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Local and Systemic Effects of Cyclosporine A on the Severity of Gingival Overgrowth in Post-Transplant Renal Patients

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ABSTRACT

Background: Cyclosporine A (CsA) is a potent immunosuppressant widely used to prevent renal post transplantation rejection. Gingival overgrowth (GO) is among various side effects of the long-term administration of CsA. Up to 90% of the patients under CsA therapy has been reported to develop CsA-induced GO. **Objectives:** The aim of the present prospective pilot study is to determine the local and systemic effects of Cyclosporine A (CsA) on the severity of gingival overgrowth and its relationship with periodontal parameters in post-transplant renal patients **Methods:** Twenty post-transplant renal patients, 12 females and 8 males, presenting gingival overgrowth were selected from Rizk Hospital's clinic in Beirut. Patient's CsA plaque levels were evaluated when CsA is administered by syrup and capsules mode. Periodontal parameters including gingival overgrowth, papillary bleeding, plaque and gingival indices were assessed for all patients. **Results:** Plaque concentration CsA levels, when administered in syrup mode, affected significantly the severity of gingival overgrowth as opposed to the administration by capsule mode. Significant correlations between severity of gingival overgrowth on one hand and plaque index, gingival index, and papillary bleeding index on the other hand were only observed in the Capsule group but not in the syrup group. A significant relationship was established between the severity of gingival overgrowth and all periodontal parameters (gingival, papillary and plaque). **Conclusion:** The present study underlines CsA dental plaque local effect, as a co-factor, in the development of gingival overgrowth. Cyclosporine plaque accumulation acts as a reservoir in the gingival inflammation and the periodontal indices seem to be the most accurate parameters associated with gingival overgrowth severity. Plaque CsA concentrations could be considered as a risk factor for inflammation and gingival overgrowth depending on CsA delivery mode in renal transplant patients.

Keywords: Cyclosporine A, dental plaque, gingival overgrowth, periodontal parameters.

1. BACKGROUND

Cyclosporine A (CsA) is a potent immunosuppressant widely used to prevent renal post transplantation rejection (1, 2). Gingival overgrowth (GO) is among various side effects of the long-term administration of CsA (3). Up to 90% of the patients under CsA therapy has been reported to develop CsA-induced GO (4, 5).

The etiology of cyclosporine-induced GO is multifactorial; it is related to systemic and local factors (6). Cyclosporine serum levels have been suggested as a systemic key element in influencing cyclosporine-induced overgrowth. On the other hand, bacterial plaque accumulation levels are considered as local co-factors that may induce an inflammatory response increasing further the overgrowth (7). Increased swelling and disfiguration of gingiva elevate the risk for infection and inflammatory complications in patients who have undergone renal transplantation and limit oral hygiene maintenance (8). Clinical and cell culture studies suggest that the mechanism of GO is a result of the interaction between the drug and its metabolites with susceptible gingival fibroblasts. Plaque-induced gingival inflammation appears to enhance this

interaction (9).

Understanding the pathogenesis of GO is incomplete at best, therefore, it is essential to explore the local effect of CsA concentrations in the dental plaque on the severity of GO.

2. OBJECTIVE

The objective of the present study is to compare the local effect of CsA present in the dental plaque (when administered in syrup form) to the systemic effect (when administered in capsule form) on the severity of GO and its relationship with periodontal parameters in renal adult transplant recipients.

3. MATERIALS AND METHODS

Patient Population

This is a pilot study conducted on 20 stable renal post-transplant patients, 12 females and 8 males, with ages ranging between 20 and 45 years were selected from the renal transplant clinics at Rizk Hospital in Beirut, Lebanon, for the last two years. A pre-medical history revealed that all patients show stable conditions, they were under a CsA oral therapy dose between 1 mg to 8 mg/kg/day, with no intake of any other medication recognized to produce GO. All patients presented at least six anterior teeth with GO and smokers were excluded from the sample. The study was approved by the Scientific committee of the Faculty of Dental Medicine of the Lebanese University under the ID, SAJF 11/04, and all patients signed the written informed consent prior to initiating the records collection.

Oral Examination

Two trained dental surgeons carried out all dental and periodontal evaluations. They assessed plaque index (PI) and gingival inflammation at the lingual, labial and inter proximal surfaces of all scorable teeth using the PI of Löe and Sillness (10) and the gingival index (GI) of Sillness and Löe, respectively (11).

Papillary bleeding index (PBI) of Saxer and Mühlemann was used to record papillary bleeding (12). GO severity evaluation was performed by means of the semi quantitative index developed by Aas (13). Each tooth was assigned with a mean index, and a mean value for all teeth was calculated for each transplant recipient.

Patients were divided into two groups based on the delivery mode: syrup (n=7) and capsule (n=13). The examiners collected plaque from each patient using a double-ended restorative dental stainless steel spatula (Heidemann Spatula-Medicaline, Dentaltix, Portugal) from the buccal surface of the six anterior lower teeth.

Cyclosporine A dental plaque levels were determined using an innovative extraction technique named Middle East Research Institute (MERI). The technique consists of the following steps: first, plaque is washed twice with saline, weighed, and then homogenized with 200ml of the MERI solution and centrifuged 100000RPM for 10 minutes. The CsA concentration in the supernatant is finally measured using the TDX instrument (TDx®/TDx FLx® Cyclosporine Monoclonal Whole Blood Assay).

Statistical analysis

For each group, the correlation between severity of GO and CsA plaque concentration was computed using Spearman rank correlation (Table 1). Since the data is not normally distributed, Wilcoxon Rank Sum Test was carried out at the 5% level to compare each of the GO and CsA plaque concentrations between genders i.e. males and females under the null hypothesis (H_0) against the alternative hypothesis (H1) where:

H_0: µMales = µFemales and H_1: µMales ≠ µFemales

All analyses were performed using IBM-SPSS version 23 (IBM Corp, Armonk, NY, USA).

The association between GO severity on one hand and CsA plaque concentrations and periodontal parameters (plaque, gingival and PBIs) on the other hand, was evaluated using Spearman's correlation (Table 2).

The Wilcoxon Rank Sum Test was carried out, again at the 5% level, as an alternative to the T-test to compare each of the three periodontal indices of the GO on one hand and the plaque CsA on the other, between the group of patients with low GO and the group of patients with high GO (Table 3) (Figure 1); this has been done under the null hypothesis (H_0) against the alternative hypothesis (H_1) where:

H_0: µLow = µHigh and H_1: µLow ≠ µHigh

Finally, subjects were divided according to the mode of delivery, syrup (n=7) versus capsule (n=13). For each group, correlations between severity of GO and other periodontal parameters were computed using Spearman's correlation coefficient (Table 4).

4. RESULTS

A "moderate" Spearman correlation of 0.377 with *p*-value = 0.084 >0.05 i.e. not significant was observed between the severity of GO and plaque CsA levels (Table 2).

Variable	Overall Mean (SD)	Female Mean (SD)	Male Mean (SD)	P-value
Gingival Overgrowth	1.46 (0.51)	1.37 (0.53)	1.55 (0.49)	0.128
CsA Plaque Concentration	48.68 (31.39)	47.47 (33.38)	50.57 (29.87)	0.439

Table 1. Summary of the gingival Overgrowth, CsA Plaque Concentration and gender differences

Variables	Correlation	p-value
Plaque Index	0.609	<0.0001
Gingival Index	0.660	<0.0001
Papillary Bleeding Index	0.642	<0.0001
Plaque CsA	0.377	0.084

Table 2. Correlation between severities of GO on one hand and the CsA Plaque Concentration and periodontal parameters on the other hand

A "strong positive" significant Spearman correlation was observed between severity of GO and all periodontal parameters (Table 2). In fact, the correlation with the PI equaled 0.609, with the GI 0.660 and with the PBI 0.642. All corresponding three p-values were significantly inferior to 0.001 (Table 2).

When comparing males to females, concerning the GO and CsA plaque concentration, the *p*-values are, respectively, equal to 0.128 and 0.439 both > to 0.05 (Table 1). We conclude that there exists no enough evidence to reject the

Variables	Low GO (SD)	High GO (SD)	p-value
Plaque Index	1.10 (0.386)	2.07 (0.63)	<0.0001
Gingival Index	1.25 (0.38)	2.27 (0.50)	<0.0001
Papillary Bleeding	0.38 (0.47)	0.98 (0.05)	<0.0001
CsA Plaque Concentration	55.42 (36.70)	48.30 (29.99)	0.645

Table 3. Comparing periodontal parameters between High and Low GO groups

Variable	Syrup group (n=7)	Capsule group (n=13)
Plaque Index	0.008	0.724*
Gingival Index	0.109	0.824*
Papillary Bleeding Index	0.550	0.623*
Plaque CsA	0.900*	-0.156

Table 4. Correlations between severity of GO and other variables stratified by mode of delivery (Syrup or capsule mode). *Significant at the 5% level

null hypothesis that each of GO and CsA plaque concentration is equal for both genders.

For all three periodontal indices i.e. PI, GI and PBI, the registered respective p-values were all largely inferior to 0.0001 (Table 3) meaning that we reject the null hypothesis and accept the alternative hypothesis. The means for all three indices are significantly higher for the group with high GO then the group with low GO.

However, when it comes to the comparison of CsA plaque concentration, the *p*-value equaled 0.645 (Table 3) largely greater >>> 0.05. Hence, we have no enough evidence to reject the null hypothesis. The CsA plaque concentration is equal for both groups of low and high GO.

Significant correlations between severity of GO on one hand and PI, GI and PBI on the other hand were only observed in the capsule group but not in the syrup group. However, there was a significant association between the severity of GO and CsA plaque concentration in the syrup group and not in the capsule group (Table 4).

A "very strong" significant correlation as measured by the Spearman rank correlation equal to 0.724 and 0.824 was observed between severity of (GO) with the PI and GI in the capsule group (Table 4) respectively.

A "strong" significant correlation as measured by the Spearman rank correlation equal to 0.623 was observed between severity of GO with the PBI in the capsule group (Table 4). A "strong" correlation as measured by the Spearman rank correlation equal to 0.550 was observed between severity of GO with the PBI in the syrup group (Table 4).

A "negligible" correlation as measured by the Spearman rank correlation equal to 0.008 and 0.109 was observed between severity of GO with the PI and GI in the syrup group (Table 4), respectively.

5. DISCUSSION

Numerous systemic risk factors such as CsA intake dose, serum concentrations and capsule delivery mode have been associated with the development of CsA-induced GO (14). Correspondingly, other local factors such as CsA levels in plaque due to intake in syrup form, gingivitis and plaque scores have been reported to be significant risk elements in the development of GO (6).

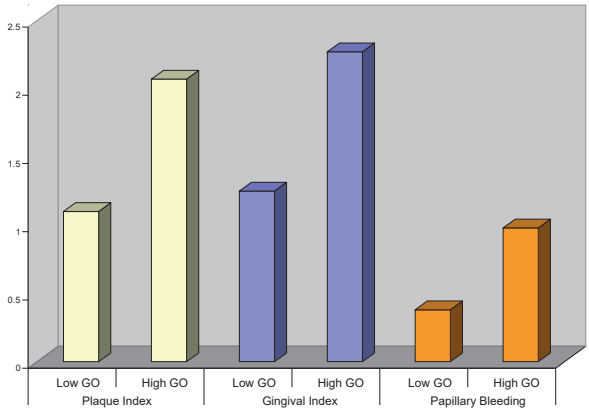

Figure 1. Comparing periodontal parameters in low and high GO

Some researches demonstrated that the total drug intake dose does not seem to be an adequate predictor of gingival changes, while other studies suggest that the development of CsA-induced GO is positively correlated with drug intake dose (14-16). In fact, CsA is a highly lipophilic drug readily present on most biological membranes. CsA serum concentration includes the fraction of unbound (free) drug, and that of CsA bound to plasma soluble lipids/proteins. In an earlier study, Nam et al. (17) suggested that CsA serum levels significantly influence the incidence of GO in transplanted patients while others did not demonstrate such correlation (18, 19). Nonetheless, Seymour et al. (7) suggest an individual specific susceptibility to develop gingival enlargements. More recently, there is a general agreement that the initiation of GO requires an initial threshold serum concentration and it has been suggested that the higher is the serum concentration, the quicker GO develops (16).

The results in the present study demonstrate a significant correlation between GO and PI, GI and PBI 0.724, 0.824 and 0.623, respectively for patients who were under capsules mode therapy (Table 4). It could be explained by the systemic dose of CsA present in the serum leading to the incidence of GO in the capsule group.

On the other hand, the type of CsA preparation has been demonstrated to have some effect on the development of GO (20). Suzuki et al's (21) findings suggested that, after CsA oral administration by the fine droplet drying process, the drug oral bioavailability, plasma concentration and biopharmaceutics properties were enhanced (21). Moreover, earlier onset of gingival changes and more severe overgrowth have been observed in patients using CsA solution when compared to patients treated with the capsule form (20).

In the present study, no significant correlation was found between CsA plaque concentrations and GO (Table 2), even when the two genders where compared (Table 1). When comparing group taking CsA by capsules versus those by syrup, the results showed a significant correlation (*p*= .900*) between severity of GO and CsA plaque concentration in the syrup group and not in the capsule one (Table 4). On the contrary, there was no correlation between GO and PI nor between GO and GI in the syrup group, 0.008 and 0.109 respectively (Table 4). In fact, Cyclosporine is a

potent immunosuppressant with a limited antimicrobial action (5). Therefore, the current differences could be explained by the local role of CsA delivered by syrup mode and the amount of CsA concentrations that could be accumulated in the dental plaque during oral CsA intake, and plaque acting consequently as a reservoir. Afterward, CsA could be released from dental plaque reservoirs through the mastication and induce gingival inflammation (22). In fact, untreated gingival inflammation leads to GO and periodontal destruction (23).

Additionally, inflammatory response increased by systemic conditions and local factors such as the presence of dental plaque suggesting that the hyperplasia can represent a response to bacterial toxins (23). It has been stated that the dental plaque has a fundamental role in the pathogenesis of GO induced by cyclosporine, and reported a significant correlation between plaque or gingivitis and the prevalence and severity of GO (7, 24). In contrast, others found no correlation between plaque or gingivitis and GO (15). However, plaque's role remains unclear; does it have a primary effect or it is a consequence of pseudo-pockets with altered gingival morphology, which makes the plaque control difficult. Although, we are not quite sure if the GO is a result of an inflammatory component, or it occurs because of the cyclosporine's simulative effect to the collagen production. In a previous study, it was found that GO inhibits plaque elimination due to an increased gingival inflammation, gingival bleeding and loss of attachment (25). Moreover, when subjects were classified in "high GO" and "low GO" groups, data showed that PI, GI and PBI were significantly greater in the "high GO" group (Table 3, Figure 1).

In the present study, a strong correlation (0.550) was established between GO and PBI in the syrup group (Table 4). Additionally, a "strong" significant correlation (0.623) was seen between severity of GO and PBI in the capsule group (Table 4).

These results are in concordance with Pejcic et al. (26) who claimed that the severity of the enlargement is often proportional to the amount of gingival inflammation existing and not the dosage of medication. Moreover, many authors suggested that tissue affected by CsA demonstrate little fibrosis, due to the innate immune response, and tend to bleed more and are more hyperemic (27, 28). In fact, the pathogenesis of epithelial thickening in GO remains obscure. Bulut and Ozdemir (9) reported that reduced keratinocyte apoptosis and decreased levels of caspase-3 may be important factors affecting the gingiva of kidney transplant recipients with CsA-induced GO. Similarly, Buduneli et al. (29) found a significantly greater number of keratinocytes in the CsA-induced GO group than in the healthy control group. There were significantly fewer numbers of apoptotic cells in the CsA group when compared with the gingivitis and healthy control groups. The authors suggested that decreased apoptosis may have a more prominent role than increased cell division in the pathogenesis of CsA-induced GO. In contrast, Alaaddinoglu et al. (30) indicated that the extent of keratinocyte apoptosis in the gingiva of kidney recipients with CsA-associated GO is similar to that observed in inflamed gingiva of healthy individuals. Accordingly, Cetinkaya et al. (31) concluded that CsA-induced gingival alterations were closely associated with increased epithelial proliferative activity.

The results of the present study and those of the above-mentioned reports highlight the primary role of gingival inflammation in the pathogenesis and severity of GO (32). Such observations, however, are not conclusive as to whether the plaque-induced changes are the "cause" or the "result" of GO. Dental plaque accumulation did not seem to be crucial, but rather an aggravating factor for the progression of the lesions. Cyclosporine A has been suggested to alter the metabolic function of gingival fibroblasts by increasing interleukin-6 secretion, which enhances collagen and glycosaminoglycan synthesis and reduces collagen breakdown (16). It also affects T-lymphocytes, which play a pivotal role in the periodontal antibacterial immune response (33).

In these cross-sectional studies, it is difficult to confirm a true relationship between plaque and GO as it is unclear whether plaque is a contributory factor or just a consequence of the gingival changes which render oral hygiene measures more difficult.

This study did not have an equal distribution between the modes of administration of CsA (capsule vs. syrup). In addition, a larger sample may be necessary in order to reach results that are more conclusive.

6. CONCLUSION

The elevated periodontal indices observed in the present study, in patients with GO, could possibly result from morphological alterations (contour of gingival tissue/papillae) and the impairment of bacterial biofilm control. Available data indicate that individual susceptibility to develop GO should be considered and may be correlated with local and systemic factors. Furthermore, attention to plaque control and removal of plaque retentive factors does improve gingival health in organ transplant patients, but these measures alone fail to prevent the development of GO, or its recurrence following surgery. Further studies are needed to elucidate the effect of periodontal therapy on the severity of GO in long-term follow-up studies. Finally GO seems to be a complex multi-factorial event related to CsA, bacterial plaque presence and individual susceptibility.

- **Authors' contribution:** SA and ZM: performed the assessment, designed and wrote the paper; ZM: directed the project, and GA: helped performing the data analysis and writing the manuscript. The first author made final proofreading.
- **Conflict of Interest:** None declared.
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REFERENCES

1. Pradier A, Papaserafeim M, Li N, Rietveld A, Kaestel C, Gruaz L, et al. Small-molecule immunosuppressive drugs and therapeutic immunoglobulins differentially inhibit NK cell effector functions in vitro. Front Immunol. 2019; 10: 556.
2. Ponticelli C, Glassock RJ. Prevention of complications from use of conventional immunosuppressants: a critical review. J Nephrol. 2019; 32(6): 851-870.
3. Diesel A, Moriello K. Medical management of Cyclosporine-induced gingival overgrowth using oral Azithromycin in six

dogs. Vet Sci. 2015; 2(1): 13-22.
4. Kilpatrick NM, Weintraub RG, Lucas JO, Shipp A, Byrt T, Wilkinson JL. Gingival overgrowth in pediatric heart and heart-lung transplant recipients. J Heart Lung Transplant. 1997; 16(12): 1231-1237.
5. Lauritano D, Palmieri A, Lucchese A, Di Stasio D, Moreo G, Carinci F. Role of Cyclosporine in gingival hyperplasia: an in vitro study on gingival fibroblasts. Int J Mol Sci. 2020; 21(2): 595.
6. Ponnaiyan D, Jegadeesan V. Cyclosporine A: Novel concepts in its role in drug-induced gingival overgrowth. Dent Res J (Isfahan). 2015; 12(6): 499-506.
7. Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. J Clin Periodontol. 2000; 27(4): 217-223.
8. Somacarrera ML, Hernandez G, Acero J, Moskow BS. Factors related to the incidence and severity of cyclosporine-induced gingival overgrowth in transplant patients. A longitudinal study. J Periodontol. 1994; 65(7): 671-675.
9. Bulut S, Ozdemir BH. Apoptosis and expression of caspase-3 in cyclosporin-induced gingival overgrowth. J Periodontol. 2007; 78(12): 2364-2368.
10. Löe H, Sillness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta Odontol Scand. 1963; 21: 533-551.
11. Sillness S, Löe HP. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand. 1964; 22: 121-125.
12. Saxer UP, Mühlemann HR. Motivation and education. SSO Schweiz Monatsschr Zahneheilkd. 1975; 85(9): 905-919.
13. Aas E. Hyperplasia gingivae diphenylhydantoinea. A clinical, histological, and biochemical study. Acta Odontol Scand. 1963; 21: 1-142.
14. Oliveira Costa F, Ferreira SD, Lages EJ, Costa JE, Oliveira AM, Cota LO. Demographic, pharmacologic, and periodontal variables for gingival overgrowth in subjects medicated with cyclosporine in the absence of calcium channel blockers. J Periodontol. 2007; 78(2): 254-261.
15. Hefti AF, Eshenaur AE, Hassell TM, Stone C. Gingival overgrowth in cyclosporine A treated multiple sclerosis patients. J Periodontol. 1994; 65(8): 744-749.
16. Ciavarella D, Guiglia R, Campisi G, Di Cosola M, Di Liberto C, Sabatucci A, et al. Update on gingival overgrowth by cyclosporine A in renal transplants. Med Oral Patol Oral Cir Bucal. 2007; 12(1): E19-25.
17. Nam HS, McAnulty JF, Kwak HH, Yoon BI, Hyun C, Kim WH, et al. Gingival overgrowth in dogs associated with clinically relevant cyclosporine blood levels: Observations in a canine renal transplantation model. Vet Surg. 2008; 37(3): 247-253.
18. Cebeci I, Kantarci A, Firatli E, Ayqun S, Tanyeri H, Aydin AE, et al. Evaluation of the frequency of HLA determinants in patients with gingival overgrowth induced by cyclosporine-A. J Clin Periodontol. 1996; 23(8): 737-742.
19. Cebeci I, Kantarci A, Gurel N, Adin S, Tuncer O, Carin M, et al. Analysis of peripheral blood leukocytes in patients with cyclosporine A-induced gingival hyperplasia. J Periodontol. 1998; 69(12): 1435-1439.
20. Wondimu B, Sandberg J, Modéer T. Gingival overgrowth in renal transplant patients administrated cyclosporin A in mixture or in capsule form: A longitudinal study. Clin Transplant. 1996; 10: 71-76.
21. Suzuki H, Moritani T, Morinaga T, Seto Y, Sato H, Onoue S. Amorphous solid dispersion of cyclosporine A prepared with fine droplet drying process: Physicochemical and pharmacokinetic characterization. Int J Pharm. 2017; 519: 213-219.
22. McGaw T, Lam S, Coates J. Cyclosporin-induced gingival overgrowth: correlation with dental plaque scores, gingivitis scores and cyclosporin levels in serum and saliva. Oral Surg Oral Med Oral Pathol. 1987; 64(3): 293-297.
23. Murakami S, Mealey BL, Mariotti A, Chapple ILC. Dental plaque–induced gingival conditions. J Clin Periodontol. 2018; 45(20): S17-S27.
24. King GN, Fullinfaw R, Higgins TJ, Walker RG, Francis DM, Wiesenfeld D. Gingival hyperplasia in renal allograft recipients receiving cyclosporine-A and calcium antagonists. J Clin Periodontol. 1993; 20(4): 286-293.
25. Kinane DF, Attström R. Advances in the pathogenesis of periodontitis. Group B consensus report of the fifth European Workshop in Periodontology. J Clin Periodontol. 2005; 32: 130-131.
26. Pejcic A, Djordjevic V, Kojovic D, Zivkovic V, Minic I, Mirkovic D, et al. Effect of periodontal treatment in renal transplant rRecipients. Med Princ Pract. 2014; 23(2): 149-153.
27. Dongari-Bagtzoglou A. Drug-associated gingival enlargement. J Periodontol. 2004; 75(10): 1424-1431.
28. Uzel MI, Kantarci A, Hong HH, Uygur C, Sheff MC, Firatli E, et al. Connective tissue growth factor in drug-induced gingival overgrowth. J Periodontol. 2001; 72(7): 921-931.
29. Buduneli N, Buduneli E, Cinar S, Lappin D, Kinane DF. Immunohistochemical evaluation of Ki-67 expression and apoptosis in cyclosporin–A induced gingival overgrowth. J Periodontol. 2007; 78(2): 282-289.
30. Alaaddinoglu EE, Karabay G, Bulut S, Oduncuoglu FB, Ozdemir H, Bulut OE, et al. Apoptosis in cyclosporin A-induced gingival overgrowth: a histological study. J Periodontol. 2005; 76(2): 166-170.
31. Cetinkaya BO, Acikgoz G, Aydin O, Korkmaz A, Keles GC. The relationship between proliferating cell nuclear antigen expression and histomorphometrical alterations in cyclosporine A-induced gingival overgrowth in rats. Toxicol Pathol. 2006; 34(2): 180-186.
32. Thomason JM, Seymour RA, Ellis JS. Risk factors for gingival overgrowth in patients medicated with cyclosporin in the absence of calcium channel blockers. J Clin Periodontol. 2005; 32(3): 273-279.
33. Yamazaki K, Nakajima T, Gemmell E, Polak B, Seymour GJ, Hara K. IL-4- and IL-6-producing cells in human periodontal disease tissue. J Oral Pathol Med. 1994; 23(8): 347-353.