

ORIGINAL ARTICLE

Gingival Enlargement in Patients who Have Undergone Renal Transplants: A Meta-Analysis

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ABSTRACT

Severe gingival enlargement (GE) is one of the most commonly observed adverse effects in patients who have undergone renal transplants due to the use of cyclosporine A. **Objectives:** We aimed to gain more insight into the prevalence of GE in patients with renal transplants. **Methods:** We searched the PubMed and Web of Science databases for relevant studies from January 1990 to January 2018. Using random effects models, we calculated summary incidence rates and 95% confidence intervals (CIs). **Results:** A total of 595 patients from 10 studies were included. Patients using cyclosporine A with or without any other drugs had a 62.6% (95% CI, 41.9%–79.5%) incidence of GE. Subgroup analysis according to diagnostic criteria showed that the incidence of GE was lower when using well-defined diagnostic criteria or scoring system. The incidence of GE was 88.2% (95% CI, 80.9%–93.0%) in patients using cyclosporine A with nifedipine. Cyclosporine A without nifedipine was associated with a significantly decreased risk of GE incidence when compared with the combination of cyclosporine A and nifedipine (odds ratio: 0.198; 95% CI, 0.083–0.473; $P < 0.001$). **Conclusions:** It is important for all clinicians to know the effects of the aforementioned drugs and the treatment options.

Key words: cyclosporine A, gingival enlargement, gingival overgrowth, renal transplantation

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INTRODUCTION

Gingival enlargement (GE) is defined as medication-related gingival overgrowth or gingival hyperplasia.¹ First reported in 1939 by Kimball,² drug-induced GE occurred with the chronic usage of phenytoin, an antiepileptic drug. Drug-induced GE occurs as a result of using three drug types: antiepileptic drugs, such as phenytoin; immunosuppressants, such as cyclosporine A; and calcium channel blockers, such as nifedipine, diltiazem, or verapamil, that are used to treat different cardiovascular disorders.³ These drugs accumulate in the extracellular matrix of gingival connective tissue, especially in the collagenous component, with several levels of chronic inflammation.⁴

Cyclosporin A is the first preference immunosuppressant agent to avoid allograft rejection in patients with organ transplantation. Cyclosporin A is also applied to treat some autoimmune diseases such as type I diabetes, psoriasis, systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis.⁵ In patients who use Cyclosporin A, hypertension is frequently observed and calcium antagonists such as nifedipine, diltiazem

and verapamil are commonly given to treat this condition. These drugs have been reported that they cause GE.⁶⁻⁸ Nifedipine is the most commonly used as calcium antagonist drug for the treatment of transplant patients with hypertension and at the same time it decreases Cyclosporin A -induced nephrotoxicity.⁹

GE can occur in the first 6 months after transplantation, and clinical appearance ranges from small variations in gingival papilla to total coverage of the dental crown, usually occurring in the vestibular face of the teeth.¹⁰ GE can cause impaired oral functioning, delayed and/or ectopic tooth eruption, speech difficulties, headache, and difficulty in maintaining oral hygiene, resulting in an increased tendency to infections, tooth decay, and periodontal disorders.¹¹ Impaired oral hygiene is a risk for the development of oral sepsis, which is potentially serious in immunocompromised patients.¹²

The most efficient treatment for drug-induced GE is withdrawing or replacing the medication.¹ The aim of this study is to increase insight into the prevalence of GE in patients who have undergone renal transplant using a meta-analysis.

METHODS

This systematic review and meta-analysis was designed and performed in accordance with the Meta-analysis Of Observational Studies in Epidemiology criteria¹³ for observational studies.

Data sources and search strategy

Both of the study investigators designed and conducted the search strategy. We systematically searched the PubMed database using the terms “renal transplant OR kidney transplant OR kidney allograft OR renal allograft” AND “gingival hyperplasia OR gingival hypertrophy OR gingival overgrowth OR oral manifestation OR oral lesion OR oral cavity OR gingival enlargement OR oral findings OR mucocutaneous manifestations OR oral mucosal lesion OR gingival status OR oral health OR gum hyperplasia OR gum hypertrophy OR gum overgrowth OR gum enlargement OR gingival changes OR gum changes OR gingival health” AND “pediatric OR children OR juvenile OR adolescent.” In addition, we manually screened reference lists of original and review articles. The final literature search was performed on February 15, 2018.

Study selection

Studies fulfilling the following criteria were included: (1) published as full-length articles in English, (2) case-control studies, cohort studies, or clinical trial cohort studies (prospective or retrospective, regardless of sample size and follow-up duration), (3) available data regarding post-transplantation drug regimen, sample size, and incidence of GE with specific drug regimen(s), and (4) included and reported data for children aged <18 years.

Studies meeting the following criteria were excluded: (1) abstracts, letters to the editor, reviews, and case reports, and (2) if there were < three studies evaluating and reporting the incidence of GE for a specific drug regimen.

All articles were screened first by title, then by abstract, and finally by full text according to the inclusion and exclusion criteria. Full texts were reviewed when the title or abstract met the selection criteria or when the status (include or exclude) could not be determined from the title and/or abstract alone.

Data extraction and quality evaluation

Data were extracted from all of the included articles by one author (NÖ), and another author independently reviewed the data for accuracy and completeness (GS). Discrepancies between the reviewers were resolved by consensus. The following data were extracted: study setting and design, name of the first author, year of publication, sample size, months of follow-

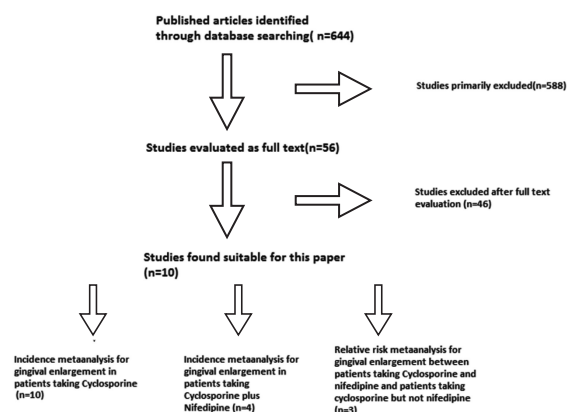


Figure 1. Flow chart of study selection process in the meta-analysis

up, mean age, adverse outcomes of interest (GE), and strategies for confirming GE cases. The quality of the included observational studies was evaluated using the Newcastle–Ottawa Scale¹⁴, and the quality of the included interventional studies was evaluated with the Methodological index for non-randomized studies (MINORS) scale¹⁵.

Outcomes assessed

The incidence rate was calculated by dividing the total number of new cases of GE by the total number of patients, and the proportion of patients with GE and 95% confidence intervals (CIs) were derived for each study. Our primary analysis focused on assessing GE incidence after exposure to immunosuppressive agents.

Statistical analysis

We calculated weighted summary estimates using generalized inverse variance with random-effects models as described by DerSimonian and Laird.¹⁶ Heterogeneity within groups was assessed with the I^2 statistic, which estimates the proportion of total variation across studies that is due to heterogeneity in study patients, design, or interventions rather than chance; I^2 values >50% suggest substantial heterogeneity. A probability level < 0.05 was considered statistically significant for all tests (except for heterogeneity). Heterogeneity was considered statistically significant when $P < 0.1$. All statistical analyses were performed using version 2 of the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ, USA). Publication bias was assessed by funnel plots, and all P values were 2-tailed. Potential publication bias was assessed by funnel plots and Egger regression asymmetry test.

Subgroup analyses

We investigated the reasons for heterogeneity on subgroup analyses when significant and substantial heterogeneity was detected between studies.

Table 1. Study characteristics and quality scores

Authors/Year	Study type	Treatment arms	Patients number	Mean Age	Gingival enlargement incidence	Gingival enlargement diagnosis/ Diagnoser	Prior drug history	Quality score
Ellis D. et al. ³⁸	Case control study	CsA+MinnesotaALG+prednisone+AZT	24	9.8	20/23	Not reported	≥15 months	5
Menni S. et al. ³⁹	Cross Sectional study	CsA± Prednisone± AZT	28	12.8	26/28	Not reported	≥1 months	5
Webb N.J.A. et al. ³⁵	Cross sectional study	CsA±AZT± MMF± Prednisolone± Sirolimus	33	13	4/33	Seymour system/ Dentist	≥6 months	6
Farge P. et al. ³⁶	Cross sectional study	CsA	106	9.6	44/106	Nunn grading/ Dentist	≥6 months	6
Silverstein D.M. et al. ³³	Interventional study	CsA+Nifedipine+ Prednisone+ AZT/MMF	24	14.8	22/24	Stable-Increased-Decreased/ Family report	≥6 months	9
Wondimu B. et al. ⁴⁰	Cross sectional study	CsA+ prednisolone±AZT	32	10	4/32	Sulcus probing depth ≥4mm without periodontal attachment loss →Positive / Dentist	≥12 months	6
Karpinia K.A. et al. ³¹	Cross sectional study	CsA	19	12.5	13/19	Present-Absent/ Dentist	≥1 months	5
		CsA+nifedipine	30		25/30			
Bökenkamp A. et al. ²⁹	Interventional study	CsA+ prednisone ±AZT	35	16	18/35	McGaw grading/ Dentist	≥12 months	14
		CsA+nifedipine+prednisone± AZT	52		46/52			
Elias D. et al. ³⁰	Cross sectional study	CsA+ prednisone+ AZT	25	14.3	19/25	Not reported	≥6 months	6
		CsA+ prednisone+ AZT+nifedipine	21		21/21			
Prokurat S. et al. ³²	Cross sectional study	CsA+ prednisone+ AZT/MMF	167	11.5	%28	Not reported	Not reported	4

RESULTS

Literature search results

A total of 644 records were identified according to the search strategy. Overall, 588 articles were excluded after removing duplicates, titles, and abstract screenings. We screened the full texts of the remaining 56 articles, and 10 studies met the inclusion criteria (Figure 1). We conducted 3 different analyses from these 10 studies: (1) we calculated GE incidence for patients treated with cyclosporine A with or without any other drugs; (2) we calculated GE incidence for patients treated with cyclosporine A along with nifedipine as

the main antihypertensive with or without any other drugs; and (3) we calculated odds ratios for GE outcome between patients taking cyclosporine with and without nifedipine.

Study Characteristics and quality

Table 1 shows the characteristics of patients and studies. The quality of the included observational studies was generally fair, with Newcastle–Ottawa Scale values between 5 and 6. Moreover, the quality of the included noncontrolled interventional studies was generally fair, with MINORS Scale values between 9 and 14.

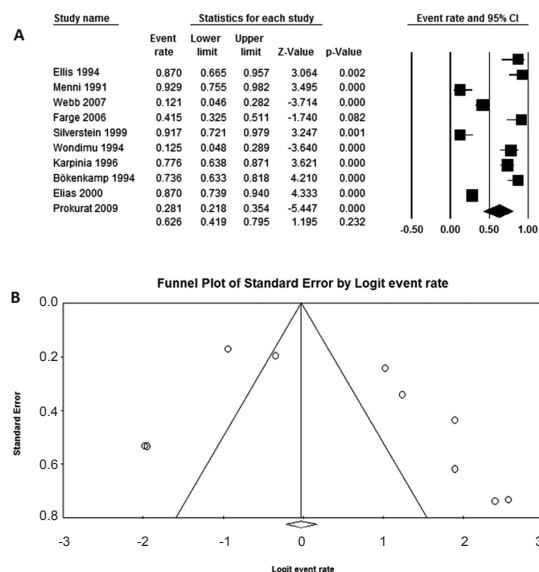


Figure 2. Forest (A) and funnel (B) plots of gingival enlargement incidence on meta-analysis in patients using cyclosporine A as the primary immunosuppressive treatment following renal transplant surgery

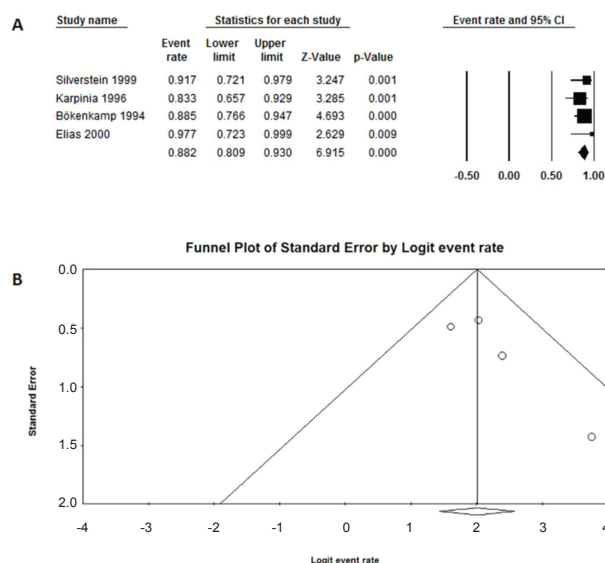


Figure 3. Forest (A) and funnel (B) plots of gingival enlargement incidence on meta-analysis in patients using cyclosporine A as the primary immunosuppressive along with nifedipine as antihypertensive treatment following renal transplant surgery

Gingival enlargement incidence in patients using cyclosporine as the primary post-transplant immunosuppressive

For this incidence analysis, patients who received cyclosporine as the primary post-transplant immunosuppressive were included regardless of whether any additional immunosuppressives or antihypertensives were used. A total of 595 patients from 10 trials were included in the analysis: GE was reported in 309 of 595 subjects with a pooled incidence of 62.6% (95% CI, 41.9%–79.5%, Figure 2A) with significant heterogeneity ($P < 0.001$; I^2

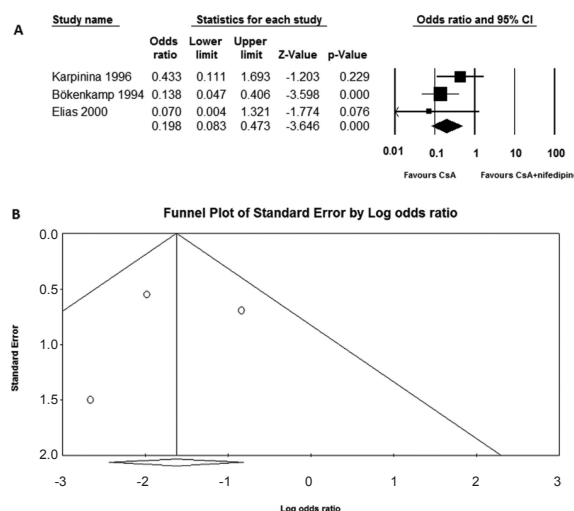


Figure 4. Forest (A) and funnel (B) plots of gingival enlargement risk in patients using cyclosporine A and nifedipine versus those using cyclosporine but not nifedipine following renal transplant surgery

= 93.6%). Funnel plot asymmetry was evident on visual inspection (Figure 2B), but the Egger regression test did not indicate a potential publication bias ($P = 0.19$).

Next, we conducted subgroup analysis to investigate the incidence of heterogeneity between studies. There was no significant difference in the interval between renal transplantation and gingival evaluation (≥ 6 months vs. < 6 months) ($P = 0.921$) between the subgroups, and there was also no significant difference between the subgroups based on GE diagnoser (dentist versus other/nonreported) ($P = 0.066$). However, subgroup analysis on GE diagnostic criteria (any defined enlargement scoring vs. not defined/not reported) revealed a significant difference between the 2 subgroups ($P = 0.029$), and well-defined diagnostic criteria or scoring system evoked less GE incidence reporting. This analysis reports the significant heterogeneity seen in the overall analysis.

Gingival enlargement incidence in patients using cyclosporine as the primary post-transplant immunosuppressive and nifedipine as the antihypertensive agent

For this incidence analysis, patients who received cyclosporine as the primary post-transplant immunosuppressive and nifedipine as an antihypertensive agent were included regardless of their use of any additional immunosuppressives or antihypertensives. We included a total of 127 patients from 4 trials in the analysis. GE was reported in 114 of 127 subjects with a pooled incidence of 88.2% (95% CI, 80.9%–93.0%, Figure 3A) with insignificant heterogeneity ($P = 0.485$; $I^2 = 0\%$). Symmetrical funnel plots were noted on visual inspection (Figure 3B), and potential publication bias was not indicated on the Egger regression test ($P = 0.146$).

Cyclosporine A without nifedipine versus cyclosporine A with nifedipine in terms of gingival enlargement

Meta-analysis results of the 3 studies revealed that cyclosporine A without nifedipine was associated with a significantly increased risk of GE incidence when compared to the combination of cyclosporine A with nifedipine (odds ratio: 0.198; 95% CI, 0.083–0.473; $P < 0.001$) (Figure 4A), with insignificant heterogeneity ($P = 0.336$; $I^2 = 8.2\%$). The funnel plot was symmetrical on visual inspection (Figure 4B), and the Egger regression test did not indicate a potential publication bias ($P = 0.853$).

DISCUSSION

When used logically, meta-analysis is a powerful method although its application includes many caveats. There is no doubt that meta-analysis is an important method in medical research, clinical practice, and public policy.¹⁷ The most important aim of a literature review may be planning the study for a subject, and the author may also learn new ideas from previous studies or mistakes. Thus, this information may be considered in preparing a new research article.¹⁸

This meta-analysis included 10 articles on the prevalence of drug-induced GE. The articles were evaluated for the risk of bias. The potential for publication bias was determined using funnel plots and Egger regression test. Potential publication bias was not found in studies that were analyzed using the three different methods.

A major limitation of our meta-analysis was that the evaluated studies had different study populations and samples, different diagnostic methods, and different types of drugs. Heterogeneity within groups was assessed with the I^2 statistic. No significant difference between subgroups was found based on the diagnostic method for GE.

The prevalence of GE mainly occurs due to use of cyclosporine A and/or nifedipine.¹⁹ The pathogenesis of drug-induced GE is not clear, but several mechanisms have been suggested. The clinical appearance and histological features of AGE due to phenytoin, cyclosporine, and calcium antagonists are significantly similar, although there are extensive differences in their corresponding chemical patterns. Thereby, some authors^{11,20,21} suggest that gingival alterations can be a result of metabolic biotransformation of the drug rather than the drug result itself. Metabolites of these drugs can be involved and behave in a similar manner.^{11,20,21} The prevalence of GE among users of cyclosporine A was reported to range from 20% to 45%. Calcium channel blockers were associated with exacerbation.^{22,23} In our meta-analysis, the prevalence estimates of

studies were between 12.1% and 100%, which may be explained by differences in the number of patients, incorrect assessment, and different local etiological situations. The combined use of cyclosporine A and nifedipine for treatment is firstly prescribed in approximately 60% of renal allograft recipients,²⁴ and although there are opposing opinions,²⁵ some authors have reported an increase in prevalence and/or severity of GE in transplant patients.^{24,26,27} A significant increase in the incidence of GE was identified in patients with renal transplants receiving nifedipine along with cyclosporine A compared with those using only cyclosporine A (51% vs. 8%).²⁶ Other reports have shown an increased prevalence and severity of GE in patients with renal transplants using both drugs. It was stated that local and pharmacological factors were not connected to enlargement and reported a trend for HLA-A19-positive patients with unexplainable findings of GE that are related to underlying genetic predisposition.²⁸ Another report by Slavin and Taylor²⁶ found that patients with renal transplants using both cyclosporine A and nifedipine had more severe GE than did patients using only cyclosporine A. Bökenkamp et al.²⁹ and Elias et al.³⁰ found that the incidence of GE was increased when nifedipine was added into the trio of drugs (cyclosporine A, prednisolone, and azithromycin). Bökenkamp et al.²⁹ also observed that GE was reduced after nifedipine withdrawal in addition to good oral hygiene with using chlorhexidine gel.

Karpinia et al.³¹ observed significantly higher degrees of GE in children treated with cyclosporine A and nifedipine than in those treated only with cyclosporine A. Similarly, in our meta-analysis, the prevalence of GE based on cyclosporine A was 62.6%. Among patients using cyclosporine A along with nifedipine, gingival growth prevalence was higher at 88.2%.

Prokurat et al.³² and Silverstein et al.³³ used similar drugs in their study. Silverstein et al.³³ also used nifedipine. With the use of nifedipine, the incidence of GE was higher than that reported by Prokurat et al.³²

Pizzo et al.³⁴ also reported that the simultaneous use of cyclosporine A and nifedipine in patients with renal transplants significantly increased the prevalence and severity of GE. They also suggested that this increase enabled that the combination of nifedipine potentiates the effects of cyclosporine A on gingiva.

As observed in Table 1, the prevalence of GE in the study by Elias et al.³⁰ was significantly higher than that in the other studies, whereas Webb et al reported the lowest prevalence of GE.³⁵ In addition, the cross-sectional studies were predominantly European studies reporting about GE. The studies from Poland and France had more patient numbers.^{32,36} According to the results of our analysis, there was no significant difference between subgroups based on the time interval between

renal transplantation and gingival evaluation (≥ 6 months vs. < 6 months) ($P = 0.921$). As seen in the study by Elias et al,³⁰ which also had the highest prevalence, prior drug history was considered to be > 6 months. However, in the study by Bökenkamp et al,²⁹ the prevalence was lower although the prior drug history was > 12 months and drug types were the same.

Children and adolescents are more frequently affected by drug-induced GE as compared to adults. Drugs effect to androgen and testosterone metabolism that was indicated as a remarkable factor in the pathogenesis of drug induced GE. In the same way, the excision of the tissue from nifedipine and cyclosporine-induced GE shows similar increase in androgen metabolism.³⁷ Hence, we preferred to research previous studies about transplantation in children.

CONCLUSION

In conclusion, drug-induced GE similarly appears in clinical practice, and its histological appearance is very similar to that seen in the present study. Further studies can help clarify the interactions between other drugs that cause GE. The incidence of GE will increase if using the aforementioned drugs; therefore, it is important for all dentists to know the effects of these drugs and their treatment options. Dental evaluation in a service would be helpful for children undergoing transplant. Increase in incidence and effectiveness of tooth brushing from a younger age would help avoid GE in children undergoing treatment with the aforementioned drugs. The incidence of periodontal disorders would also decrease in adulthood.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

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