ORIGINAL ARTICLE

Asian Pacific Journal of
Allergy and Immunology

APJAI

# Allergic sensitization in kidney transplanted patients – Is it a result of immunosuppressive agents or the sensitization of living donor?

*Dilek Doğruel,[1] Aytül Noyan,[2] Hasan Dursun,[2] Nurcan Cengiz[2]*

## Abstract

**Background:** Allergic sensitization has been reported increasingly in organ transplant recipients. However, the pathogenesis of this sensitization has still not been clearly understood.

**Objective:** The aim of this study was to evaluate allergic sensitization in kidney transplanted children and adolescents under immunosuppressive treatment.

**Method:** Twenty seven kidney-transplanted subjects were studied by standardized interviews from the International Study of Asthma and Allergies in Childhood criteria, skin prick test (SPT) and measurement of specific immunoglobulin E (s-IgE). Patients were considered to have allergic sensitization when presenting a positive SPT and/or s-IgE >0.35 kUA/l to at least one of the tested allergens. Patients with a history of allergic diseases accompanied by sensitization were accepted as allergic. We also performed SPT on the living donors of the allergic groups.

**Results:** Seven patients (25.9%) were found to be sensitized to ≥1 common inhalant and 3 subjects (11.1%) additionally reported a corresponding present history of allergic diseases. All of the living donors' sensitized patients were allergic. New-onset post-transplantation food allergy was not documented in any patients.

**Conclusions:** This study supports the concept that not only immunosuppressant agents but also sensitization of living donors could be a significant contributor to allergic sensitization in kidney recipients.

**Keywords:** allergy, allergic sensitization, donor, immunosuppressive treatment, kidney transplantation

**From:**
[1] Department of Pediatric Allergy and Immunology, Baskent University Faculty of Medicine, Turkey
[2] Department of Pediatric Nephrology, Başkent University Faculty of Medicine, Turkey

**Corresponding author:**
Dilek Doğruel
Department of Pediatric Allergy and Immunology, Baskent University Faculty of Medicine, Turkey
E-mail: dilekkaragoz1977@hotmail.com

## Introduction

Transplant–acquired allergy was first identified after bone marrow transplantation as transplant–acquired food allergy (FA). In due course, allergic diseases have started to be reported after liver, lung, heart and even kidney transplantations.[1] Transplant-acquired allergy is commonly seen after liver transplantation in little children receiving tacrolimus treatment, and is frequently in the form of FA. However, various studies have also reported urticaria, angioedema, eosinophilic gastroenteritis, atopic dermatitis (AD), allergic rhinitis (AR) and asthma.[2] Although similar immunosuppressive treatment is used in kidney transplant receivers, allergic diseases are being reported less frequently post-transplantation.[3]

Although allergic diseases are being reported after tacrolimus and cyclosporine (CsA), which are given post transplantation in order to prevent organ rejection, there are higher ratios after tacrolimus; in particular, the ratios in FA are higher.[4] By reducing tacrolimus and CsA IL2 production, Th1/Th2 balance affects the Th2 in allergic immune response in favor of the lymphocyte.[5,6] At the same time, IL5.10 and 13 increase the eosinophil and IgE production by increasing the cytokine production.[7] It has been detected that, with the increased exposure to allergenic proteins because of increased intestinal permeability due to intestinal injury,

specific immunoglobulin E (s-IgE) production against these proteins and tacrolimus treatment in fields is more distinctive. In the light of these findings, it is suggested that allergic diseases are developed independent of transplantation type, but related to the immunosuppressive treatment.[8]

In this study, we aimed to research allergic diseases with skin prick test (SPT) and pulmonary function test (PFT), eosinophilia, total and s-IgE level in children and adolescents who had not previously received immunosuppressive treatment, but received immunosuppressive treatment post-kidney transplantation.

## Methods

### *Study Population and Study Design*

In total, 52 recipients of kidney allograft at the Başkent University, Adana Teaching and Research Hospital from 2010 to 2016 were evaluated in this study. Renal transplanted patients with a history of anatomical and/or functional disorder who were treated with immunosuppressive for at least 3 months were included in the study. Patients, who received transplantation because of end stage renal failure due to glomerulonephritis, who received any type of immunosuppressive treatment pre-transplantation, who had allergic disease symptoms or who had been clinically diagnosed with allergic diseases, were excluded from the study. In total, 27 patients aged between 5-18 years were selected to participate in this study (**Figure 1**). The immunosuppressive protocol was based on tacrolimus 0.1-0.3 mg/kg/day (target blood trough level, 5-10 ng/ml at 1 year post-transplantation) or CsA 12-15 mg/kg/day (target blood trough level, 250-450 ng/ml). Concomitant immunosuppressive therapy included corticosteroid and mycophenolate mofetil. The corticosteroid was initially administrated twice daily at 2 mg/kg/day and tapered gradually after 1 week during the first 2 months with maintenance of low dose metil prednisolone afterwards. Mycophenolate mofetil was given at a dose of 500-600 mg/m$^2$/day. Immunosuppressive treatment duration changed from 3 to 60 months.

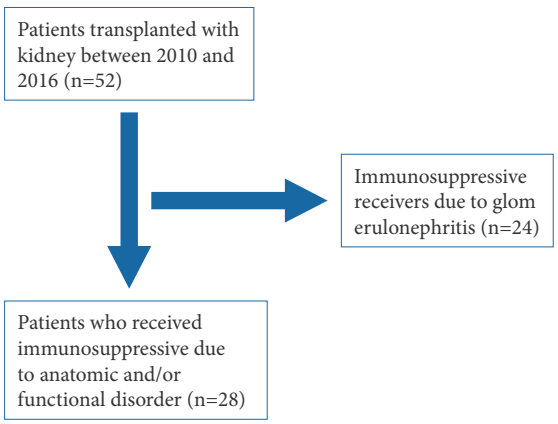


**Figure 1. Identification of paticipants in the study**

Data of patients (the underlying disease leading to kidney transplantation, timing of transplantation, immunosuppressive medication type since transplantation, age at transplantation) were collected from the medical records (**Table 1**). Via a questionnaire taken from the patients and parents, detailed information was obtained regarding a history of atopic signs and symptoms post-transplant. Questionnaires included information on allergic diseases (asthma, AR and AD) with validated questions from the International Study of Asthma and Allergies in Childhood questionnaire and adverse reactions to other foods.[9] Asthma diagnosis was made in accordance with the Global Initiative for Asthma guidelines,[10] AR was in accordance with the Allergic Rhinitis and its Impact on Asthma guideline,[11] and AD diagnosis was made in accordance with the Hanifin and Rajka criteria[12] on the basis of the patient questionnaire and clinical characteristics.

**Table 1. Characteristics of patients who underwent kidney transplantation**

| Variables | |
|---|---|
| **Male/female** | 18/9 |
| **Mean age** (mean±SD) (years) | 14.63±4.10 |
| **Mean age at the time of transplantation** (mean±SD) (years) | 11.99±3.91 |
| **Mean duration of after transplantation** (mean±SD) (months) | 31±19.88 |
| **Type of transplantation** | |
| Cadaveric donor | 9 (33.3%) |
| Living donor | 18 (66.7%) |
| **Primer renal disease**, *n (%)* | |
| VUR | 18 (66.7%) |
| Hereditary renal disease | 4 (14.8%) |
| Etiology unknown | 3 (11.1%) |
| Renal dysplasia/hypoplasia | 2 (7.4%) |
| **Allergic sensitization**, *n (%)* | 7 (25.9%) |
| **Allergy**, *n (%)* | 3 (11.1%) |

Allergic sensitizations were evaluated by serum s-IgE measurements and SPT. Patients were considered to have allergic sensitization when presenting a positive SPT and/or s-IgE >0.35 kUA/l to at least one of the tested allergens. Patients with a history of allergic diseases accompanied by allergic sensitization were accepted as allergic. We also performed SPT in their living donors.

This study was approved by Başkent University Institutional Review Board and Ethics Committee (Project no: KA 14/231). Written informed consent was obtained from the parents of each patient who was enrolled.

### *Total and serum specific immunoglobulin E measurement*

Total serum IgE levels and s-IgE antibodies to a panel of inhalant and food allergens were measured by using commercial kits (Immulite 2000 XPi; Siemens Diagnostic Products Corporation, Los Angeles, CA, USA). Panels tested in all patients comprised house dust mite, cat and dog dander, Bermuda grass, Timothy grass, birch, common ragweed, English plantain, Japanese ceddar, parietaria officinalis, penicillium notatum, *Alternaria tenuis* for inhalant allergens and cow's milk, hen's egg, wheat flour, codfish, soy bean, and

peanut for food allergens. When indicated by the patient's history, additional allergens that were not included in this panel were also tested by SPT. Specific IgE levels ≥0.35 kUA/l were accepted as positive.

### *Blood differential count*

Total eosinophil count and percentage were studied by a hemocytometer (Sysmex XN 1000; Flowcytometri, Japan). Eosinophilia was considered when the eosinophil count in peripheral blood was over 500/mm$^3$.[13]

### *Skin Prick Test*

An SPT was performed using commercially available extracts of major inhalant allergens (Allergopharma, Germany): tree mixture (alder, hazel, poplar, elm, sallow), mold mixture (*Alternaria alternata*, *Cladosporium herparum*, *Fusarium moniliforme*), grass pollen mixture (grass, barley, oat, rye, wheat, velvet, orchard, rye, timothy, blue grass, and meadow fescue), Mediterranean herbs, *Dermatophagoides pteronyssinus* and *farinea*, latex and food allergens (milk, egg, wheat, peanut, and codfish). Patients were advised to stop the antihistaminic treatment at least 2 weeks prior to the skin prick test. The SPTs were performed using standard methods and by the same investigator. Histamine (10 mg/mL) and sodium chloride (0.9%) were used as positive and negative controls, respectively. The result for each allergen was defined as positive if the mean wheal size was >3 mm larger than the negative control.[14]

### *Pulmonary Function Tests*

Pulmonary functions were measured as forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), forced vital capacity (FVC) and forced expiratory flow from 25% to 75% (FEF 25-75) of vital capacity values by spirometer (Vmax 22, SensorMedics Corp., Yorba Linda, CA, USA). Pulmonary function tests were performed according to the American Thoracic Society (ATS).[15] Criteria and the results were expressed as percentages of the predicted values for age and height. Patients were divided into three groups on the basis of findings on spirometry. Normal spirometry was defined as FVC and FEV1 greater than 80% predicted and FEV1/FVC greater than 70% predicted. An obstructive pattern was defined as the presence of FEV1/FVC less than 70% predicted. Patients with restrictive pattern had FEV1 and FVC values of less than 80% predicted and a preserved FEV/FVC ratio (>70%).[16]

### *Statistical analysis*

Statistical analysis was performed using the statistical package SPSS software (Version 17.0, SPSS Inc., Chicago, IL, USA). All numerical data are expressed as mean values ± SD or as proportions. The Mann-Whitney *U* test was used to compare the groups' pulmonary function tests. A p value < 0.05 was considered statistically significant for all tests.

## Results

### *Patient characteristics*

A total of 27 patients were enrolled in the study; 19 of the patients (70.3%) were male and 8 (29.7%) were female. The average age of the patients was 14.63±4.10, and the average transplantation age was 11.99±3.91 years.

The most frequent reason for transplantation was end-stage kidney disease because of VUR (66.7%). Nine of the patients (33.3%) had undergone cadaveric kidney transplantation and the remaining 18 patients (66.7%) had undergone living-related kidney transplantation. The mean follow-up period after transplantation was 31±19.88 (3-60) months (**Table 1**).

### *Total immunoglobulin and eosinophilia*

Mean IgE level was 58.50±83.66 IU/ml (range 1.2-257) and IgE level was elevated in eight patients (26.6%). While eosinophilia was present in 6/30 patients (mean: 340.46±422.49 (range: 4-2065)) before transplantation, no eosinophilia was detected in patients after transplantation (mean: 43.29±53.21 (range: 0-208)). Eosinophil counts before transplantation were markedly higher than in after transplantation (p=0.001) (data not shown).

### *Allergic Sensitization*

Among the 27 patients, 7 (25.9%) were found to be sensitized to inhalant allergens, with 1 patient (14.3%) showing only s-IgE and 6 subjects (85.7%) having a positive SPT and

**Table 2. Characteristics of sensitized patients**

| No. | Gender | Age year | Primary renal disease | Donor's atopy | Total IgE IU/ml | Specific IgE kUA/L | SPT | Symptoms | PFT |
|---|---|---|---|---|---|---|---|---|---|
| **1** | M | 16 | VUR | HDM | 102 | 11,2 | HDM | None | Restrictive |
| **2** | F | 17 | Renal dysplasia | HDM | 257 | 19,6 | HDM, GPM, MH | None | Normal |
| **3** | M | 18 | VUR | * | 128 | 12,2 | HDM, GPM | Asthma | Obstructive |
| **4** | M | 18 | VUR | HDM | 14 | 1,08 | Latex | AR | Normal |
| **5** | F | 15 | VUR | HDM | 12 | 2,94 | HDM, TM | AR | Normal |
| **6** | M | 16 | VUR | GPM | 49 | 9,3 | - | None | Normal |
| **7** | M | 5 | VUR | GPM | 237 | 4,5 | GPM | None | Normal |

F indicates female; M, male; VUR, Vesicoureteral reflux; HDM, house dust mite; GPM, grass pollen mixture; MH, mediterranean herbs; TM, tree mixture; AR, allergic rhinitis; PFT, Pulmonary Function Tests; SPT, Skin Prick Test;
*Cadaveric donor

s-IgE to at least 1 allergen. Specific IgE levels of patients with allergic sensitization changed from 1.08 to 19.6. The major allergens determined with the SPT were: dust mite (n=4) followed by grass pollen mixture (n=3), mediterranean herbs (n=1), tree mixture (n=1) and latex (n=1) (**Table 2**). No food allergens were detected in the skin prick tests of the patients, also, no positive food s-IgE was detected in serum samples. Three patients (11.1%) additionally reported a corresponding clinical history of type 1 allergic diseases and therefore were accepted as allergic (AR, n=2; asthma, n=1) (**Table 2**). The living donors of patients with allergic sensitization all had allergic diseases. There was no history of anaphylactic reactions in any patient. Patients with no allergic sensitization also had no allergic disease symptoms.

***Pulmonary function tests***

All 27 patients performed pulmonary function tests. The mean values of pulmonary function tests of all of the patients were within normal range before and after transplantation. There was no statistical significance in FEV1, FVC, PEF, FEF25-75 and FEV1/FVC ratio before and after renal transplantation. (**Table 3**). In classifying the spirometry results, the subjects were divided into three groups, normal ventilatory function, obstructive and restrictive disorders. Five patients had restrictive disorder before and after transplantation in pulmonary function tests. One patient had restrictive pattern prior but obstructive pattern after the renal transplantation. Besides this patient, who had an obstructive pattern in his PFT, none of the patients had clinical findings and/or history regarding asthma.

**Table 3. Pulmonary function of the study subjects**

| | Before Tx | After Tx | *p*-value |
|---|---|---|---|
| **FVC (%pred)** | 82.96±23.50 | 84.96±22.25 | 0.538 |
| **FEV1 (%pred)** | 92.19±26.45 | 92.96±26.26 | 0.167 |
| **FEV1/FVC% (%pred)** | 89.26±19.37 | 91.48±23.35 | 0.256 |
| **PEF (%pred)** | 84.15±22.26 | 87.25±21.89 | 0.572 |
| **MEF 25-75% (%pred)** | 103.11±30.35 | 107.61±31.85 | 0.612 |

Tx:Transplantation

## Discussion

In our study we have shown that kidney organ-transplant recipients of pediatric and adolescent age show sensitizations to common inhalants and the presence of allergic diseases. The prevalences of allergic sensitization and allergic diseases found in the present study (25.9% and 11.1%, respectively) were actually comparable to those of other studies.[4,17]

Although the pathogenesis of transplantation-originated allergy is still not fully known, various factors are being suggested. These are factors such as the development of retarded type hypersensitivity, immunosuppressive protocol type, the transplanted organ, injury in the intestines due to a reduction in energy production with tacrolimus treatment, s-IgE or the transfer of the lymphocytes from the donor to the recipient.[1] The possibility of a relationship between tacrolimus treatment and FA development was first reported in the literature by Lacaille et al. after a liver transplantation.[18] Thereafter, the frequency of FA in patients with transplantations was shown to be 6-57% in various studies. Post-transplantation FA is typically reported within the year after the transplantation as multiple food allergies, during childhood and frequently in patients who received liver transplantation.[1]

Less frequent cases of food allergies are being reported in patients with kidney transplantation compared to liver transplantations. In our study, food allergies were not detected in any of our patients. The lack of new onset FA in patients with kidney transplants is compatible with reports in the literature.[3] In the pediatric age group, in the long-term monitoring of 232 children who had received kidney transplantation, none of the children who had received kidney transplantation developed new onset FA, only two cases which had kidney transplantation along with liver transplantation were detected with new onset FA.[3] This study has reported that although the kidney transplantation recipients were given similar dosages of tacrolimus treatment as liver transplantation recipients, they developed a lower rate of allergic diseases. The probable cause for this is thought to be that kidney transplantation recipients were given a higher dosage of prednizone treatment (prednol inhibits mast cell degranulation in response to allergic foods), additionally they were given the mycophenolate mofetil treatment (mycophenolate mofetil, suppresses humoral immunity and consequently the IgE production).[19]

In the study by Gruber et al. on the adult age group of patients with kidney transplantation, it was shown that there is a correlation between allergic sensitization and Tacrolimus and CsA treatment. In this study, it was found that allergic disease frequencies were twice more frequent in patients who received Tacrolimus treatment than those who received CsA. Inhalant allergen sensitization was detected at a higher rate than the food allergens, and in the group which received both treatments, allergic diseases were substantially presented as AR and rhinoconjunctivitis.[4] Nevertheless, in a study carried out to the pediatric age group, it has been pointed out that in patients who received a kidney and liver transplantation, there were similar frequencies and patterns of allergen sensitizations.[17] In our study, only inhalant allergen sensitization was detected in our patients, in accordance with the literature. Except for one patient who was shown to have allergic sensitization, all patients had received transplantations from living donors being their mother or father. Inhalant allergen sensitization was detected in all living donors. With these results, our study brings a new point of view to allergic sensitization transmission through kidney transplantation.

In addition, there was no history of allergic disease and usage of drugs to suppress allergic symptoms prior to the transplantation period in any of the patients who were detected with allergic sensitization. Our study is important in terms of being the first study to indicate the allergic sensitization in patients who received transplantation due to end stage renal failure which is not related to the immune system, like glomerulonephritis. Likewise, none of our patients had received immunosuppressive treatment, including prednisolone, before the transplantation period.

Our study has potential limitations. First, there were no pre-transplantation allergic data of the patients who were enrolled in the study. Although our study shows that immunosuppressive agents cannot prevent the development of allergic sensitization or allergic diseases, it also limits us to make the comment that these diseases might emerge due to immunosuppressive treatment. Secondly, we could not further comment on the donor's atopy being a risk factor for allergic sensitization, due to cadaveric donor use in some patients.

In conclusion, this cross-sectional study demonstrates that the inhalant allergen sensitization and allergic symptoms in children who have received kidney transplantation are comparable with other studies in the literature. Our study highlights the lack of FA in kidney recipients despite immunosuppressive treatment. Our results matter in terms of the patients in the study group not receiving immunosuppressive treatment before, and the detection of inhalant sensitization in the sensitized group's donors. Future prospective studies should also focus on allergic sensitization already existing prior to transplantation and / or that diseases cannot be taken under control with immunosuppressive treatment or might develop during the treatment, and define risk factors such as the type of immunosuppressive treatment, the transplanted organ, the etiology of the primer disease of the recipient (whether it is an immune or non-immune disease) as well as the allergic status of the donor.

## Conflict of interest

The authors have no conflicts of interest to declare.

## References

1. Ozdemir O. New developments in transplant-acquired allergies. World J Transplant. 2013:24:30-5.
2. Topal E, Çatal F, Selimoğlu MA, Karabiber H, Kılıç T, Başkıran A, et al. Acquired atopic disease after liver transplantation in children; similarities to and differences from adults: a preliminary study. Eur J Gastroenterol Hepatol. 2014:26:1055-9.
3. Levy Y, Davidovits M, Cleper R, Shapiro R. New-onset post-transplantation food allergy in children – Is it attributable only to the immunosuppressive protocol? Pediatr Transplant. 2009:13:63-9.
4. Gruber S, Tiringer K, Dehlink E, Eiwegger T, Mayer E, Konstantin H, et al. Allergic sensitization in kidney-transplanted patients prevails under tacrolimus treatment. Clin Exp Allergy. 2011:41:1125-32.
5. Kawamura N, Furuta H, Tame A, Kobayashi I, Ariga T, Okano M, Sakiyama Y. Extremely high serum level of IgE during immunosuppressive therapy: paradoxical effect of cyclosporine A and tacrolimus. Int Arch Allergy Immunol. 1997:112:422-4.
6. Manuyakorn W, Sinitkul R, Treepongkaruna S, Kamchaisatian W, Vilaiyuk S, Srisala S, et al. In vitro cytokine changes after pediatric liver transplantation. Asian Pac J Allergy Immunol. 2015:33:52-8.
7. Dumont FJ, Staruch MJ, Fischer P, DaSilva C, Camacho R. Inhibition of T cell activation by pharmacologic disruption of the MEK1/ERK MAP kinase or calcineurin signaling pathways results in differential modulation of cytokine production. J Immunol. 1998:160:2579-89.
8. Gabe SN, Bjarnason I, Tolou-Ghamari Z, Tredger JM, Johnson PG, Barclay GR, et al. The effect of tacrolimus (FK-506) on intestinal barrier function and cellular energy production in humans. Gastroenterology. 1998:115:67-74
9. Hohmann C, Pinart M, Tischer C, Gehring U, Heinrich J, Kull I, et al. The development of the MeDALL core questionnaires for a harmonized follow-up assessment of eleven European birth cohorts on asthma and allergies. Int Arch Allergy Immunol. 2014:163:215–24.
10. GINA report. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. Available from: http://www.ginasthma.org.
11. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008:63:8-160.
12. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh). 1980:92:44-7.
13. Granot E, Yakobovich E, Bardenstein R. Tacrolimus immunosuppression -an association with asymptomatic eosinophilia and elevated total and specific IgE levels. Pediatr Transplant. 2006:10:690-3.
14. Visitsunthorn N, Visitsunthorn K, Aulla S, Bunnag C, Jirapongsananuruk O. Comparison of different local and imported histamine concentrations used as a skin prick test positive control. Asian Pac J Allergy Immunol. 2016 Jun 30. doi: 10.12932/AP0737.
15. American Thoracic Society. Standardization of spirometry. Am J Respir Crit Care Med. 1995:152:1107-36.
16. Habesoglu MA, Ugurlu AO, Eyuboglu FO. Clinical, radiologic, and functional evaluation of 304 patients with bronchiectasis. Ann Thorac Med. 2011:6:131-6.
17. Dehlink E, Gruber S, Eiwegger T, Gruber D, Mueller T, Huber WD, et al. Immunosuppressive Therapy Does Not Prevent the Occurrence of Immunoglobulin E– Mediated Allergies in Children and Adolescents With Organ Transplants. Pediatrics. 2006:118:764-70.
18. Lacaille F, Laurent J, Bousquet J. Life-threatening food allergy in a child treated with FK506. J Pediatr Gastroenterol Nutr. 1997:25:228-9.
19. Rentenaar RJ, vanDiepen FN, Meijer RT, Surachno S, Wilmink JM, Schellekens PT, et al. Immune responsiveness in renal transplant recipients: mycophenolic acid severely depresses humoral immunity in vivo. Kidney Int. 2002:62:319-28.