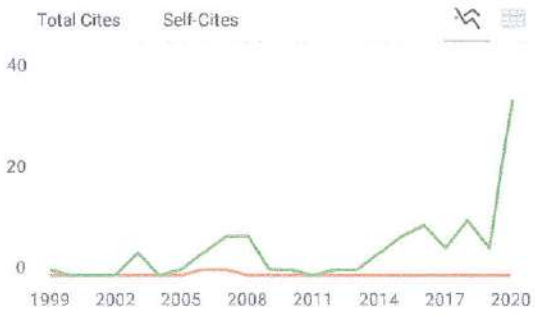
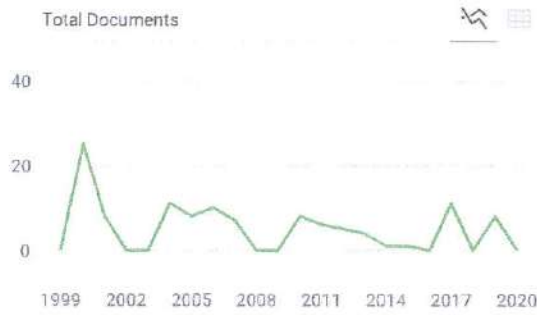
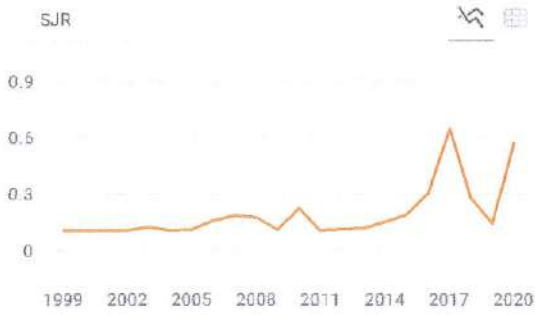
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Singapore	Dentistry Dentistry (miscellaneous)	Elsevier (Singapore) Pte Ltd	11
Universities and research institutions in Singapore			

PUBLICATION TYPE	ISSN	COVERAGE	INFORMATION
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SCOPE

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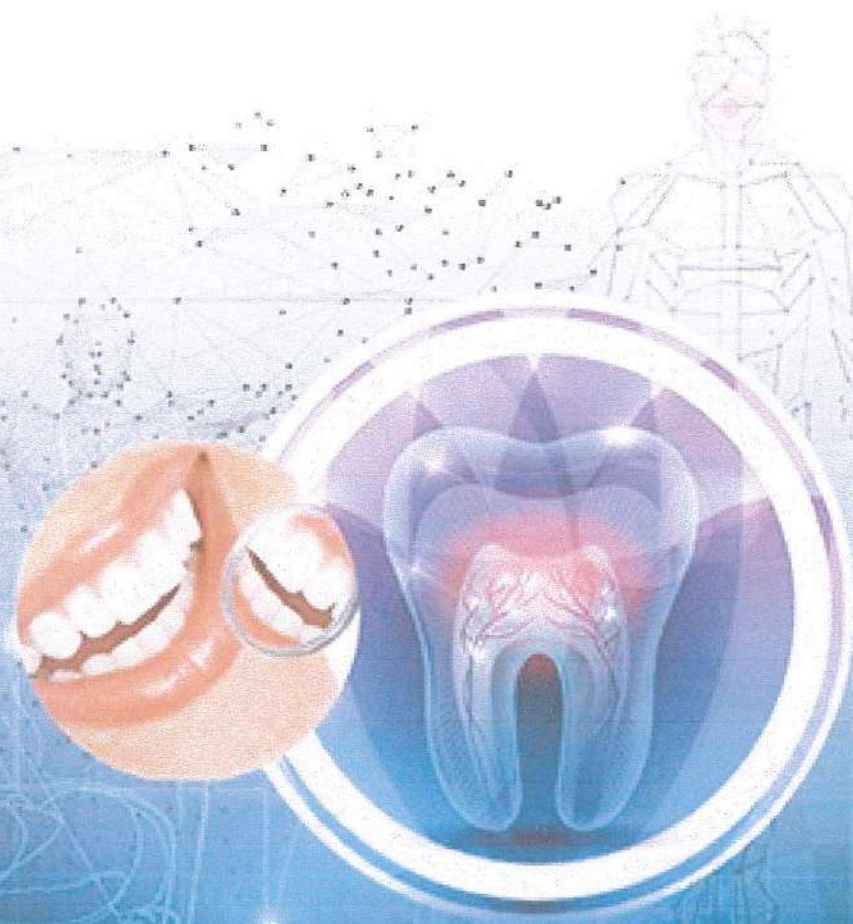
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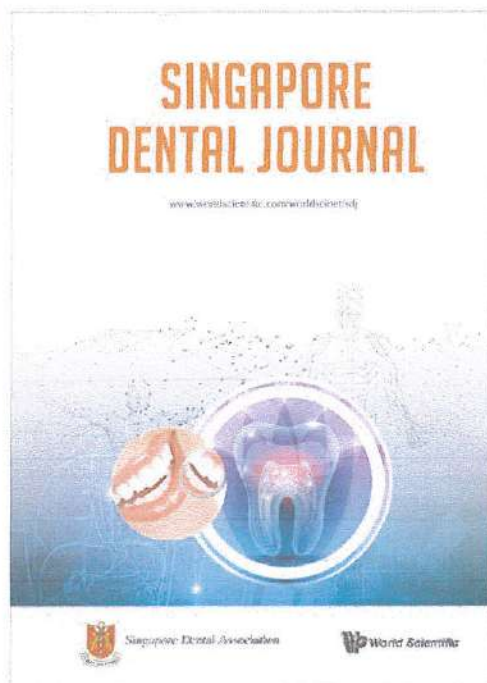
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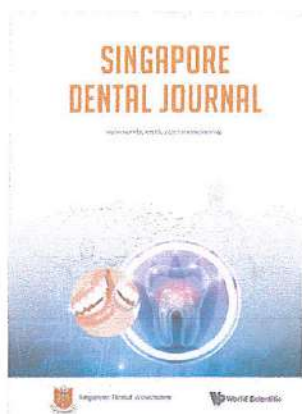
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Sindy Cornelia Nelwan, Ricardo Adrian Nugraha, Anang Endaryanto, Frisma Dewi, Prawati Nuraini, Udijanto Tedjosongko, Daniel Haryono Utomo and on behalf of Indonesian Association of Pediatric Dentistry

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Effect of scaling and root planing on level of immunoglobulin E and immunoglobulin G₄ in children with gingivitis and house-dust mite allergy: A pilot randomised controlled trial

Sindy Cornelia Nelwan^{*,||}, Ricardo Adrian Nugraha[†], Anang Endaryanto[‡], Frisma Dewi*, Prawati Nuraini*, Udijanto Tedjosongko*, Daniel Haryono Utomo[§], on behalf of Indonesian Association of Pediatric Dentistry[¶]

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Keywords:

Dental scaling
Gingivitis
House-dust mite
Immunoglobulin E
Root planing

A B S T R A C T

Background and Objective: There is a pressing need for developing innovative strategies to prevent allergic diseases among children. As house-dust mite (HDM) allergy is often seen in children with gingivitis, strategies should be derived from a conceptual framework of allergen elimination and pathogen eradication; one such strategy is dental scaling and root planing (SRP) to remove dental plaque and periodontal pathogens. The study aimed to evaluate the beneficial effects of comprehensive 6-months dental SRP to reduce the level of immunoglobulin E (IgE) and immunoglobulin G₄ (IgG₄) in children with gingivitis and HDM allergy. IgE and IgG₄, whose production is controlled mainly by Th-2 cells and B cells, are proven biomarkers for atopic inflammatory responses.

Methods: The present study conducted a non-blinded randomised controlled trial with superiority design. A total of 10 subjects (age range 6–16 years) with gingivitis and positive skin-prick test to HDM from Pediatric Allergy Outpatient Clinic, Dr. Soetomo General Hospital were enrolled in the present study. Of the 10 subjects, only five received dental SRP. We further evaluated total serum IgE and IgG₄ level before and 6 months after treatment.

Results and Discussion: Subjects in the standard treatment group showed a slight decrease in the IgE level ($p = 0.019$) but no change in the IgG₄ level ($p = 0.839$), while subjects in the intervention group showed a significant decrease in IgE ($p < 0.001$) and IgG₄ levels ($p = 0.001$).

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Conclusion: The study results suggest that 6-month comprehensive dental scaling combined with root planing may help to reduce IgE and IgG₄ levels in children with gingivitis and HDM allergy. Furthermore, untreated or undertreated gingivitis is often associated with worsening allergic manifestation and thus should be avoided.

Trial Registration: ISRCTN31416107, retrospectively registered on 17 April 2018.

Background

Indonesia has a major issue with house dust mites (HDMs) compared to other countries, because HDMs generally thrive in warm-temperate and humid climate, particularly in some urban and rural areas of Indonesia.¹ HDM allergy is very common among children and adults living in Indonesia.² In the general population, 1 in 20 preschool children and 1 in 5 school-going children show positive results when tested for HDM allergy, though not all have symptoms.³

HDM, remains the most common major perennial allergen source.⁴ It is one of the most common allergens, of size 0.1–0.5 mm, and lives in pillows, mattresses, blankets, carpets and other soft materials.⁴ They are actually harmless, as they neither bite nor transmit disease. However, for children with predisposition to allergies, HDM droppings contain approximately 14 fully identified proteins such as cysteine, protease and chymotrypsin, which have the potential to induce atopic inflammatory responses.⁵ Sensitisation to HDM is an important trigger of asthmatic exacerbations and allergic diseases in children.⁶ According to the World Health Organization, approximately 70% of asthma and hay fever are caused by HDM worldwide.⁷ As HDM is mostly found in homes in Indonesia, the exposure to this allergen is inevitable.⁷

Despite the proven record of specific allergen immunotherapy (SIT) in managing HDM allergy in the developed countries, it is still only a control measure that requires a very strict and expensive medical procedure for longer period of time to enhance desensitisation effect and sustained clinical remission.^{8,9} The present study aimed to develop an alternative strategy to induce faster desensitisation effect and to improve biomolecular markers of atopy in children with HDM allergy.

Atopic disorders in children share a common pathogenesis, being mediated by immunoglobulin E (IgE).¹⁰ Atopic inflammatory responses are reflected by the production of IgE and IgG₄, which are controlled mainly by B cells and Th-2 cells.¹¹ Not only IgE but also IgG₄ are manifested as high-frequency type I hypersensitivity.¹² Allergens of different sources are characterised by their tendency to induce IgE and IgG₄ antibodies to induce host inflammatory response.¹² An IgE serological concentration cutoff value of >900 ng/mL and plasma IgG₄ titer

>135 mg/dL or serological IgG₄/IgG >8% >8% cutoff value of IgG₄ were used as standard for triggering allergies.^{13,14}

Some versions of the hygiene hypothesis proposed that gut microbiota has been found to contribute to systemic immune effects.¹⁵ These gut microbiotas influence immune maturation during childhood and are involved in protecting children from developing allergies early in life.¹⁶ Unlike gut microbiota, periodontal bacteria have not been subjected to allergy research. However, recent studies have revealed that the periodontal pathogen *Porphyromonas gingivalis* (Pg) adversely affects the host immune response and affects even remote tissue sites.¹⁷ The colonisation of gingival bacteria, either acute or chronic in nature, is nearly universal among children and adults.¹⁸ Some components of Pg antigens (e.g. lipopolysaccharide [LPS]) may enhance atopic inflammatory responses, whereas gut microbiota consistently inhibits atopic inflammatory responses.¹⁹ Interactions between bacterial antigens and local B cells lead to the production of antibodies within the periodontal tissues, which is essential for bacterial phagocytosis, and the interactions of bacterial antigens with peripheral dendritic cells lead to the production of systemic antibodies, such as IgE and IgG₄.²⁰ Proinflammatory cytokines are also released, thus leading to an imbalance between Th-1 and Th-2 cytokines and resulting in a chronic state of systemic inflammation.²¹ Therefore, dysbiotic oral microbiota ecologies even in children may create permissive conditions for Th-2 cell patterns involved in IgE-mediated allergy.^{22–24}

It was evidenced from an animal model that oral infection due to Pg in rats was a risk factor for the development of allergies.²⁵ While this was an interesting finding for future research in the management of allergies, further clinical studies are needed to verify this finding. According to our knowledge, one of the most potent periodontal bacteria affecting the oral cavity is Pg, which is a major cause of gingivitis and gingival inflammation.²⁶ The LPS of this bacterium may disrupt inflammatory responses.²⁷ As such, targeting this periodontal pathogen and its LPS by dental scaling and root planing (SRP) as a potential tool to control allergies has recently garnered much attention and interest from numerous research studies in our dental laboratory. Moreover, a minimum 6-month comprehensive dental SRP is needed to prevent recurrent infection with this periodontal pathogen.²⁸

Aims and hypotheses

The main aim of this current study was to evaluate the beneficial effects of a comprehensive 6-month dental SRP and investigate whether dental plaque and calculus removal can improve IgE and IgG₄ biomarkers of atopy as mentioned above in subjects with HDM allergy at Pediatric Allergy Outpatient Clinic, Dr. Soetomo General Hospital, Surabaya. The specific aim and hypotheses are as follows:

Specific aim 1: To evaluate the total change in the IgE level following a comprehensive 6-month dental SRP.

Hypothesis 1: A comprehensive 6-month dental SRP reduces the IgE level.

Specific aim 2: To evaluate the total change in the IgG₄ level following a comprehensive 6-month dental SRP.

Hypothesis 2: A comprehensive 6-month dental SRP reduces the IgG₄ level.

Ethics statement

The study was approved by the Institutional Review Boards of Universitas Airlangga – Dr. Soetomo General Hospital Ethics Committee for Health Research (20/Panke. KKE/1). The study was performed according to the guidelines of Good Clinical Practice standards and the declaration of Helsinki. The results of this study will be disseminated through peer-reviewed publications within 1-year after completion.

Methods

Study design

This pilot study is an investigator-initiated, randomised, non-blinded, placebo-controlled clinical study conducted to assess the beneficial effects of dental SRP in children with gingivitis and HDM allergy. This clinical trial included two groups of pre-test and post-test superiority-group designs, consisting of a 6-month standard allergic treatment run-in period and a comprehensive 6-month dental SRP. The experimental procedure included enrolling subjects for this study, conducting pre-tests, doing randomisation and allocation, engaging in a comprehensive 6-month dental SRP or just standard allergic treatment, and conducting post-tests. This trial was registered with the ISRCTN Clinical Trials Registry (registration no. ISRCTN31416107, available at <http://www.isrctn.com/ISRCTN31416107>).

Study setting

The trial was conducted at the Faculty of Dental Medicine of Universitas Airlangga (UNAIR)'s Oral and Dental Laboratory. The experimental study was performed from January to December 2017 at Pediatric Allergy Outpatient

Clinic, Dr. Soetomo General Hospital, and data analysis was performed at the Institute of Tropical Diseases of Universitas Airlangga.

Sample size estimation

The sample size is based on a substantially significant change in IgE level observed in the group. Korn *et al.*²⁹ stated that ELISA can be used to assay free IgE in a concentration range of 1–2,000 IU/mL from peripheral blood samples with a substantially significant change in IgE level due to immunomodulating therapy with 0.5 IU/mL, and the expected standard deviation (SD) of IgE concentration is assumed to be 0.01 IU/mL.²⁹

For clinical superiority design with a dichotomous variable, the formula for calculating the size (N) is³⁰:

$$N = 2x \left(\frac{z_{1-\alpha} + z_{1-\beta}}{d - \delta} \right)^2 \frac{p}{1-p}$$

The parameters were assumed as follows: mean change of IgE in intervention group = 10 pg/mL; mean change of IgE in control group = 0 pg/mL; $\alpha = 0.05$; $\beta = 0.20$; $\delta = 10$ IU/mL; $s = 7$; $s^2 = 49$. The value of N was calculated to be 7.71. This estimate required eight patients, four in each group, to obtain 80% statistical power with 5% significance level for independent samples and paired t -tests. Because this study was a pilot study, a minimum of 10 subjects were enrolled to compensate for an estimate of 20% dropouts.

Recruitment

Subjects were enrolled by direct invitation and pamphlets from Pediatric Allergy Outpatient Clinic, Dr. Soetomo General Hospital with minimum eligibility criteria, so that the intervention can be tested in “real-world” clinical settings.

Participants

After sampling, 22 subjects were selected from this hospital. They were pre-screened from January 31, 2017 to February 28, 2017. Based on the inclusion and exclusion criteria mentioned in Table 1, 12 subjects were eligible for the study, of which, 10 parents agreed and 2 parents declined to participate in the study. After consenting, enrolling in the study, and completing baseline questionnaires, 10 selected subjects were randomised into two parallel groups, intervention and control.

Randomisation and allocation

Subjects were randomised (1:1) into intervention and control groups, using a computer-generated allocation

Table 1

Eligibility criteria for clinical study and participants.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Children aged 6–16 years of any gender and ethnic • Have been diagnosed with HDM allergies by positive skin-prick test • Have been diagnosed with gingivitis by ≥ 2 plaque index according to Silness-Löe criteria • Have high baseline IgE titer (>90 pg/mL), suggesting a positive childhood allergic potency • Understand and able to cooperate with the study protocol • Subjects' parents can voluntarily, sign written consent in accordance with our institutional policies 	<ul style="list-style-type: none"> • Taking any antihistamines or steroid within 1 month, which commonly interfere with results of skin-prick test • received any immunotherapy before treatment • received dental scaling and root planing within 6 months before treatment • The presence of low-grade fever due to infections rather than gingivitis • Recent blood disorders or congenital abnormalities • Any medical conditions that may be harmful to be involved in this study

sequence. The allocation sequence was generated by a statistician who had no involvement in the recruitment and intervention delivery. The study protocol has been explained completely to the parents of the subjects, who were instructed not to allow the subject to use neither antibiotic nor other dental treatment within the study period. Data collection was performed at baseline and follow-up for both groups. As this study was a non-blinded study, subjects' parents, principal investigator and entire research team were allowed to know about treatments being given to each subject. Following randomisation, subjects were informed by telephone in which group they are allocated to (see flow chart in Fig. 1).

Materials

The following materials were used: skin-prick test kit with 16 commercial test solutions and fresh material (inc. HDM); dental mirror; dental instrument kit; periodontal probe; dental ultrasonic scaler (vibrates in the ultrasonic range of 20–30 kHz); syringe (3 mL, Terumo) with needle; BD Vacutainer® (EDTA tubes, 3 mL); high-speed refrigerated micro centrifuge (MX-307, Tomy); microbiological safety cabinet; deep freezer to maintain temperature at -80°C (or -112°F); the monoclonal antibody against IgE and IgG₄ (R&D System Europe Ltd., Abingdon, UK) used according to the manufacturer's instructions; human IgE and IgG ELISA kit (GWB-2E2ECD) containing chromogenic substrate (12 mL of 3,3',5,5'-tetramethylbenzidine, TMB), diluent buffers, and washing buffer.

Intervention

The intervention group received a three-component intervention for 6 months: dental scaling, root planing, and standard allergic treatments (glucocorticoid and/or 2nd generation antihistamines). The control group received only standard allergic treatments (glucocorticoid and/or 2nd

generation antihistamines). Dental scaling is a procedure involving the removal of dental plaque and calculus from the oral cavity. Root planing is a procedure involving the removal of dental plaque and calculus on the root surface inside the periodontal pocket. Dental SRP was performed based on the procedure described by Tonetti and colleagues, using ultrasonic dental scaler following the administration of local anaesthesia.³¹ The intervention was performed by registered dental professionals over three visits; baseline, 3 months and 6 months post-baseline. The comprehensive dental SRP was successfully evaluated by visual inspection using optimum illumination using a dental mirror with air spray to keep the mirror clean. The surfaces of teeth were examined using a periodontal probe, through which the entire surface of both the supra-gingival and sub-gingival teeth can be ensured to be smooth and clean.

Outcomes

The primary outcome was the total change in the level of IgE, defined as the difference in the level of IgE changes from baseline to the end of the intervention between the intervention and control groups. Secondary outcomes include the total change in the level of IgG₄, defined as the difference in the level of IgG₄ from baseline to termination of the intervention, in children with gingivitis and allergies to HDM.

Assessment and data collection

Subjects were followed up for 6 months after treatment. During follow-up, all subjects were advised to visit the outpatient clinic every month. Data were collected prior to treatment and 6 months after treatment by collecting blood sample for measuring total serum IgE and IgG₄. The total serum IgE and IgG₄ were assessed by using direct-sandwich ELISA (R&D System Europe Ltd., Abingdon, UK), following the manufacturer's instructions. Briefly, the total serum IgE

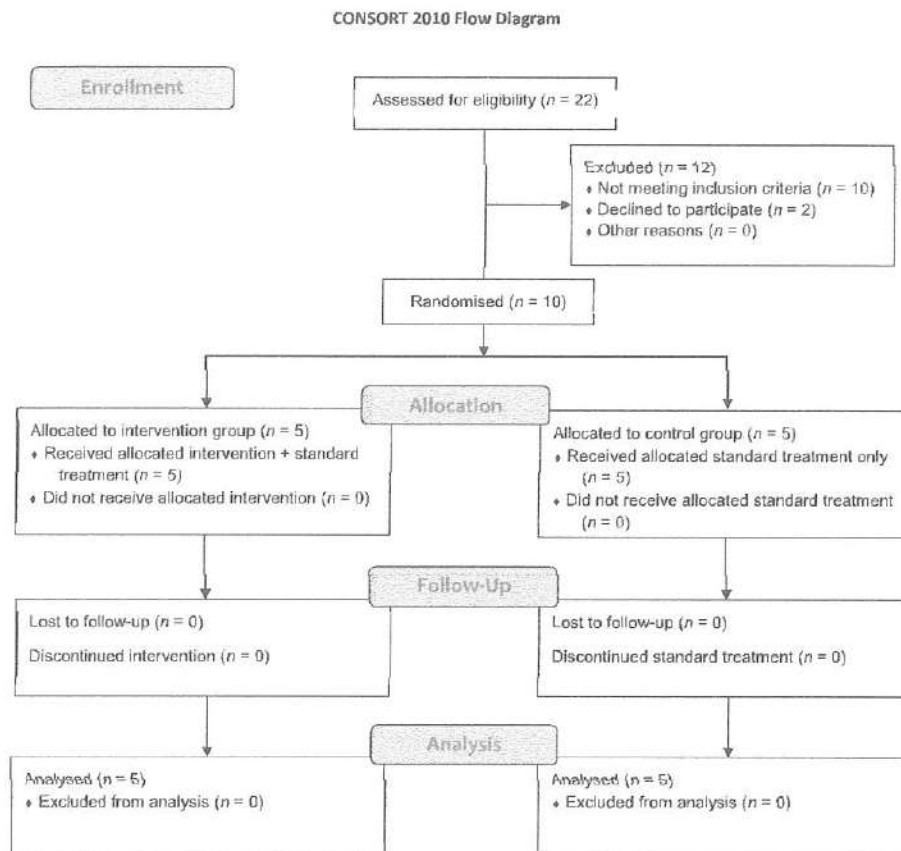


Fig. 1. Flow chart of participants in the study.

was detected by phosphate-buffered saline (pH 7.4) in 1:200 dilutions, transferred to pre-coated plates and added the supplied conjugate. However, total serum IgG₄ were detected using matched monoclonal antibody pairs against IgG₄, followed by additions of 0.1% bovine serum albumin as blocking solution and incubation buffer, diluted plasma sample (1:100,000) or standards, and conjugate, with washing between the steps. Total serum IgE and IgG₄ ELISA solutions were prepared with the supplied TMB substrate and stop solutions. The total serum IgE and IgG₄ concentrations were determined using assay-specific 7-point calibration curves generated following the manufacturer-supplied standard. A value of 0.01 pg/mL was assigned for concentrations below the limit of detection. All measurements were performed in duplicates and values were averaged for analysis.

Adverse event reporting

Data on adverse events were collected at treatment and follow-up visits. Adverse events such as pain, low-grade

fever, and headache during SRP, or pain and hematoma during venesection, were recorded by technicians. The participants and their parents were also instructed to report any adverse events. The trial was also compliant with a UK regulation with a real-time serious adverse event reporting process to identify serious adverse reaction and suspected unexpected serious adverse reaction that could suspend/stop the trial if warranted. However, no adverse event was reported by 10 subjects during treatment and follow-up periods.

End of the trial

The trial was ended when the last patient had their last data collected.

Statistical analysis

The results of the study were reported in accordance with CONSORT guidelines.³² Statistical analysis was performed using SPSS software version 17.0 (IBM Corp.,

Chicago, USA). The assumption of the normality for the complete data was assessed by the one-sample Kolmogorov-Smirnov test. Statistical analyses were also performed by paired *t*-test and independent samples *t*-test. The results are presented as mean \pm SD. Paired *t*-test was used to compare the total change in IgE and IgG₄ levels in the intervention group before and after treatment. Independent samples *t*-test was used to compare the differences in IgE and IgG₄ levels between the intervention group and the control group. The significant differences were based on two-tailed tests with a *p*-value of less than 0.05.

Results

Baseline characteristics investigations

At baseline, parents reported their allergic histories, parent and children's racial and ethnic backgrounds, number of families/caregivers living in their home, their children's insurance status (private, public or none), and the highest level of parental education. Children's gender, body weight, date of birth (to calculate age), date of allergy diagnosis (to calculate the duration of allergy) and date of gingivitis diagnosis (to calculate the duration of gingivitis) were extracted from their medical records (Table 2).

Table 2
Baseline characteristics of clinical trial participants.

Characteristic	Intervention (n = 5)	Control (n = 5)	p Value
Age (year, mean)	10.2 \pm 3.9	9.8 \pm 2.4	0.270
Gender			
Male	2	2	
Female	3	3	0.738
Body weight (kg, mean)	27.8 \pm 5.2	27.8 \pm 4.5	0.761
Ethnic			
Java	4	4	0.778
Madura	1	1	
Others	0	0	
People living in home (n, mean)	4.6 \pm 1.5	5.4 \pm 1.7	0.776
Parents education			
Unschooling	1	2	0.717
Elementary school	2	1	
High school	2	2	
College/University	0	0	
Insurance status			
Public	5	5	N/A
Private	0	0	
None	0	0	
Self-reported allergic histories			
Asthma	4	5	0.292
Eczema	1	0	
Hay fever	0	0	
Food allergies	0	0	
Asymptomatic allergies	0	0	
Duration of allergies (year, mean)	2.0 \pm 1.4	2.1 \pm 0.7	0.072
Gingival index according to Silness-Löe plaque score			
0-0.9	0	0	0.490
1.0-1.9	0	0	
2.0-2.9	2	1	
3.0-3.9	3	4	
Duration of gingivitis (year, mean)	2.3 \pm 1.0	2.4 \pm 1.1	0.829
Baseline lipopolysaccharide of <i>Porphyromonas gingivalis</i> (μ g)	8.03 \pm 0.99	9.49 \pm 1.12	0.061
Baseline IgE (pg/mL)	99.84 \pm 2.16	139.42 \pm 1.49	<0.001
Baseline IgG ₄ (ng/mL)	28.62 \pm 3.88	38.66 \pm 1.85	0.001

Table 3
Comparison of pre-test and post-test total serum IgE and IgG₄ levels between two groups.

Variable groups	Pre-test (T1)		Post-test (T2)		Difference (T2-T1)		t-Test
	Mean	SD	Mean	SD	Mean	SD	
Immunoglobulin E							Effect size: 6.413
Intervention group	99.84	2.16	80.03	1.65	-19.81	0.96	46.087***
Control group	139.42	1.49	138.48	1.45	-0.94	0.56	7.858*
Immunoglobulin G ₄							Effect size: 4.898
Intervention group	28.62	3.88	18.05	2.38	-10.57	3.00	3.780**
Control group	38.66	1.85	38.75	1.87	0.09	1.01	-0.217

Notes: Two tailed test results: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Differences in the total serum of immunoglobulin E (IgE) and immunoglobulin G (IgG₄) at baseline and 6 months after treatment

Table 3 presents the mean changes in IgE and IgG₄ levels between baseline and 6 months after treatment. In the intervention group (both SIT and scaling and polishing at 6 months), there was a significant decrease in both the total serum of IgE ($p < 0.001$) and total serum of IgG₄ ($p = 0.001$) compared to baseline. On the other hand, the control group (SIT only) also showed a significant decrease in the total serum of IgE ($p = 0.019$) but failed to achieve a significant decrease in the total serum of IgG₄ ($p = 0.839$) compared to baseline (Table 3).

Differences in the total change in immunoglobulin E (IgE) level between two groups

After 6 months, the total serum of IgE in the intervention group decreased by 19.81 ± 0.96 pg/mL, while it decreased by 0.94 ± 0.56 pg/mL in the control group. An independent *t*-test shows a significant difference in the total change in IgE between the two groups ($p < 0.001$) (Fig. 2).

Differences in the total change in immunoglobulin G₄ (IgG₄) level between two groups

After 6 months, the total serum of IgG₄ in the intervention group decreased by 10.57 ± 3.00 ng/mL, while it increased by 0.09 ± 1.01 ng/mL in the control group. All subjects in the intervention group showed a decrease in the total change in IgG₄ levels. However, in the control group, only two subjects showed a decrease in IgG₄ level, whereas the remaining three subjects showed an increase in the IgG₄ level. An independent samples *t*-test shows a significant difference in the total change in IgG₄ level between the two groups ($p < 0.001$) (Fig. 3).

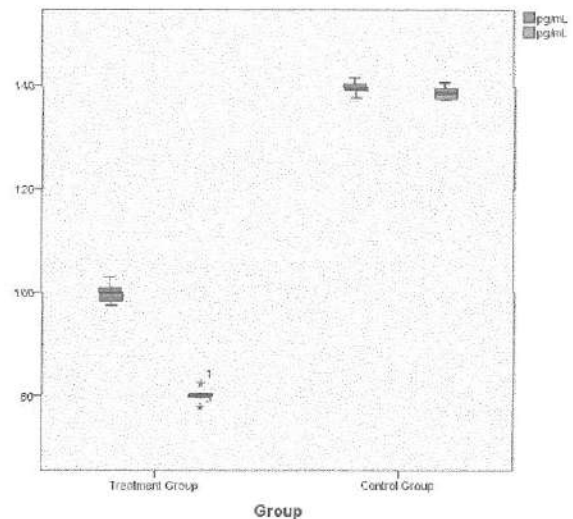


Fig. 2. Level of immunoglobulin E (IgE) between two groups before and after treatment.

Discussion

This study was conducted to evaluate the beneficial effects of a comprehensive 6-month dental SRP to improve biomolecular markers of atopy. The results showed that, in the intervention group, a comprehensive 6-month dental SRP along with SIT showed more marked improvement in the biomolecular markers of atopy than the control group. This finding supports compelling evidence that comprehensive 6-month dental SRP is inversely related to the level of IgE and IgG₄ in children with gingivitis and HDM allergies.

As gingival inflammation may induce elevated atopic inflammatory mediators and dental plaque appears to form more rapidly in children aged 8–12 years, many studies have begun to scrutinise the effect of periodontal pathogen

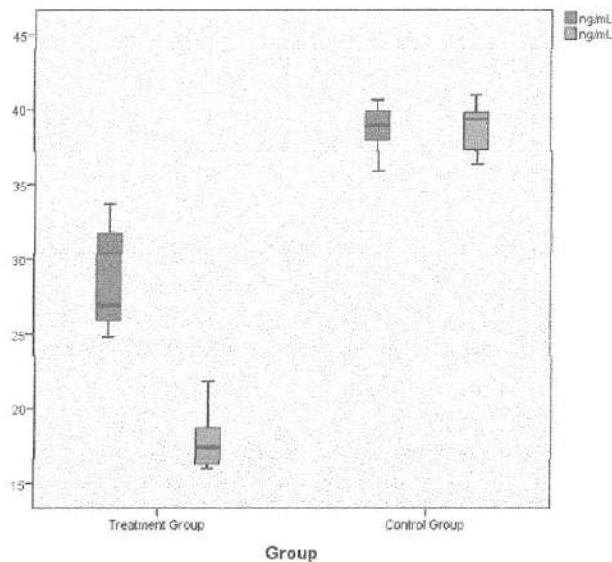


Fig. 3. Level of immunoglobulin G₄ (IgG₄) between two groups before and after treatment.

infections and gingival inflammation on the appearance of allergies in children aged 8–12 years.^{33–35} Children with HDM allergies have more dental plaque and calculus and tend to have more severe gingivitis.³⁶ A previous study by Cortelli *et al.* have shown that children with gingivitis have significantly higher levels of systemic LPS levels than gingival healthy individuals.³⁷ The main purpose of dental SRP is to restore healthy gingivae by completely removing dental plaque, calculus and toxic substances such as LPS that trigger gingival inflammation, from the tooth surface.³⁸ This strategy may cause a drastic reduction in the number of subgingival microorganisms as well as a change in the composition of the plaque from one with more gram-negative anaerobic bacteria (*Pg*) to one with more gram-positive facultative bacteria (*Streptococcus salivarius*, *Streptococcus gordonii*, *Streptococcus mutans*, *Streptococcus sanguinis* and some *Lactobacillus* species). Therefore, this leads to less exposure to LPS, which is mainly produced by gram-negative bacteria.³⁹

Kalash *et al.* observed a significant decrease in systemic LPS among each subsequent time point following dental SRP, where initially the serum LPS level appeared to slightly decrease at 3 months and slightly rebound at 6 months, but reached to a significant reduction at 12 months.⁴⁰ To our knowledge, for clinical purpose, the American Dental Association advises periodical visit for SRP every 6–12 months due to the nature of periodontal pathogen formation and rebound of systemic LPS at 6 months. On the other hand, for research purpose, a comprehensive 6-month dental SRP is enough to maintain the level of local or systemic LPS and to prevent rebound.⁴¹

Interactions between allergens, periodontal bacteria and pro-inflammatory cytokines have been previously reported.⁴² Lipopolysaccharide of *Pg* is a gram-negative endotoxin, which is ubiquitous in the environment and can therefore exacerbate allergic responses.⁴³ At very low concentration, LPS may induce atopic inflammatory responses by Th-1 shifting into Th-2, which is more potent to stimulate antibodies production.⁴⁴ Lipopolysaccharide binds to toll-like receptor 4 (TLR4) and highly enhances the response of TLR4-transfected cells. Thus, damage due to LPS extends beyond the exhaustion of host innate immunity.⁴⁵ Previous studies demonstrated the pathogenic role of *Pg* dental biofilm to stimulate LPS-driven inflammatory responses,⁴⁶ and therefore, lack of dental plaque and calculus in supra-gingival surface, sub-gingival surface and human epithelial cell rests of Malassez accounted for the lack of response to LPS to induce sensitisation of atopic inflammatory responses.^{47,48} Moreover, given the unique LPS-induced atopic inflammatory responses, we can control atopic inflammatory responses by removing dental biofilm. This reduces the subject body's load of LPS-triggered mast cells derived from periodontal inflammation.^{49,50}

Following dental SRP, there is also evidence of increasing certain *Lactobacilli* populations, which are beneficial for controlling atopic inflammatory pathway.⁵¹ It is widely accepted that *Lactobacilli* in the oral cavity may determine the population of *Lactobacilli* in the gut.⁵² Therefore, an increase in the amount of *Lactobacilli* species can result in the induction of IgA antibodies and CD4⁺ T regulatory cells (producing IL-10 and IFN- γ).⁵³ Due to its beneficial role in inhibiting IL-4 and IL-5 secretion, *Lactobacilli* markedly suppress total and antigen-specific IgE, and thus may control atopic inflammatory pathways.⁵⁴

Considering the above findings, it is believed that the combination of decreasing systemic LPS of *Pg* and increasing of *Lactobacilli* species following dental SRP may regulate atopic inflammatory responses system, particularly for children with HDM allergies. Finally, controlling microbiota in the gut and the oral cavity plays an important role in the attenuation of IgE sensitisation induced by dust allergens.

Limitations

In this study, the sample size was small. A total of 10 children with gingivitis and HDM allergies participated, with only five subjects per group. Baseline serum IgE and IgG₄ levels between intervention group and control group were significantly different ($p < 0.001$ and $p = 0.001$, respectively), implying that difference in baseline IgE and IgG₄ levels may influence the results of this trial as a confounding factor. The samples used in this study were limited to the result acquired by using this study design and sampling method. Therefore, the result could not be

extrapolated to the manifestation of allergic diseases and children matching the criteria of exclusion. Based on the principles of ethics, this study respects the parent's free will to choose the regular schedule for dental SRP within 6-months duration of treatment. Thus, the intervention was determined by the parents' choices. Therefore, it is impossible to exclude the effect of different schedules in the intervention group to participate in the intervention plan on the intervention results. Future recommendations include the profile of cytokines and number of colony-forming units of periodontal bacteria in the gum to correlate the stability of the achieved results could be considered and larger sample size with longer duration of treatment and strict regular schedule could be considered for significant results.

Conclusion

Based on the study results and discussion, it can be inferred that reduction in IgE and IgG₄ levels in children with gingivitis may be attributed to direct or indirect effects of dental SRP. Within the limitations of this study, it can be concluded that dental SRP can improve biomolecular markers of atopy in children with gingivitis and HDM allergies. Furthermore promising results from this pilot study may lead to the next phase of clinical trials to refine and further evaluate the beneficial effects of dental SRP intervention in children with gingivitis and HDM allergies. The data collected in this pilot study comprise essential preliminary data to seek funding for conducting a larger, fully powered randomised controlled trial.

List of Abbreviations

CD4	cluster differentiation 4
CONSORT	Consolidated Standards of Reporting Trials
ELISA	enzyme-linked immunosorbent assay
IFN- γ	γ -interferon
IL	interleukin
HDM	house dust mite
IgE	immunoglobulin E
IgG ₄	immunoglobulin G ₄
ISRCTN	International Standard Randomised Controlled Trial Number
LPS	lipopolysaccharide
ng/mL	nanogram per millilitres
pg/mL	pictogram per millilitres
Pg	<i>Porphyromonas gingivalis</i>
SIT	specific immunotherapy
SRP	scaling and root planing
Th-0	naïve T-cell
Th-1	helper T-cell type 1
Th-2	helper T-cell type 2
TLR-4	toll-like receptor 4
TMB	3,3',5,5'-tetramethylbenzidine

Declarations

Ethics approval and consent to participate

Institutional Review Boards of Universitas Airlangga – Dr. Soetomo General Hospital's Ethics Committee for Health Research reviewed and approved the study (ethics approval number 20/Panke.KKE/I). Informed consent was validated by the Dr. Soetomo General Hospital Ethics Committee for Health Research. All parents provided written informed consent to participate and were allowed to withdraw at any time.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets generated and/or analysed during the study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Faculty of Dental Medicine of Universitas Airlangga. This funding source had no role in the design of this study, its execution, analyses, interpretation of the data or decision to submitting results.

Authors' Contributions

S.C.N. is the principal investigator of this work. Conception and design: F.D. and S.C.N.; acquisition of data: S.C.N., A.E., R.A.N., and F.D.; analysis and interpretation of data: R.A.N. and F.D.; drafting of the manuscript: R.A.N. and M.T.; critical revision: P.N. and U.T.; statistical analysis: F.D. and D.H.U.; supervision and general advice for the study: A.E., P.N., and U.T. Guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors read and approved the final manuscript.

Acknowledgements

This research is funded by a Research Project Grant from the Faculty of Dental Medicine of Universitas Airlangga.

We would like to thank and appreciate the significant contributions of members of the Indonesian Association of Pediatric Dentistry (IDGAI) Surabaya branch: Seno Pradopo, Soegeng Wahlujo, Els Sunarsih, Teguh Wibowo, Satiti Kuntari, Tania Saskianti, Betadion Sinaredi, Mega Moehar-yono, Ardianti Maartrina and Dimas Prasetyanto, who performed dental SRP for our subjects. We would like to acknowledge the contribution of Dr. Soetomo General Hos-pital, including Harsono (director of the hospital) and Zahrah Hikmah (head of Pediatric Allergy Outpatient Clinic) who allowed this study carried out. We also would like to acknowledge Darmawan Setijanto from College of Dentistry for his precious advice and corrections of the manuscript. Finally, parents and their children who participated in this trial also need to be acknowledged for their significant contributions.

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