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Brief Communication

Effects of Serum Vitamin D and Efficacy of Subcutaneous Immunotherapy in Adult Patients With Allergic Rhinitis

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ABSTRACT

Immunotherapy is the standard of treatment for long-life relief of symptoms of allergic rhinitis. Vitamin D may affect the outcomes of treatment. This study evaluated the clinical efficacy of subcutaneous allergen immunotherapy in adult patients with allergic rhinitis based on the serum level of vitamin D. Patients with persistent allergic rhinitis and positivity for skin prick test were evaluated by Sino-nasal Outcome Test (SNOT-22) and Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) before subcutaneous allergen immunotherapy and during the maintenance phase to assess the relation of the serum level of vitamin D and the clinical efficacy of immunotherapy. After immunotherapy, the greatest reduction in SNOT-22 scores were reported in patients with vitamin D sufficiency (39.0 ± 9.2), followed by vitamin D suboptimal provision (35.1 ± 12.1), insufficiency (25.0 ± 7.5), and deficiency (18.3 ± 6.0) ($P < 0.001$). The MiniRQLQ reduction in patients with vitamin D sufficiency, suboptimal provision, insufficiency, or deficiency was 30.7 ± 8.7, 27.1 ± 8.7, 20.0 ± 8.6, or 17.4 ± 7.1, respectively ($P < 0.001$). Both of SNOT-22 and MiniRQLQ scores decreased significantly following immunotherapy in patients with different levels of vitamin D. However, these effects were more pronounced when the level of vitamin D was sufficient.

Keywords: Allergic rhinitis; immunotherapy; vitamin D

INTRODUCTION

Allergic rhinitis, one of the most prevalent medical conditions, accompanies severe disabilities interfering the daily life and compromising the quality of life by affecting work/academic performance.[1,2] Allergic rhinitis is a chronic condition that affects the conjunctiva and the nasal mucosal tissue locally; however, new data reveals that there are several underlying systematic processes involving the adaptive immune response through eliciting

Disclosure

There are no financial or other issues that might lead to conflict of interest.

the T helper 2 (Th2)-predominant response to allergens which leads to immunoglobulin E (IgE) overproduction.[3,4]

While nasal corticosteroids, decongestants, and antihistamines act by inducing local inhibitory effects and treat the patients symptomatically, subcutaneous and sublingual allergen immunotherapies induce their systemic effects by modifying Th2-directed immune responses through modulation of the innate and adaptive immune systems, resulting in long-term resolving the problems of allergic rhinitis by inducing a sustained immunologic change.[5] The response to allergen immunotherapy is not equal in all patients and is affected by factors such as high serum IgE level, continuing cigarette smoking during immunotherapy, and a family history of atopy.[6,7] Recently, vitamin D is proposed as a potential factor affecting the outcome of immunotherapy.

Vitamin D insufficiency is one of the possible factors affecting the response to the allergen immunotherapy.[7,8] Previous data has shown an adverse relation between the level of serum vitamin D and the development of allergic rhinitis.[9] The immunomodulatory actions of vitamin D lead to down-regulation of proinflammatory signaling pathways and affect the Th1/Th2 balance; therefore, in the absence of these effects of vitamin D, the immune system intensively responds to allergens by the overproduction of IgE and interleukin (IL)-4.[10,12] Beside this systematic action, it is proposed that vitamin D play a role in the stability and integrity of epithelial barrier of mucosal tissue and its insufficiency leads to the inappropriate exposure to antigens.[13] Further research indicates that supplementation of vitamin D may enhance the outcome of treatment as monotherapy or in combination with allergen immunotherapy.[7,8,14] Although data regarding the interaction of vitamin D and the response to allergen immunotherapy are considerable controversies exist. Therefore, this study aimed to evaluate the clinical efficacy of subcutaneous allergen immunotherapy in adult patients with allergic rhinitis based on the serum level of vitamin D.

MATERIALS AND METHODS

Patients and inclusion criteria

In this cross-sectional study, 18- to 50-year patients with persistent allergic rhinitis and positivity for skin prick test were evaluated by Sino-nasal Outcome Test (SNOT-22) and Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) before and 1 year after primary build-up period (20 weeks) of subcutaneous allergen immunotherapy to assess the relation between the serum level of vitamin D and the clinical efficacy of immunotherapy. The study was conducted in Mashhad, the northeast of Iran during 2016-2018.

The diagnosis of allergic rhinitis was established based on "International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis" and its severity was determined by medical history, detailed physical examination, and SNOT-22 and MiniRQLQ scores.[5,15] All patients have the definitive diagnosis of allergic rhinitis at least 3 years before the enrolment and have the indications of beginning of subcutaneous allergen immunotherapy including severe persistent allergic rhinitis without optimal response to nasal corticosteroids, decongestants, and anti-histamines, and occurrence of side effects of medical treatments. Patients who were pregnant, suffer from allergic disorders rather than allergic rhinitis or comorbidities affecting the serum level of vitamin D, use medication alternating the vitamin D serum levels (including vitamin D supplements), and experience previous immunotherapy

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were excluded. Also, patients who need to be treated with more than 1 allergen for immunotherapy and showed poor response to initial immunotherapy (after 1 year from the beginning of treatment) were excluded.

The study protocol was approved by the Ethics Committee of the Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1397.263). Written informed consent was obtained from all patients. In cases of vitamin D deficiency or insufficiency, appropriate treatment were administered.

Subcutaneous allergen immunotherapy

A single allergen extract (The Stallergenes Greer, Boston, MA, USA) was used for skin-prick test as allergen challenge test before subcutaneous allergen immunotherapy. The test was considered positive if there was a positive clinical relevance, *i.e.*, the patient symptoms exacerbated during high volume exposure to the specific allergen determined by skin-prick test. Then, subcutaneous allergen immunotherapy was administered weekly for 20 weeks (build-up period) and dose/density was gradually increased. The build-up period followed by monthly maintenance injections until 3 years if there is at least a partial response.

Efficacy assessment, symptom-medication scores, and vitamin D measurement

SNOT-22 and MiniRQLQ were performed before subcutaneous allergen immunotherapy and during the exacerbation period within the second year. Both questionnaires were completed by each patient during a clinic visit. SNOT-22 has 22 questions based on a 0–5 scale (no problems with the given symptom rated as 0 to problem as bad as it can be scored as 5). Patients were requested to mark the most important items affecting their health. This is a validated and easy-to-used patient-reported measure of outcome established to delineate the presence and severity of sino-nasal disorders.[16,17] MiniRQLQ has 14 questions evaluating 5 domains (limitation in daily activities, practical problems, olfactory symptoms, ophthalmic symptoms, and non-nose/eye symptoms). Each parameter rated from 0 (not troubled) to 6 (extremely troubled) and sum of all scores considered as total MiniRQLQ score.[15]

As evaluation of symptoms by questionnaires, skin-prick tests were performed according to the standardized International Study of Asthma and Allergies in Childhood (ISAAC) Phase II protocol.[18] All patients were advised to avoid using antihistamines at least one week before the test. The sensitivity to common outdoor and indoor aeroallergens was chosen based on a recent study by Mahboubi Oskouei *et al.*[19] including Weed Mix (Pigweed, Lamb's quarter, Cocklebur, and Mugwort), Salsola Kali, Grass Mix (Timothy-, Orchard-, and Kentuckey-grass), and Tree Mix (Willo and Ash). Standardized allergen extracts and control solutions were provided by Greer Labs (The Stallergenes Greer). A drop of each allergen extract and of the positive (histamine 10 mg/mL^{-1}) and negative controls (diluents) were brought on the skin of the volar side of the left forearm using lancets. After 15 minutes, the outside contour of the wheal reaction was measured as the mean of the longest diameter and the length of the perpendicular line through its middle. A positive skin reaction was defined as a wheal size of ≥ 3 mm after subtraction of the negative control.

A 25-OH vitamin D ELISA kit (EUROIMMUN, Lübeck, Germany) was used to assess the total serum 25(OH) vitamin D level. Based on a recent study and Meta-Analysis by Nouri Saeidlou *et al.*[20] and Tabrizi *et al.*,[21] respectively, the prevalence of vitamin D deficiency among the Iranian population is considerable, which is consistent with our result. Moreover, previous

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studies have shown that most of people living in the northeast of Iran suffer from lack of sun exposure due to dry and hot weather of the region of Iran as well as hijab (a restricted legal and religious rule that women and men must cover most parts of their body in public); hence, there are minimal differences in the level of vitamin D among different seasons.[20,22] In addition, based on the text book Middleton's allergy principles and practice,[23] assessment of the efficacy of immunotherapy is possible at least 12 months after initiation of treatment. Therefore, we obtained patient symptoms and vitamin D levels at minimal intervals to assess the efficacy of immunotherapy in the season when symptoms of patients exacerbated with respect to the allergen.

Statistical analysis

Considering the response rate of allergic rhinitis to subcutaneous allergen immunotherapy (80%) using the following formula:

$$n = \frac{(Z_{1-\frac{\alpha}{2}})^2\{P_1(1-p_1)\}}{d^2}$$

if $d = 0.15p$ and $P = 0.8$, the minimum sample size to detect a response was estimated at 44 patients.[24] The Wilcoxon signed-rank test was used to assess the difference in skin-prick test results before and after immunotherapy. The differences in SNOT-22 and MiniRQLQ scores before and after immunotherapy were compared by the paired *t* test. To evaluate changes in SNOT-22 and MiniRQLQ scores in patients with different levels of vitamin D, the analysis of variance and Scheffe's procedure were used. A *P* value of less than 0.05 was considered significant. The software used for statistical analysis was SPSS version 10 (SPSS Inc., Chicago, IL, USA).

RESULTS

Fifty-five patients were enrolled in the study. Of those, 31 (56.4%) were male and their mean age was 34.42 years (95% confidence intervals, 31.42–37.42). The most common pollens were Salsola Kali and 4 weed mixtures (41.8%), followed by grass (12.7%), and tree (3.6%) (**Table 1**).

Vitamin D deficiency (< 10 ng/mL), insufficiency (10–19), suboptimal provision (20–30), and sufficiency (> 30) were presented in 27.3%, 18.2%, 34.5%, and 20% of the participants, respectively.

Adherence to subcutaneous allergen immunotherapy was excellent and all patients received the same period of treatment with the same dose.

Both of SNOT-22 and MiniRQLQ scores decreased significantly following immunotherapy in patients with different levels of vitamin D (**Table 2**). However, these effects were more pronounced when the level of vitamin D was normal or higher. The SNOT-22 chart shows that the greatest reduction was observed in patients with vitamin D level of higher than 30 ng/mL (39.0 ± 9.2), 20–30 ng/mL (35.1 ± 12.1), 10–19 ng/mL (25.0 ± 7.5), and lesser than 10 ng/mL (18.3 ± 6.0). Moreover, the MiniRQLQ reductions in patients with vitamin D sufficiency, suboptimal provision, insufficiency, and deficiency were 30.7 ± 8.7, 27.1 ± 8.7, 20.0 ± 8.6, and 17.4 ± 7.1, respectively ($P < 0.001$) (**Figure**). After treatment, the skin prick test grade of all

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Table 1. Demographic data of the study patients

Variable (N = 55)	Level of vitamin D (ng/mL)				Total
	< 10	10–19	20–30	> 30	
Age (yr)	33 (26.82–43.58)	34.5 (26.75–40.25)	35 (28.87–36.71)	37 (29.30–44.70)	34.42 (31.42–37.42)
Sex					
Male	10 (66.7)	8 (80)	11 (57.9)	2 (18.2)	31 (56.4)
Female	5 (33.3)	2 (20)	8 (42.1)	9 (81.8)	24 (43.6)
Familial history of allergic disorders	2 (13.3)	3 (30)	3 (15.7)	2 (18.1)	10 (18.1)
Smoking	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pollens					
Salsola Kali	6 (40)	6 (60)	6 (31.6)	5 (45.5)	23 (41.8)
4 weed mixture	7 (46.7)	3 (30)	9 (47.4)	4 (36.4)	23 (41.8)
Grass	2 (13.3)	1 (10)	3 (15.8)	1 (9.1)	7 (12.7)
Tree	0 (0)	0 (0)	1 (5.3)	1 (9.1)	2 (3.6)
Response to skin prick test, SNOT-22 and MiniRQLQ scores after SCIT					
SPT (mm)	Before SCIT		After SCIT		Test
≤ 3	0		6 (10.9)		$P < 0.001$*
4–9	20 (36.4)		46 (83.6)		
≥ 10	35 (63.6)		3 (5.5)		
SNOT-22	73.9 ± 9.1		44.3 ± 13.1		$t = 17.8$; $P < 0.001$†
MiniRQLQ	55.4 ± 8.3		31.4 ± 9.5		$t = 18.3$; $P < 0.001$†

Values are presented as number (95% confidence interval) or number (%).
MiniRQLQ, Mini Rhinoconjunctivitis Quality of Life Questionnaire; SNOT-22, Sino-nasal Outcome Test; SPT, skin prick test; SCIT, Subcutaneous immunotherapy.
*The Wilcoxon signed-rank test shows significant differences; †The paired t test shows differences.

Table 2. SNOT-22 and MiniRQLQ scores during the immunotherapy

Vitamin D	Before SCIT (n = 55)	After SCIT (n = 55)	Test
SNOT-22 (ng/mL)			
< 10	72.8 ± 6.9	54.4 ± 9.1	$t = 11.7$; $P < 0.001$
10–19	72.8 ± 10.6	47.3 ± 11.0	$t = 10.7$; $P < 0.001$
20–30	76.9 ± 10.4	41.8 ± 12.8	$t = 12.6$; $P < 0.001$
> 30	71.3 ± 7.3	32.2 ± 8.8	$t = 14.0$; $P < 0.001$
MiniRQLQ (ng/mL)			
< 10	57.5 ± 5.8	40.1 ± 6.9	$t = 9.4$; $P < 0.001$
10–19	54.9 ± 7.2	34.9 ± 7.4	$t = 7.3$; $P < 0.001$
20–30	55.5 ± 9.4	28.4 ± 7.4	$t = 13.4$; $P < 0.001$
> 30	52.4 ± 9.8	21.7 ± 4.9	$t = 11.6$; $P < 0.001$

MiniRQLQ, Mini Rhinoconjunctivitis Quality of Life Questionnaire; SNOT-22, Sino-nasal Outcome Test; SCIT, subcutaneous immunotherapy.

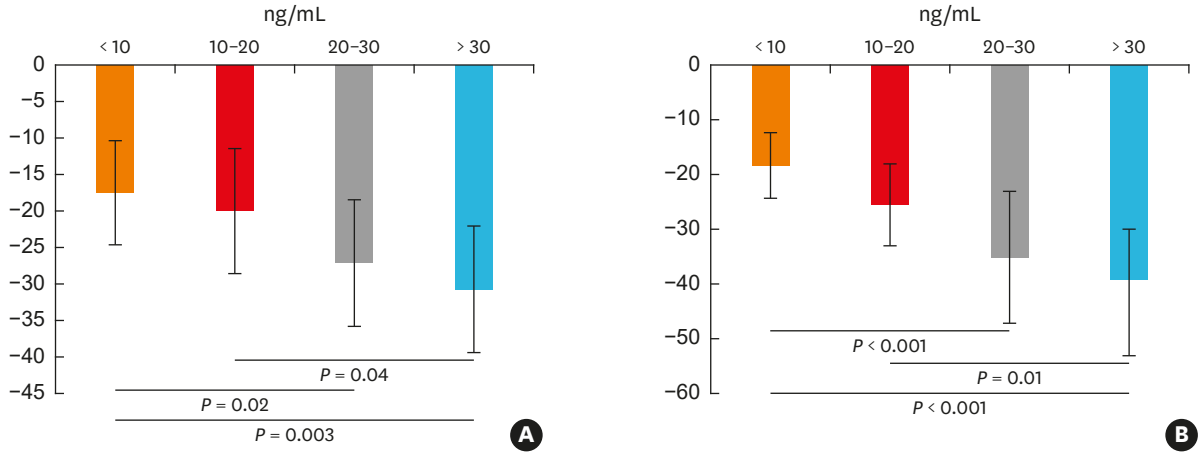

Figure. Changes in MiniRQLQ (A) and SNOT-22 (B) scores after treatment with SCIT. The greatest reduction in SNOT-22 scores was observed in patients with higher levels of vitamin D, *i.e.*, SNOT-22 scores were 39.0±9.2, 35.1±12.1, 25.0±7.5, and 18.3±6.0, respectively, in patients with vitamin level > 30, ≥20–30 → 20–30, 10–<20 → 10–19, and < 10 ng/mL. In addition, the chart on the left side reveals that the greatest reduction in MiniRQLQ scores were 30.7±8.7, 27.1±8.7, 20.0±8.6, and 17.4±7.1, respectively, in patients with vitamin D level of higher than 30, 20–30, 10–19, and lesser than 10 ng/mL.

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participants ($P < 0.001$) also based on vitamin D level, *i.e.*, vitamin D deficiency ($P = 0.002$), insufficiency ($P = 0.5$), suboptimal provision ($P < 0.001$), and sufficiency ($P < 0.001$) were significantly decreased.

DISCUSSION

This study evaluated the clinical efficacy of subcutaneous allergen immunotherapy in patients with allergic rhinitis based on the serum level of vitamin D. Both of SNOT-22 and MiniRQLQ scores were significantly decreased following immunotherapy in patients with different levels of vitamin D. However, these effects were more pronounced when the level of vitamin D was sufficient. To our knowledge, it is the first study evaluating the relation between the serum vitamin D level and response to the subcutaneous allergen immunotherapy. However, there are some limitations including not controlling for other confounding variables which can affect the outcome and its small sample size.

The potential immunomodulatory effects of vitamin D or even its immunotherapy-independent effects may play a role in the enhancement of clinical efficacy of immunotherapy. Overall, vitamin D affects innate immunity (through inhibitory effects on Toll-like receptors) and adaptive immunity (through inhibitory effects on cytokines secretion resulting in inhibition of T-cell proliferation). Specifically in allergic conditions, vitamin D affects the human immune system through inhibitory functions against human dendritic cells growth cycle and T-cell functions modulating these cells by increasing IL-10 secretion.[25,26] Additionally, studies have shown that it play a critical role in maintaining the epithelial integrity of nasal mucosa making it a strong barrier against environmental allergens.[27] Moreover, there is growing evidence for the role of vitamin D in mast cell stabilization through inhibitory effects on its receptor.[28,29]

Many studies have reported the role of vitamin D supplementation as monotherapy in allergic rhinitis. In a placebo-controlled clinical trial by Chen *et al.*,[30] treatment of adult patients with refractory moderate to severe allergic rhinitis using vitamin D calcium chewable tablets significantly improved symptoms compared to the control group. Another randomized, placebo-controlled trial by Jerzyńska *et al.*[14] have documented that treatment of children with allergic rhinitis using vitamin D tablets during the pollen season is associated with several immunomodulatory effects leading to improvements in clinical symptoms. In addition, some studies have shown potential effects of vitamin D supplementation adjunct to immunotherapy in patients with allergic rhinitis. Baris *et al.*[7] showed that immunotherapy more effectively controls the symptoms of patients with allergic rhinitis than comparing pharmacotherapy alone; however, the outcome of treatment with combination therapy (subcutaneous allergen immunotherapy plus vitamin D supplementation) was more favorable. Jerzyńska *et al.*[8] recrnited children with allergic rhinitis to evaluate the effects of combination of vitamin D and sublingual immunotherapy. Their results have demonstrated that vitamin D supplementation during sublingual immunotherapy is significantly effective and that most patients tolerate the therapy well.

None of the previous studies examined the important and potential effects of serum vitamin D on outcome of immunotherapy. However, a better response observed in patients treated with vitamin D supplementation may suggest that adult patients with allergic rhinitis are suffering from an underlying suboptimal/insufficient/deficient level of serum vitamin D. Therefore,

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routine vitamin D testing in adult patients with allergic rhinitis is highly recommended before the start of immunotherapy.[31]

This study has limitations. Small sample size due to limited resources and the limited number of patients can limit generalization of results of the present study to a larger population. Moreover, the short period of follow-up is another limitation. Assessment of results of immunotherapy at the end of the second or third year may be more appropriate.

In conclusion, in this study, the relation between serum vitamin D and the outcome of immunotherapy in patients with persistent allergic rhinitis and positivity for skin prick test were evaluated by SNOT-22 and MiniRQLQ. Our results indicated that immunotherapy can improve clinical symptoms and promote the quality of life in patients with persistent allergic rhinitis. However, these effects were more pronounced when the level of vitamin D was sufficient. Considering the high prevalence of vitamin D deficiency and excessive expenses of immunotherapy, evaluation of serum vitamin D is strongly recommended before start of immunotherapy.

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