

1-1-1999

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### Recommended Citation

İLGENLİ, TUNÇ; ATILLA, GÜL; CİRİT, MUSTAFA; and AZMAK, NEZİH (1999) "The Role of Serum Lipids on Cyclosporine-Induced Gingival Overgrowth in Renal Transplant Patients," *Turkish Journal of Medical Sciences*: Vol. 29: No. 3, Article 15. Available at: <https://journals.tubitak.gov.tr/medical/vol29/iss3/15>

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## The Role of Serum Lipids on Cyclosporine-Induced Gingival Overgrowth in Renal Transplant Patients

Received: February 10, 1997

**Abstract:** Cyclosporine-A (CsA) is widely used to prevent organ rejection in recipients of transplanted organs and also in the treatment of various systemic diseases. CsA has a number of side effects, including gingival overgrowth (GO). However, the pathogenesis of CsA-induced GO remains uncertain. It has been postulated that CsA alters fibroblast activity. CsA is transported in plasma by binding to lipid components. It is possible that changes in serum lipid levels could alter the interaction between the CsA and gingival fibroblasts within the gingival tissues. It has also been reported that CsA may alter serum lipid levels in the transplant population. The aim of this study was to investigate the relationship between the serum lipids and CsA-induced GO. A total of 47 renal transplant recipients receiving CsA, azathioprine and prednisolone were the subjects of this study. Periodontal measurements were taken including plaque index (PII) and GO scores (GO). GO was classified into four categories according to the clinical changes. The whole blood CsA concentration, serum total cholesterol, triglyceride and ceratinine levels, and duration of CsA theraph of these patients

were obtained from the subject's medical records. These were assessed monthly. CsA-treated recipients were divided for statistical purposes into two groups according to their GO scores. The recipients having sites with clinically significant GO (scores of 2 and 3) were classified as responders, and those without evidence of overgrowth (GO score=0) as non-responders. There were no differences in age, plaque scores, duration of CsA therapy, and azathioprine and prednisolone dosage between responders and non-responders. Similarly, no statistically significant differences in serum lipids and whole blood CsA concentration were found between these two groups. These data indicate that CsA-induced GO is unrelated to serum lipid components. To our knowledge, this is the first report describing the relationship between the serum lipids and CsA-induced GO. We believe that additional studies will be necessary for complete understanding of the mechanism of gingival overgrowth.

**Key Words:** cyclosporine-A, gnigival overgrowth, renal transplant, cholesterol, triglyceride

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### Introduction

CsA is an immunosuppressant used successfully to prevent organ rejection in recipients of transplanted organs and also in the treatment of several immunologically based diseases (1, 2). CsA has a number of side effects, including nephrotoxicity, hepatotoxicity, neurotoxicity, hypertrichosis, lymphoma, fibrosis of pulmonary, pericardial and renal tissues and gingival overgrowth (GO) (2, 3). CsA-induced GO cases were first reported in 1983 (3, 4). The reported incidence of CsA-induced GO ranges from 8% to 70% (4, 5, 6). Despite the widespread use of CsA, both the pathogenesis of CsA-induced GO and the relationship with local and general variables have not yet been completely understood. It has

been stated that GO may be related to drug variables, plaque-induced inflammatory changes in the gingival tissues and genetic factors (7).

Investigations that have examined the effects of CsA on serum lipids in renal transplant recipients have produced conflicting results. Some researchers have found that serum lipid levels increased in renal transplant recipients receiving CsA (8, 9, 10), whereas others have found no difference when compared with healthy controls (11). Elevated serum lipid levels have been reported in more than 60% of renal transplant recipients (12). Reported changes of serum lipids include an increase in total cholesterol and triglyceride levels (9). An increase in serum total cholesterol and triglyceride levels in the early

posttransplant period (first 6 months) has been found to be related with the mechanism of some CsA side effects (9, 13). In addition, it has been reported that lipid abnormalities persist into the very late posttransplant period (10). It has also been observed that CsA-induced GO occurs within the first 6 months of dosage in most cases (14).

CsA is known to be highly lipophilic; up to 80% of the drug is transported in plasma, principally by binding to lipoproteins (9, 13, 15). Lemaire et al. (16) have suggested that the variable CsA binding and distributing to the tissues may be due to the large inter- and intra-subject variability of the blood lipo-protein component. The amount of CsA binding to the gingival fibroblasts may modulate fibroblast activities. Since CsA is transported in plasma by binding to lipids, the changes of serum lipid level could alter the interaction between the drug and gingival fibroblasts within the gingival tissues. While serum lipid components may be important in the expression of other unwanted effects associated with CsA, the role of serum lipids on the CsA-induced GO in renal transplant recipients has not yet been investigated. The aim of the present study was to determine whether there was any relationship between the levels of serum lipid and CsA-induced GO in renal transplant recipients.

## Material and Methods

A total of 47 renal transplant recipients were examined, 28 subjects receiving CsA and exhibiting clinically significant GO (aged from 24 to 51 years) and 19 subjects receiving CsA and not exhibiting GO (aged from 19 to 45 years). The mean age of the subjects was  $34.21 \pm 12.3$ . All recipients had been on a CsA-based immunosuppression regimen for at least 6 months (range, 11-62 months). The dose of CsA was adjusted according to trough (12 hr postdose) CsA blood levels and renal function. No intravenous CsA was used on any subjects. CsA therapy was supplemented with azathioprine (1-15 mg/kg/day) and prednisolone (10 mg/day or less) in all subjects. All the recipients had stable renal function and were excluded if they were receiving any additional drug therapy which would affect the gingival tissues.

The periodontal parameters were determined by the same periodontist and these measurements were recorded for all teeth in each subject. Each patient's oral hygiene was assessed using the plaque index (PII) of Quickkey-Hein (17). The severity of GO was assessed on the basis of clinical criteria. The degree of GO was classified in four categories on the basis of the criteria of

Angelopoulos and Goaz (18), modified by Pernu et al. (6). The criteria for each score of GO were: a score of 0=no gingival overgrowth; a score of 1=mild gingival overgrowth (thickening of the marginal gingiva and/or lobular granulation of the gingival pocket as well as overgrowth covering the gingival third of the crown or less); a score of 2=moderate gingival overgrowth (overgrowth covering two thirds of the crown); and a score of 3=severe gingival overgrowth (overgrowth covering two thirds of the crown or the whole attached gingiva being affected). GO scores of 2 and 3 were suggested by Pernu et al. (6) as indicative of clinically significant gingival overgrowth. Therefore, CsA-treated recipients were divided for statistical purposes into two groups according to their GO scores: recipients having sites with clinically significant GO (scores of 2 and 3) were classified as responders, and those without evidence of overgrowth (GO score=0) as non-responders.

Whole blood samples were obtained from each patient before the morning dose of CsA. Whole blood levels of CsA were determined by the whole blood polyclonal Abbott TDX fluorescence polarization immunoassay (FPIA) (Abbott Diagnostics Division, Melbourne, Australia). The whole blood CsA concentration, serum total cholesterol, triglyceride and creatinine levels, and the total duration of CsA therapy (in months) were obtained from the subject's medical records. These measurements were assessed monthly during the post-transplant period and have formed a part of the regular monitoring procedure for renal transplant patients in the Medical Center of Ege University, Izmir.

The results are presented as mean values  $\pm$  standard deviation for subjects, periodontal and pharmacokinetic parameters. The means were calculated for each subject and these values used to determine the sample means. The statistical significance of the differences between the responder and non-responder groups was determined using the non-parametric Mann-Whitney U-test. Pearson's correlation coefficient was used for the correlation of serum total cholesterol and triglyceride levels with GO scores.  $p < 0.05$  was taken to be significant.

## Results

The subjects, periodontal and pharmacokinetic variables and the differences between the responders and non-responders are shown in Table 1. There were no significant differences between the responder and non-responder groups in age and in the duration of CsA therapy ( $p > 0.05$ ). Similarly, no statistically significant differences between these two groups were found for

	Non-responders (n=19)	Responders (n=28)	p values
sex distribution (M:F)	12:7	18:10	
age (years)	35.13±10.2	33.62±12.01	>0.05*
plaque index score	1.96±1.33	3.2±1.44	>0.05
duration of CsA therapy (months)	28.21±11.67	24.64±12.65	>0.05
whole blood CsA concentration (ng/ml)	345.66±131.12	376.72±111.2	>0.05
azathioprine dosage (mg/kg/day)	1-1.5	1-1.5	
corticosteroid dosage (mg/day)	10 or less	10 or less	
serum total cholesterol level (mg/dl)	239.43±57.71	221±49.33	>0.05
serum triglyceride level (mg/dl)	192.37±72.18	171±93.8	>0.05
serum creatinine concentration (mg/dl)	1.25±0.31	1.06±0.24	>0.05

Values are means ± SD

\* not significant (p>0.05)

whole blood CsA concentration, serum total cholesterol, triglycerides or creatinine levels (p>0.05). Although the mean PII was higher in the responder group than in the non-responder group, this difference was not statistically significant (p>0.05). No correlation was found between the GO score and both serum total cholesterol and triglyceride levels (p>0.05).

## Discussion

Multiple-drug regimens (CsA, azathioprine and prednisolone) are currently used for prophylactic immunosuppression in many transplant centers. It is well established that GO is one of the unwanted side effects of CsA (3, 4, 5, 6, 7). However, neither azathioprin nor corticosteroids are known to be associated with GO (19, 20). Despite the widespread use of CsA, its mechanism of action and side effects are not yet completely understood. The precise mechanism of CsA-induced gingival overgrowth is also uncertain. The relationship between CsA pharmacokinetic variables and the prevalence and severity of GO has remained a contentious issue. Some studies have suggested that plaque score, CsA blood concentration and the duration of drug therapy may be important determinants in the development and expression of GO while others have failed to substantiate these findings (5, 6, 19, 20, 21, 22). In the present study, the results indicated that GO is not related to whole blood CsA concentration, the duration of CsA therapy or plaque index.

Disturbances of lipid metabolism are frequently encountered after renal transplantation and have been ascribed to the use of CsA and corticosteroids, but the individual contribution of each of these drugs remains

uncertain (9, 13, 14). Few studies have examined the effects on serum lipids of CsA used in a multiple-drug immunosuppression protocol. Conflicting results have been reported regarding the effect of CsA on serum lipid metabolism (9, 3, 23). Although corticosteroids may also alter lipoproteins, this is a dose-dependent phenomenon. A daily dose of 12.5 mg or less of corticosteroid has only a minimal effect on cholesterol (13, 24). In the present study, all the recipients used the multiple-drug regimens and there were no differences between the doses of prednisolone and azathioprine used by the responders and non-responders. Additionally, non-responders had higher serum creatinine levels than the responders, but this difference was not statistically significant. This finding may reflect the lower severity of GO in the non-responder group, which is in agreement with previous findings (25).

The incidence of GO with the administration of CsA is widely reported in renal transplant recipients (3, 4, 6, 19, 20, 21, 22). Although most of the data in the literature has been obtained from renal transplant recipients, there is no information about the incidence and pathogenesis of CsA-induced GO in patients with autoimmune diseases such as rheumatoid arthritis. However, Daley et al. (5) have suggested that CsA therapy, not the patient's systemic conditions, cause GO. It is possible that the mechanism of CsA-induced GO is more important than the patient's disease. Seymour et al. (7) have suggested that CsA-induced GO is not simply a drug-related problem, but is multifactorial. The total cholesterol and triglyceride serum levels of the groups in the present study could not be compared with those of any other studies as there have been no other such studies. Lemaire et al (16) have suggested that blood lipids vary between

Table 1. Subject, PII, drug and pharmacokinetic variables and the differences between responders and non-responders.

individuals, which may result in variable CsA binding and distribution to the tissues. Therefore, at the local level of CsA within gingival tissues, fibroblast activity may be modulated depending on the amount of CsA binding with gingival fibroblasts (26, 27). However, our study found no evidence of relationship between lipid component levels and CsA-induced GO in renal transplant recipients. For this reason, we agree with the opinions of some investigators that lipid components might play a major role in the transport of CsA, but not in its cellular uptake

(15, 28). As yet the molecular mechanism of CsA-induced GO are unknown, although it has been postulated that CsA increases fibroblastic activity through alterations in the levels of various growth factors and cytokines (2). Since it is estimated that approximately 1 billion patients will use CsA within the next decade, we believe that additional studies will be necessary to completely understand the mechanism of gingival overgrowth. As a result, CsA-induced gingival overgrowth may be prevented or treated.

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