

# Gingival Enlargement and Its Risk Factors in Kidney Transplant Patients Receiving Cyclosporine A

Ali Ghafari,<sup>1</sup> Reza Poorabbas,<sup>2</sup> James Anviah Takieh,<sup>3</sup>  
Nariman Sepehrvand,<sup>4</sup> Catauoun Kargar,<sup>4</sup> Sanaz Hatami<sup>4</sup>

<sup>1</sup>Department of Nephrology,  
Imam Khomeini Training  
Hospital, Urmia University of  
Medical Sciences, Urmia, Iran

<sup>2</sup>School of Dentology, Tabriz  
University of Medical Sciences,  
Tabriz, Iran

<sup>3</sup>School of Dental Medicine,  
Tabriz University of Medical  
Sciences, Tabriz, Iran

<sup>4</sup>Urmia University of Medical  
Sciences, Urmia, Iran

**Keywords.** gingival  
enlargement, kidney  
transplantation, cyclosporine

**Introduction.** Gingival enlargement is one of the most cumbersome complications of cyclosporine A. It affects patient's life style by impairing the appearance and function of masticatory tract. This study was conducted on a sample of Iranian kidney transplant recipients to determine the frequency and risk factors of cyclosporine-induced gingival enlargement.

**Materials and Methods.** A total of 200 kidney transplant recipients (mean age,  $39.7 \pm 13.2$  years) were enrolled in this study. All of the participants were receiving cyclosporine for at least 12 months prior to the study. Factors including age, gender, cyclosporine dose, serum concentration of cyclosporine, duration of immunosuppressive administration, plaque, and gingival indexes were evaluated.

**Results.** Seventy kidney transplant recipients (35%) showed various degrees of gingival enlargement. Serum cyclosporine concentration and the intensity of gingival enlargement (McGraw index) had a significant correlation ( $r = 0.35$ ,  $P < .001$ ). Multiple regression analysis revealed an independent association between gingival enlargement and either serum concentrations of cyclosporine and plaque index ( $P < .05$ ). The other variables failed to show a significant relationship with gingival enlargement.

**Conclusions.** The prevalence of cyclosporine-induced gingival enlargement in our patients seems to be almost greater than the prevalence reported in previous studies. There was a significant relationship between cyclosporine immunosuppressive treatment and gingival overgrowth in Iranian kidney transplant recipients.

IJKD 2010;4:66-70  
www.ijkd.org

## INTRODUCTION

Gingival enlargement is the painless enlargement of buccal and lingual gingival.<sup>1</sup> The drug-induced gingival enlargement is a side effect of some immunosuppressive drugs such as cyclosporine A, which is the drug of choice in kidney transplant patients.<sup>2</sup> Prevalence of cyclosporine-induced gingival enlargement has been reported to be 30%, mostly in children.<sup>3,4</sup> Based on previous studies, intake of more than 500 mg/d of cyclosporine could cause gingival enlargement.<sup>1</sup> It seems that the

intensity of this side effect is more dependent on the serum cyclosporine concentration than the oral hygiene.<sup>4</sup> In a study of Spolidorio and colleagues on the effects of cyclosporine on gingival diseases in rats, after 60 and 120 days of cyclosporine administration, gingival enlargement developed with significant increase in buccal mucosa and relevant tissues, decrease in osteal density, and increase in osteoclastic activity.<sup>5</sup> Mathur and coworkers also reported developing gingival enlargement due to cyclosporine and its resolution

after discontinuing the drug.<sup>6</sup>

Seyrafi and coworkers performed a study among Iranian graft recipients, which demonstrated a correlation between cyclosporine treatment and gingival overgrowth.<sup>7</sup> Baharvand and Ranjbar-Pazooki reported higher rates of gingival overgrowth in younger ages and in concurrent use of cyclosporine with calcium channel blockers.<sup>8</sup> The amplified incidence of gingival overgrowth in concurrent use of cyclosporine and some other drugs (ie, calcium channel blockers) were mentioned by some other studies, too. The study of Khoori and associates on Iranian kidney graft recipients, demonstrated higher prevalence and severity of gingival overgrowth in co-administration of cyclosporine and nifedipine.<sup>9</sup>

Considering the limited enrolled sample size in all previous Iranian studies and some controversial results, the current study was implemented with the aim to determine the frequency of gingival enlargement and to evaluate its risk factors in Iranian kidney transplant recipients receiving cyclosporine.

## MATERIALS AND METHODS

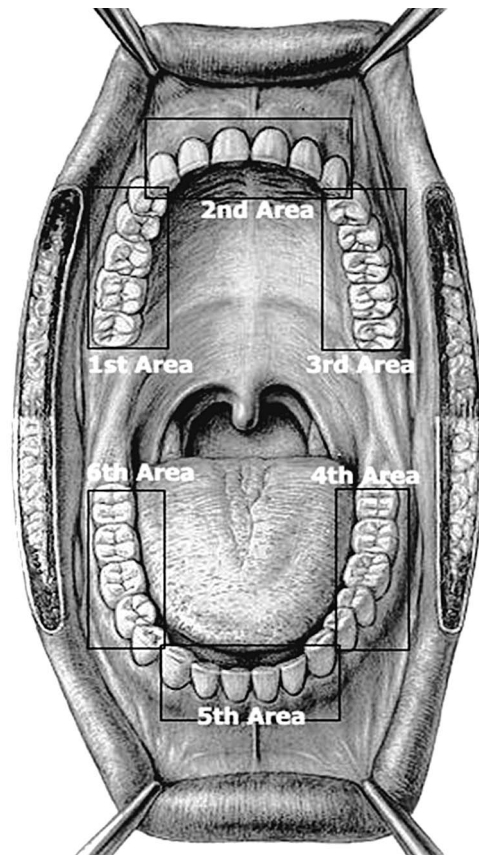
This study was performed after being reviewed and approved by the scientific and ethical committees of Urmia University of Medical Sciences. Two hundred kidney graft recipients who underwent kidney transplantation at least 12 months prior to the beginning of this study and receiving maintenance care at the transplant clinic of Urmia University of Medical Sciences were enrolled after signing an informed consent. The exclusion criteria included recipients with oral respiration and open bite, pregnant women, and patients with diabetes mellitus, cardiovascular disease, or epilepsy (because of probable drug interactions which could lead to gingival enlargement). Also patients with prosthetic crown, fixed or removable partial prostheses, and severe dental crowding were excluded.

All of the patients received cyclosporine A and prednisolone for their immunosuppression, but 132 (66%) received mycophenolate mofetil (Cellcept) and 68 (34%) received azathioprine as complement to their immunosuppressive regimen. A same brand of cyclosporine A was administered for all patients in the form of gelatin capsules (Novartis, Basel, Switzerland). Recipients with a

hypertensive background received antihypertensive drugs including calcium channel blockers (such as nifedipine or diltiazem) or angiotensin-converting enzyme inhibitors (such as enalapril or captopril).

Data were collected regarding age, gender, immunosuppressive regimen with dosage (mg/kg) and duration of treatment (months) of each immunosuppressive drug, and type of administered antihypertensive treatment from the enrolled patients' medical records. Serum concentration of cyclosporine was determined using a radioimmunoassay method. All mentioned information was registered in the checklist of the study.

Dental examination was implemented by only one experienced dentist for all patients. While the examination, disposable sets were applied. In order to determine the affected area, the oral cavity was divided into 6 areas (sextant), including 2 anterior and 4 posterior areas demonstrated in the Figure. The number of teeth was assigned according to its distance from the midline. In order to study the



The 6 buccal areas in the oral cavity.

intensity of gingival enlargement, the McGraw index was used,<sup>10,11</sup> and it was graded as follows and recorded in each patient's checklist:

Grade 0: no gingival enlargement (with thin margins)

Grade 1: gingival enlargement only in intradental papilla

Grade 2: gingival enlargement covers less than one-third of dental crown

Grade 3: gingival enlargement covers more than one-third of dental crown

The collected data were analyzed by the SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA). First, the frequency of gingival enlargement was determined using descriptive statistics. The chi-square test was used to compare the frequencies among different sex groups. Descriptive statistical methods were used to determine the most prevalent age. The 1-way analysis of variance test was used to compare the severity of gingival enlargement in patients using different drugs and its severity in different areas, and the Tukey test was used to study the most prevalent cases. Possibility of a correlation between gingival enlargement and drug dosage, duration, and serum cyclosporine concentration was studied using the Pearson correlation test. *P* values less than .05 were considered significant.

## RESULTS

In this study, 200 kidney transplant recipients who met the inclusion criteria were studied. The results are demonstrated in Table 1. Seventy patients (35%), including 43 men and 27 women, developed gingival enlargement. The lower anterior and then the upper anterior buccal areas were the most affected areas by gingival enlargement (Table 2). The mean McGraw index was  $1.5 \pm 0.61$  in the patients with gingival enlargement. Serum cyclosporine

**Table 2.** The Percentage of Gingival Enlargement (McGraw Index) in Each Buccal Area

Area	Percent
1	10.0
2	45.7
3	10.0
4	11.4
5	94.3
6	10.0

level was significantly higher in patients with gingival enlargement ( $P = .005$ ). However, there was no significant correlation between age, drug dosage, and duration of use (months) on the one hand and gingival enlargement on the other hand, while serum cyclosporine concentration and the intensity of gingival enlargement (McGraw index) had a significant correlation ( $r = 0.35$ ,  $P < .001$ ).

One hundred and thirty-two patients (66%) received cyclosporine, prednisolone, and mycophenolate mofetil, of whom 48 (36.3%) exhibited gingival enlargement. The remaining 68 patients (34%) received cyclosporine, prednisolone, and azathioprine, of whom 22 (32.3%) developed gingival enlargement. The two groups under different immunosuppressive protocols revealed no significant difference in gingival enlargement, but the incidence of gingival enlargement increased with higher doses of micophenolate mofetil and azathioprine.

Overall, 103 patients (51.5%) were receiving antihypertensive therapy; 20 were on enalapril, of whom 6 (30%) exhibited gingival enlargement; 58 were on diltiazem, of whom 29 (50%) had gingival enlargement; and 25 were on nifedipine, of whom 11 (44%) exhibited gingival enlargement. Among 97 patients with no antihypertensive drugs, 24 (24.7%) developed gingival enlargement. Gingival enlargement increased in concomitant use of

**Table 1.** Age, Sex, and Immunosuppressive Treatment in Kidney Transplant Recipients With and Without Gingival Enlargement

Characteristic	Gingival Enlargement (n = 70)	No Gingival Disease (n = 130)	Total
Age, y	41.3 ± 14.3	40.1 ± 15.6	39.7 ± 13.2
Sex			
Male	43	83	126
Female	27	47	74
Duration of treatment, mo	50.86 ± 27.14	52.24 ± 41.23	56.05 ± 39.61
Cyclosporine dose, mg/kg	3.21 ± 1.19	3.35 ± 0.77	3.45 ± 0.81
Serum cyclosporine, ng/mL	113.67 ± 8.43	108.56 ± 7.91	109.88 ± 7.24

antihypertensive drugs and cyclosporine.

Multivariate regression analysis demonstrated that gingival enlargement has the strongest correlation with serum cyclosporine concentration and dental plaque ( $P = .005$ ). There was no correlation between gingival enlargement and age, sex, or dosage and duration of cyclosporine administration.

## DISCUSSION

The frequency of gingival enlargement in cyclosporine-receiving kidney transplant recipients was 35% in our cohort, which is to some extent higher than its frequency in the study of Baharvand and Ranjbar-Pazooki and several other studies reported significantly higher frequencies (75% to 88%).<sup>8,12-14</sup> The limited sample size in most of the studies might be the cause of this discrepancy; however, all the mentioned studies emphasized on the association between treatment with cyclosporine and development of gingival enlargement. The different inclusion criteria and probable drug interactions may also play a role in resulting different frequencies.

In this study, we noticed that the serum cyclosporine concentration had the most significant correlation with development of gingival enlargement ( $P < .001$ ). There is considerable evidence in concordance with this finding.<sup>15-17</sup> Gingival enlargement was assumed to occur in the first year after beginning the immunosuppressive treatment. Since our study was not a longitudinal one, we were not able to comment about the exact occurrence time of gingival overgrowth following immunosuppressive treatment.

Dental plaque had the second most significant correlation with gingival hyperplasia in our patients ( $P = .005$ ). This finding was supported by Thomas and colleagues,<sup>16</sup> but it is in contrast with some other studies.<sup>4,12,14,18</sup> A few animal studies demonstrated the correlation between dental plaque and gingival enlargement, but did not signify it as a trigger. The literature indicated that professionally delivered and frequently repeated supragingival tooth cleaning, combined with careful self-performed plaque control had a marked effect on the subgingival microbiota, and so reduces gingivitis.<sup>19</sup>

In our study, prevalence of gingival enlargement was mostly visible in the lower front and upper front of the buccal cavity, which is supported by

other studies.<sup>12,16</sup> Concerning age, we did not find any relationship between gingival enlargement and any age group. In contrast, Baharvand and Ranjbar-Pazooki reported more frequent gingival enlargement cases in younger patients. However, this finding is not supported by some other studies.<sup>12,16,18</sup> We did not find any significant correlation between dose and administration duration of cyclosporine and development of gingival enlargement either, and many other reports have shown the same finding.<sup>12,14,15,18</sup>

Comparison of two immunosuppressive regimens of cyclosporine and prednisolone along with mycophenolate mofetil or azathioprine revealed no difference in terms of gingival enlargement. However, gingival enlargement increased in patients using antihypertensive drugs such as nifedipine and diltiazem along with cyclosporine, but enalapril, when used as the only antihypertensive drug, did not have any additional significant impact. These findings have been supported by many other studies, as most of the researchers believe gingival enlargement prevalence is higher in patients who use cyclosporine and calcium channel blockers compared to patients who use only cyclosporine.<sup>9,10,11,20</sup>

Some recent studies discussed the smaller effect of developing gingival hyperplasia in patients using tacrolimus compared to patients under treatment with cyclosporine.<sup>21,22</sup> Reasons favoring tacrolimus over cyclosporine are not limited to gingival problems. Other side effects of administering cyclosporine such as hyperlipidemia, hypertension, and hypertrichosis were reported to be resolved and improved after conversion to tacrolimus.<sup>23</sup>

## CONCLUSIONS

The prevalence of cyclosporine-induced gingival enlargement in our patients seems to be almost greater than the prevalence reported in previous studies. There was a significant relationship between cyclosporine immunosuppressive treatment and gingival overgrowth in Iranian kidney transplant recipients. Considering the lower chance of the availability of tacrolimus for the patients in Iran, and also the much higher costs of prescribing that for patients and the healthcare system, cyclosporine is yet the most frequent administered drug in Iran. Thus, frequent dental examination should be considered for the patients receiving cyclosporine.

## ACKNOWLEDGMENTS

The authors would like to thank Urmia University of Medical Sciences for the grants provided for our study.

## CONFLICT OF INTEREST

None declared.

## REFERENCES

- Carranza FA, Hogan EL. Gingival enlargement. In: Carranza FA, Newman M, Takei H, editors. *Clinical periodontology*. Philadelphia: WB Saunders; 2002. p. 279-96.
- Bach JF. Lessons for transplant immunosuppression from the usage of cyclosporine in autoimmune diseases. *Transplant Proc*. 1994;26:3077-81.
- Hassell TM. Evidence for production of an inactive collagenase by fibroblasts from phenytoin-enlarged human gingivae. *J Oral Pathol*. 1982;11:310-7.
- Seymour RA, Smith DG, Rogers SR. The comparative effects of azathioprine and cyclosporin on some gingival health parameters of renal transplant patients. A longitudinal study. *J Clin Periodontol*. 1987;14:610-3.
- Spolidorio LC, Spolidorio DM, Holzhausen M. Effects of long-term cyclosporin therapy on the periodontium of rats. *J Periodontal Res*. 2004;39:257-62.
- Mathur H, Moretti AJ, Flaitz CM. Regression of cyclosporin-induced gingival overgrowth upon interruption of drug therapy. *Gen Dent*. 2003;51:159-62.
- Seyrafi M, Khaleghjou A, Sadeghi Y. The effect of Cyclosporine A (CsA) on gingival overgrowth in renal allograft recipients. *Shahid Beheshti Med Sci Univ J Dent Sch*. 1999;17:106-12.
- Baharvand M, Ranjbar-Pazooki M. Determination of risk factors in Cyclosporine A induced gingival overgrowth. *Shahid Beheshti Med Sci Univ J Dent Sch*. 2002;20:155-64.
- Khoori AH, Einollahi B, Ansari G, Moozeh MB. The effect of cyclosporine with and without nifedipine on gingival overgrowth in renal transplant patients. *J Can Dent Assoc*. 2003;69:236-41.
- James JA, Marley JJ, Jamal S, et al. The calcium channel blocker used with cyclosporin has an effect on gingival overgrowth. *J Clin Periodontol*. 2000;27:109-15.
- Radwan-Oczko M, Boratynska M, Klinger M, Zietek M. Risk factors of gingival overgrowth in kidney transplant recipients treated with cyclosporine A. *Ann Transplant*. 2003;8:57-62.
- Allman SD, McWhorter AG, Seale NS. Evaluation of cyclosporin-induced gingival overgrowth in the pediatric transplant patient. *Pediatr Dent*. 1994;16:36-40.
- Karpinia KA, Matt M, Fennell RS, Hefti AF. Factors affecting cyclosporine-induced gingival overgrowth in pediatric renal transplant recipients. *Pediatr Dent*. 1996;18:450-5.
- Schincaglia GP, Trombelli L, Zangari F, Scabbia A, Griselli A, Calura G. Gingival overgrowth in patients under cyclosporin-A treatment. A clinical study. *Minerva Stomatol*. 1994;43:429-34.
- Somacarrera ML, Hernández G, Acero J, Moskow BS. Factors related to the incidence and severity of cyclosporin-induced gingival overgrowth in transplant patients. A longitudinal study. *J Periodontol*. 1994;65:671-5.
- Thomas DW, Baboolal K, Subramanian N, Newcombe RG. Cyclosporin A-induced gingival overgrowth is unrelated to allograft function in renal transplant recipients. *J Clin Periodontol*. 2001;28:706-9.
- Wondimu B, Berg U, Modéer T. Renal function in cyclosporine-treated pediatric renal transplant recipients in relation to gingival overgrowth. *Transplantation*. 1997;64:92-6.
- Ilgeli T, Atilla G, Cirit M, Azmak N. The Role of Serum Lipids on Cyclosporine-Induced Gingival Overgrowth in Renal Transplant Patients. *Tr J Med Sci*. 1999;29:297-301.
- Hellström MK, Ramberg P, Krok L, Lindhe J. The effect of supragingival plaque control on the subgingival microflora in human periodontitis. *J Clin Periodontol*. 1996;23:934-40.
- Thomason JM, Seymour RA, Ellis JS, et al. Determinants of gingival overgrowth severity in organ transplant patients. An examination of the rôle of HLA phenotype. *J Clin Periodontol*. 1996;23:628-34.
- Ellis JS, Seymour RA, Taylor JJ, Thomason JM. Prevalence of gingival overgrowth in transplant patients immunosuppressed with tacrolimus. *J Clin Periodontol*. 2004;31:126-31.
- James JA, Jamal S, Hull PS, et al. Tacrolimus is not associated with gingival overgrowth in renal transplant patients. *J Clin Periodontol*. 2001;28:848-52.
- Margreiter R, Pohanka E, Sparacino V, et al. Open prospective multicenter study of conversion to tacrolimus therapy in renal transplant patients experiencing cyclosporin-related side-effects. *Transpl Int*. 2005;18:816-23.

Correspondence to:

Ali Ghafari, MD

Department of Internal Medicine, Imam Training Hospital, Urmia, West-Azerbaijan, Iran

Tel: +98 914 145 2477

E-mail: ghaf-ali@yahoo.com

Received July 2009

Revised September 2009

Accepted October 2009