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Gingival overgrowth in subjects under immunosuppressive regimens based on cyclosporine, tacrolimus, or sirolimus

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Abstract

Aim: To assess the prevalence and variables associated with gingival overgrowth (GO) in renal transplant recipients medicated with cyclosporine (CsA), tacrolimus (Tcr), or sirolimus (Sir).

Materials and Methods: One hundred and thirty-five eligible subjects were divided in CsA, Tcr, and Sir groups comprising 45 subjects each. GO was visually assessed and subjects were assigned as GO+ or GO − in a *post hoc* definition. Saliva samples were collected and the presence of periodontal pathogens was assessed through polymerase chain reaction. Variables of interest were compared between GO+ and GO − subjects through univariate and multivariate analysis.

Results: Prevalence of GO was of 60.0% for CsA, 28.9% for Tcr, and 15.6% for Sir groups. Within the CsA group, GO was associated with papillary bleeding index ($p = 0.001$); within the Tcr group, GO was associated with CsA previous use ($p = 0.013$), and calcium channel blockers (CCB) use ($p = 0.003$); within the Sir group, GO was associated with papillary bleeding index ($p = 0.018$), and CCB use ($p = 0.020$). A higher frequency of *Tannerella forsythia* was observed among GO+ subjects medicated with Tcr.

Conclusion: Pharmacological and periodontal variables were associated with GO in different immunosuppressive regimens. Integration between the medical and the dental team may be an important approach in the post-transplant maintenance routine.

Key words: cyclosporine; gingival overgrowth; immunosupressants; microbiology; renal transplantation; risk factors; sirolimus; tacrolimus

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Renal transplantation is the best therapeutic approach for most subjects with end-stage renal diseases. It has become a safe and routine procedure (Callaghan & Bradley 2006). The first decades of renal transplantation were characterized by the search for immunosuppressive agents directed towards reducing the incidence and the severity of acute rejection (Hariharan et al. 2000, Gourishankar et al. 2002, Callaghan & Bradley 2006). The introduction of the calcineurin inhibitors (CNIs) cyclosporine-A (CsA), in the early 1980s, and tacrolimus (Tcr), in the early 1990s, drastically decreased acute rejection rates. CNIs have turned into the fundamental base of immunosuppressive maintenance therapy since then. However, these agents presented significant nephrotoxicity over the time, leading to long-term deterioration characterized by chronic rejection of the irreversible form (Gourishankar & Halloran 2002, Gourishankar et al. 2002).

Currently, maintenance immunosuppressive therapies in renal transplantation focus on improving the long-term graft survival and reducing drug-related side effects (Gourishankar et al. 2002, Jorga & Johnston 2005). The use of

Conflict of interest and sources of funding statement

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sirolimus (Sir) and mycophenolate mofetil (MMF), new antiproliferative drugs, brought the expectation of lower nephrotoxic effects (Gourishankar et al. 2002, Ciancio et al. 2004, Jorga & Johnston 2005). Indeed, different protocols, comprising different drug combinations, have been tested in relation to outcomes of patient and graft survival in short and long terms (Gourishankar et al. 2002, Jorga & Johnston 2005, Callaghan & Bradley 2006).

Gingival overgrowth (GO) has been described as an important side effect of immunosuppressive regimens in renal transplant recipients. Different studies have shown that GO is commonly present in immunosuppressive regimens based on CsA, and that the use of adjunctive agents, such as prednisone, azathioprine, and calcium channel blockers (CCB), as well as gingival inflammation, appears to have an influence on the occurrence and severity of this event (Costa et al. 2006, 2007, Greenberg et al. 2008, Lima et al. 2008). Some studies that evaluated immunosuppressive agents based on Tcr failed to demonstrate GO within Tcr-based therapies (James et al. 2001, McKaig et al. 2002, Greenberg et al. 2008), while others demonstrated a lower prevalence and severity of GO when compared with CsA-based therapies (Costa et al. 2006, 2007, Lima et al. 2008). Gingival status of renal transplant recipients under Sir-based regimens has been recently assessed (Cota et al. 2008), and the occurrence of GO did not reach clinically significant thresholds. The influence of pharmacological and periodontal variables was also described in relation to immunosuppressive regimens based on Tcr (Costa et al. 2006, Cezário et al. 2008, Lima et al. 2008) and Sir (Cota et al. 2008).

There are scarce data related to comparisons of prevalence and severity of GO within different immunosuppressive regimens, as well as associated variables, in particular, the absence of studies including Sir-based maintenance regimens. Therefore, the purpose of the present study was to evaluate the prevalence and severity of GO among renal transplant recipients under immunosuppressive regimens based on CsA, Tcr, or Sir, as well as to investigate the effects of potential demographic, pharmacological, clinical, and microbiological periodontal variables associated with GO in this group of subjects.

Materials and Methods

Study design and sampling strategy

The present study used a cross-sectional design and involved a subset of renal transplant recipients under immunosuppressive maintenance therapies from Belo Horizonte City, Brazil. It was approved by the Federal University of Minas Gerais Research Ethics Committee (ETIC 514/05). All participants were informed of the goals of the study and provided a written informed consent before their participation in the study. Subjects' rights were protected at all times.

An eligible sample was selected and recruited from the organ transplant units of two public hospitals, where subjects were seen on a regular basis to monitor drug therapy and graft survival. During the period of data collection (from September 2007 to October 2008), patients meeting the inclusion criteria were invited to participate in the study according to the accessibility and availability of the subjects in the post-transplant maintenance routine.

In this approach, every eligible subject was examined and included in the study groups according to the main immunosuppressive agent. They were also assigned as controls (absence of GO = GO − subjects) or cases (presence of any degree of GO = GO+subjects) in a *post hoc* definition. Hence, a convenience sample of 135 subjects were formed and divided as the CsA group ($n = 45$), the Tcr group ($n = 45$), and the Sir group ($n = 45$).

The following inclusion criteria were adopted: (1) at least 2-month post-renal transplant period under an immunosuppressive therapy based on CsA, Tcr, or Sir as the main immunosuppressive agent; (2) 18 years of age or more at the time of examination; and (3) a minimum of six of the 12 most anterior teeth in the upper or lower dental arches. In addition, subjects were excluded if they were under combined therapies including CsA, Tcr, and Sir, if they were medicated with antibiotics 3 months before the examination, as well as current and former smokers. They were all from low socioeconomic status and multiethnic group. Ethnicity was not established due to the difficulty in determining race or ancestry based on physical appearance in a multiethnic population such as that of Brazil as reported previously (Parra et al. 2003).

Medical and pharmacological variables

Medical and pharmacological data were obtained from each subject's medical records. As part of long-term management, transplant recipients were screened regularly for whole blood and serum concentrations of the main immunosuppressive agent. Data from the most recent assessment, usually on the last medical examination (0–30 days, range of time between medical exam and study visit), were recorded. Gender, age, body weight, donor type, time since transplant, main immunosuppressive agent dosage and serum level, creatinine level, as well as the use of CCB, prednisone, azathioprine, and MMF were used in the analysis. Patients' medical records were thoroughly examined and data were confirmed (or updated when pertinent) by the organ transplant medical group.

Gingival assessments

After the examination of patients' medical records and after applying exclusion and inclusion criteria, subjects were scheduled for gingival evaluation. Examinations were performed at a separated room at the hospital units under proper lighting and infection control conditions. Prevalence and severity of gingival inflammation were assessed through the percent of papilla with bleeding upon stimulation and through papillary bleeding index (scores from 0 to 4) (Saxer & Mühlemann 1975), respectively. Oral hygiene status was assessed through plaque index (Silness & Löe 1964). This methodological approach was supported by cross-sectional studies that demonstrating that gingival bleeding has been a good indicator of the role of inflammation induced by bacterial plaque in GO severity (Costa et al. 2006, 2007, 2008, Cezário et al. 2008).

Gingival evaluation was performed by one trained and calibrated periodontist who was blinded to each patient's identity, medical history, and immunosuppressive regimen. Examiner calibration was performed at the beginning of the study and repeated 1 month later to determine intra-examiner reliability. For this purpose, papillary bleeding index and GO scores of 10 subjects were evaluated. All unweighted κ scores were >0.92 and intra-class correlation coefficients were >0.90.

The present study has assessed GO in the 12 most anterior teeth as described

previously and justified (Costa et al. 2006, 2007, 2008, Cezário et al. 2008). Briefly, upper and lower papilla related to the anterior teeth were evaluated through visual inspection in relation to horizontal and vertical enlargement. Scores between 0 and 5, depending on the sum of both horizontal (scores from 0 to 3) and vertical (scores from 0 to 2) enlargement, were assigned to each buccal and lingual papilla of the six most anterior upper and lower teeth. Likewise, according to the number of anterior teeth available on each dental arch, a total of 20 such papilla could be selected and examined. A potential maximum GO score of 100 could be assigned and expressed as percentage. Subjects with GO scores $\geqslant 30$ were classified as having clinically significant overgrowth as suggested previously (Thomason et al. 1993).

Table 1. Species-specific sense and antisene primers used in the saliva polymerase chain reaction (PCR) analysis

Bacteria	Primers	PCR products
Aggregatibacter actinomycetemcomitans	Sense 5′-AAACCCATCTCTGAGTTCTTCTTC-3′ Antisense 5′-ATGCCAACTTGACGTTAAAT-3′	550 bp
Porphyromonas gingivalis	Sense 5′-AGGCAGCTTGCCATACTGCGG-3′ Antisense 5′-ACTGTTAGCAACTACCGATGT-3′	404 bp
Parvimonas micra	Sense 5′-AGTGGGATAGCCGTTGGAAA-3′ Antisense 5′-GACGCGAGCCCTTCTTACAC-3′	328 bp
Treponema denticola	Sense 5′-TAATACCGAATGTGCTCATTTACAT-3′ Antisense 5′-TCAAAGAAGCATTCCCTCTTCTTCTTA-3′	316 bp
Tannerella forsythia	Sense 5′-GCGTATGTAACCTGCCCGCA-3′ Antisense 5′-TGCTTCAGTGTCAGTTATACCT-3′	641 bp

Sample collection and microbiological assessment

Detection of specific periodontal pathogens was realized in saliva samples. For each and every participant, samples of non-stimulated whole saliva were collected in sterile tubes, and immediately diluted in reduced Ringer's solution (Oxoid Ltd., Basingstoke, Hampshire, UK) (0.1 ml saliva/1 ml Ringer) and frozen (-20°C) (Cortelli et al. 2005b). For sample processing, suspensions were thawed and centrifuged at 12,000 *g* for 3 min., and DNA was extracted using a DNA isolation and purification kit (InstaGene Matrix – BioRad Laboratories, Hercules, CA, USA) following the manufacturer's instructions. Extraction process was confirmed through the amplification with universal primers. Subsequently, the presence of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Parvimonas micra*, *Treponema denticola*, and *Tannerella forsythia* was assessed by polymerase chain reaction (PCR) with species-specific primers (Invitrogen, Carlsbad, CA, USA) under standardized conditions (Cortelli et al. 2005a). Briefly, 5 μl of the sample DNA was added to 45 μl of the reaction mixture containing 5 μl of 10 $\times$ PCR buffer (Promega, Madison, WI, USA), 1.25 U of *Taq* DNA polymerase (Promega), and 0.2 mM of deoxyribonucleotide mixture (Pharmacia LKB, Piscataway, NJ, USA). Bacterium-specific primers used in the present study are described in Table 1.

After electrophoresis in 1.5% agarose gel, the DNA fragments were stained with 0.5 μg/ml ethidium bromide and visualized by UV 300 nm light illumination. Amplification products were compared with positive and negative controls.

Statistical analysis

Normality of the data were assessed through the Lilliefors test. At first, total sample (subjects altogether independently of the main immunosuppressive agent), and subsequently all immunosuppressive groups separately (CsA, Tcr, and Sir), were described in relation to variables of interest. The total sample and each of the immunosuppressive groups were divided according to the presence (GO+) and absence (GO $-$) of gingival overgrowth. GO+ and GO $-$ subjects within each immunosuppressive group were compared in relation to demographic, pharmacological, and periodontal variables, as well as the salivary frequency of periodontal pathogens, through appropriate tests.

Bivariate analysis included the Student *t*-test, Mann–Whitney test, and χ^2- test. One-way ANOVA was used to estimate the overall variance of parametric data, followed by the *post hoc* Tukey's test for pair-wise comparisons. The Kruskal–Wallis test was used to estimate the overall variance of non-parametric data, followed by the *post hoc* Dunn test for pair-wise comparisons. To avoid spurious significance among multiple comparisons, the Bonferroni correction was used. Therefore, *p*-values <0.017 were regarded as statistically significant test results in *post hoc* comparisons.

Multivariate analysis was performed through logistic regression. All corresponding variables for each regression analysis were selected to enter the model and retained if significant *p*-values were attained ($p<0.05$). First-order interactions among time since transplant and other pharmacological variables were also tested and retained in the models if significant. All collected data were analysed with statistical software (Statistical Package for Social Sciences, Version 16.0 for Windows – SPSS Inc., Chicago, IL, USA) and estimates were considered significant if $p<0.05$.

Results

Characteristics of the sample in relation to the presence and severity of GO are presented in Table 2. The number of GO+ subjects (presenting any score of GO) was 47 (34.8%) with a mean GO score of 16.88 ± 13.71, in the total sample. Out of the 47 GO+, 10 subjects (7.4%) were classified as presenting clinically significant GO (scores $\geqslant 30\%$). When GO was evaluated in each immunosuppressive group, the number of GO+ subjects was significantly different among them, being 27 (60.0%), 13

Table 2. Characteristics of total sample and immunosuppressive groups in relation with gingival overgrowth

Variables	GO+ subjects				p^*
	total sample $n = 135$	CsA group $n = 45$	Tcr group $n = 45$	Sir group $n = 45$	
Number of subjects	47 (34.8%)	27 (60.0%)	13 (28.9%)	7 (15.6%)	$<0.001^{\dagger}$
Number of subjects with GO scores					
From 1 to 10%	24 (17.8%)	13 (28.8%)	7 (15.5%)	6 (13.3%)	
From 11 to 20%	5 (3.7%)	2 (4.4%)	2 (4.4%)	1 (2.2%)	
From 21 to 29%	8 (5.9%)	8 (17.8%)	0 (0.0%)	0 (0.0%)	$0.048^{\dagger}$
$\geqslant$30% (clinically significant)	10 (7.4%)	6 (13.3%)	4 (8.9%)	0 (0.0)%	
Mean GO score (%)	16.88 ± 13.71 (2.00–52.00)	19.20 ± 13.95 (3.00–52.00)	17.08 ± 15.25 (2.00–44.00)	7.57 ± 2.44 (4.00–22.00)	$<0.001^{\ddagger}$
Mean GO score per papilla	0.84 ± 0.69 (0.10–2.60)	0.96 ± 0.70 (0.15–2.60)	0.85 ± 0.76 (0.10–2.20)	0.38 ± 0.12 (0.20–0.6)	$<0.001^{\ddagger}$
% of papilla affected by GO	34.31 ± 23.15 (5.00–95.00)	41.20 ± 24.25 (10.00–95.00)	30.77 ± 20.40 (5.00–80.00)	14.29 ± 4.50 (10.00–20.00)	$<0.001^{\ddagger}$

*Comparisons between CsA, Tcr, and Sir groups.
†χ^2-test.
‡Kruskal–Wallis test [groups differ through Dunn's test, after adjusting p-value using Bonferroni's correction ($\alpha < 0.05$) $p < 0.017$].
CsA, cyclosporine; Tcr, tacrolimus; Sir, sirolimus; GO, gingival overgrowth; mean ± SD (range) unless specified; percents in relation to the total number of subjects in the group.

(28.9%), and 7 (15.6%) in CsA, Tcr, and Sir groups, respectively (Table 2). The number of subjects classified as presenting clinically significant GO was significantly different among the groups, being 6 (13.3%) in CsA group, 4 (8.9%) in Tcr group, and 0 (0.0%) in Sir group. It can also be verified in Table 2 that the mean GO score was significantly different among the groups, being 19.20 (± 13.95), 17.08 (± 15.25), and 7.57 (± 2.44) in CsA, Tcr, and Sir groups, respectively.

Demographic, pharmacological, and periodontal variables of subjects in the total sample, divided according to the presence/absence of GO, are detailed in Table 3. GO+ subjects, independently of the immunosuppressive regimen, presented higher body weight ($p = 0.045$), higher time since transplant ($p < 0.001$), higher dosages of prednisone ($p = 0.001$), azathioprine ($p = 0.008$), lower dosages of MMF ($p = 0.042$), higher frequency of concomitant CCB use ($p < 0.001$), higher papillary bleeding index ($p < 0.001$), and higher percent of papilla with bleeding upon stimulation ($p < 0.001$).

In the same manner of the univariate analysis for the total sample, demographic, pharmacological, and periodontal variables of interest [gender, age, body weight, donor type, time since transplant, daily dosage and serum level of the main immunosuppressive agent, daily dosages of prednisone, azathioprine, and MMF, creatinine level, concomitant CCB use, CsA previous use (for Tcr group), CNI previous use (for Sir group), plaque index, papillary bleeding index, and percent of papilla with bleeding upon stimulation] were tested for CsA, Tcr, and Sir groups, with subjects divided according to the presence/absence of GO. Statistically significant variables for these analyses are shown in Table 4. GO+ subjects medicated with CsA presented higher frequency of concomitant CCB use ($p = 0.001$), higher papillary bleeding index ($p < 0.001$), and a higher percent of papilla with bleeding upon stimulation ($p < 0.001$). GO+ subjects medicated with Tcr presented higher frequency of concomitant CCB use ($p < 0.001$), higher frequency of CsA previous use ($p = 0.009$), higher papillary bleeding index ($p = 0.008$), and higher percent of papilla with bleeding upon stimulation ($p < 0.001$). GO+ subjects medicated with Sir presented higher frequency of concomitant CCB use ($p = 0.016$), higher frequency of CNI previous use ($p < 0.001$), higher papillary bleeding index ($p = 0.027$), and higher percent of papilla with bleeding upon stimulation ($p = 0.006$) (Table 4).

Characterization of the sample in relation to the salivary frequency of periodontal pathogens is presented in Table 5. GO+ subjects showed a higher frequency of *T. forsythia* ($p = 0.040$) when evaluated in the total sample, and a higher frequency of *T. forsythia* ($p = 0.020$) within Tcr group. No difference was observed in relation to any of the other evaluated pathogens in any of the immunosuppressive groups.

Table 6 shows the multivariate logistic regression final models for GO occurrence. The occurrence of GO in the total sample was associated with the percent of papilla with bleeding upon stimulation (OR = 1.05; $p < 0.001$), and to the concomitant CCB use (OR = 7.99; $p < 0.001$). For subjects medicated with CsA, the occurrence of GO was associated with the papillary bleeding index (OR = 359.8; $p = 0.001$). For subjects medicated with Tcr, the occurrence of GO was associated with the CsA previous use (OR = 18.27; $p = 0.013$), and the concomitant CCB use (OR = 29.70; $p = 0.003$). For subjects medicated with Sir, the occurrence of Go was associated with the percent of papilla with bleeding upon stimulation (OR = 1.06; $p = 0.018$), and the concomitant CCB use (OR = 12.51; $p = 0.020$).

Discussion

Studies having evaluated the occurrence of GO among renal recipients, independently of the immunosuppressive regimen, reported an overall prevalence rate of 47.0% (Lima et al. 2008) and 34.0% (Greenberg et al. 2008). Findings from the present study showed an overall prevalence rate of GO of 34.8%.

When GO was evaluated within specific drug regimens, different authors reported higher prevalence rates for subjects medicated with CsA when compared with those medicated with Tcr (Ellis et al. 2004, Costa et al.

Table 3. Characteristics of the sample in relation to demographic, pharmacological, and periodontal variables of interest, according to the presence/absence of gingival overgrowth

Variables	Total sample ($n = 135$)	GO+ subjects ($n = 47$)	GO − subjects ($n = 88$)	p*
Male (*n*)	79 (58.5%)	30 (63.8%)	49 (55.7%)	
Female (*n*)	56 (41.5%)	17 (36.2%)	39 (44.3%)	0.360†
Age	42.89 ± 10.75	42.64 ± 9.94	43.02 ± 11.21	
(years)	(18–70)	(24–63)	(18–70)	0.844‡
Body weight	65.39 ± 15.14	68.96 ± 17.21	63.49 ± 13.64	
(kg)	(42.50–120.00)	(44.00–120.00)	(42.50–108.00)	0.045§
Donor type				
Living donor	78 (57.8%)	26 (55.3%)	52 (59.1%)	
Cadaver	57 (42.2%)	21 (44.7%)	36 (40.9%)	0.673†
Main immunosuppressive agent				
Cyclosporine (CsA)	45 (33.33%)	27 (57.4%)	18 (20.5%)	NA
Tacrolimus (Tcr)	45 (33.33%)	13 (27.7%)	32 (36.4%)	
Sirolimus (Sir)	45 (33.33%)	7 (14.9%)	38 (43.2%)	
Time since transplant	62.46 ± 51.10	85.72 ± 51.62	50.03 ± 46.52	
(months)	(4.00–237.00)	(4.00–237.00)	(4.00–186.00)	< 0.001§
Daily dosage of prednisone	5.34 ± 4.46	7.03 ± 4.59	4.43 ± 4.13	
(mg)	(0.00–20.00)	(0.00–20.00)	(0.00–20.00)	0.001§
Daily dosage of azathioprine	15.00 ± 40.33	29.79 ± 53.12	7.10 ± 28.85	
(mg)	(0.00–250.00)	(0.00–250.00)	(0.00–175.00)	0.008§
Daily dosage of micofenolate	756.22 ± 562.90	605.11 ± 685.06	836.93 ± 470.07	
(mg)	(0.00–2000.00)	(0.00–2000.00)	(0.00–2000.00)	0.042§
Creatinine level	1.66 ± 0.89	1.54 ± 0.58	1.72 ± 1.02	
(mg/dl)	(0.60–6.00)	(0.66–4.70)	(0.60–6.00)	0.190§
Concomitant CCB use	47 (34.8%)	31 (66.0%)	16 (18.2%)	< 0.001†
Plaque score	1.40 ± 0.73	1.56 ± 0.68	1.31 ± 0.74	
	(0.08–3.00)	(0.37–3.00)	(0.08–3.00)	0.058§
Papillary bleeding index	0.20 ± 0.25	0.38 ± 0.26	0.11 ± 0.19	
	(0.00–1.05)	(0.00–1.05)	(0.00–1.00)	< 0.001§
% papilla with bleeding upon stimulation	27.75 ± 31.27	51.90 ± 31.57	14.85 ± 22.28	
	(0.00–100.00)	(0.00–100.00)	(0.00–100.00)	< 0.001§

*Comparisons between GO+ and GO − subjects.
†χ^2-test.
‡Student's *t*-test.
§Mann–Whitney test.
GO, gingival overgrowth; CCB, calcium channel blockers; NA, not applicable; mean ± SD (range) unless specified.

2006, Gong et al. 2008a, b, Greenberg et al. 2008, Lima et al. 2008). Indeed, prevalence rates of GO within CsA regimens have been reported to vary in the literature from 15 to 80% (AAP 2004, Costa et al. 2006, 2007, Gong et al. 2008a, b, Greenberg et al. 2008, Lima et al. 2008) and within Tcr regimens from 0 to 30% (McKaig et al. 2002, Ellis et al. 2004, Costa et al. 2006, 2007, Cezário et al. 2008). Findings from the present study also demonstrated a higher occurrence of GO among subjects under CsA regimens when compared with Tcr. Comparisons among regimens based on CsA, Tcr, and Sir have not been identified previously in the literature. When evaluating the occurrence of GO among subjects medicated with Sir, the present study showed a lower occurrence of GO when comparing with CsA or Tcr. This occurrence was similar to a previous study (Cota et al. 2008) that reported a prevalence rate of 20.8%.

It has been suggested that variations in GO prevalence rates can be related to the immunosuppressive regimen, to the daily dosage of the main immunosuppressive agent, to time since transplant, and to different combinations of auxiliary drugs within the immunosuppressive regimen (Seymour et al. 2000, Ellis et al. 2004, Costa et al. 2006, Cezário et al. 2008, Cota et al. 2008, Greenberg et al. 2008). Certainly, when evaluating immunosuppressive regimen-related GO, as an alternative to pure immunosuppressant-induced GO, the assessment of pharmacological variables is crucial.

The association of some pharmacological variables and the occurrence of GO have shown some controversy (Seymour et al. 2000). Dosage and serum level of the main immunosuppressive agent appeared to be poor predictors for gingival alterations (Seymour & Jacobs 1992, Seymour et al. 2000, Costa et al. 2006, Cezário et al. 2008) and the pharmacokinetic profile of the drugs has been discussed (Wondimu et al. 1996, Seymour et al. 2000). However, some significant associations were reported (Ellis et al. 2004, Cota et al. 2008, Greenberg et al. 2008). The occurrence of GO in the present study showed no association with dosage and serum level of any main immunosuppressive agent.

Some authors have demonstrated that the use of adjunctive agents in immunosuppressive therapies, such as prednisone and azathioprine, can influence GO (AAP 2004, Thomason et al. 2005, Costa et al. 2006, Cezário et al. 2008). These auxiliary agents have anti-inflammatory properties and also contribute to the use of lower dosages of the main immunosuppressive agent. In this manner, they appeared to have a protective effect in the occurrence and severity of GO (Seymour et al. 2000). The bivariate analysis showed that these variables were associated with GO in the

Table 4. Significant demographic, pharmacological, and periodontal variables for immunosuppressive groups, according to the presence/absence of gingival overgrowth

Variables	Total sample	GO+ subjects	GO − subjects	p^*
CsA group	$n = 45$	$n = 27$	$n = 18$	
Concomitant use of CCB	23 (51.1%)	18 (66.7%)	5 (27.8%)	0.011†
Papillary bleeding index	0.31 ± 0.30	0.44 ± 0.30	0.10 ± 0.18	
	(0.00–1.05)	(0.00–1.05)	(0.00–0.55)	<0.001‡
% Papilla with bleeding upon stimulation	39.47 ± 36.37	55.90 ± 34.74	14.84 ± 22.49	
	(0.00–100.00)	(0.00–100.00)	(0.00–70.00)	<0.001‡
Tcr group	$n = 45$	$n = 13$	$n = 32$	
Concomitant use of CCB	14 (31.1%)	9 (69.2%)	5 (15.6%)	<0.001†
CsA previous use	12 (26.7%)	7 (53.8%)	5 (15.6%)	0.009†
Papillary bleeding index	0.19 ± 0.24	0.33 ± 0.22	0.13 ± 0.23	
	(0.00–1.00)	(0.00–0.80)	(0.00–1.00)	<0.001‡
% Papilla with bleeding upon stimulation	26.57 ± 30.60	51.54 ± 30.23	16.42 ± 24.64	
	(0.00–100.00)	(0.00–100.00)	(0.00–100.00)	<0.001‡
Sir group	$n = 45$	$n = 7$	$n = 38$	
Concomitant use of CCB	10 (22.2%)	4 (57.1%)	6 (15.8%)	0.016†
CNI previous use	14 (31.1%)	5 (71.4%)	9 (23.7%)	<0.001†
Papillary bleeding index	0.12 ± 0.17	0.24 ± 0.07	0.09 ± 0.17	
	(0.00–0.93)	(0.15–0.30)	(0.00–0.93)	<0.001‡
% Papilla with bleeding upon stimulation	17.20 ± 21.56	37.14 ± 16.04	13.52 ± 20.53	
	(0.00–100.00)	(20.00–60.00)	(0.00–100.00)	<0.001‡

*Comparisons between GO+ and GO − subjects.
†χ^2-test.
‡Kruskal–Wallis test [GO+ and GO − subjects differ through Dunn's test, after adjusting p-value using Bonferroni's correction ($\alpha < 0.05$) $p < 0.017$].
GO, gingival overgrowth; CsA, cyclosporine; Tcr, tacrolimus; Sir, sirolimus; CCB, calcium channel blockers; CNI, calcineurin inhibitors; mean ± SD (range) unless specified.

Table 5. Salivary frequency of periodontal pathogens in the total sample, according to the presence/absence of gingival overgrowth

Periodontal pathogens	Total sample	GO+ subjects	GO − subjects	p^*
Total sample	$n = 135$	$n = 47$	$n = 88$	
Aa	1 (0.7%)	1 (2.1%)	0 (0.00%)	0.170
Pg	52 (38.5%)	22 (46.8%)	30 (34.1%)	0.148
Pm	64 (47.4%)	27 (57.4%)	37 (42.0%)	0.088
Td	62 (45.9%)	26 (55.3%)	36 (40.9%)	0.109
Tf	91 (67.4%)	37 (78.7%)	54 (61.4%)	**0.040**
CsA group	$n = 45$	$n = 27$	$n = 18$	
Aa	1 (2.2%)	1 (3.7%)	0 (00.0%)	0.409
Pg	19 (42.2%)	13 (48.1%)	6 (33.3%)	0.324
Pm	27 (60.0%)	18 (66.7%)	9 (50.0%)	0.264
Td	21 (46.7%)	13 (48.1%)	8 (44.4%)	0.807
Tf	30 (66.7%)	20 (74.1%)	10 (55.6%)	0.197
Tcr group	$n = 45$	$n = 13$	$n = 32$	
Aa	0 (0.00%)	0 (0.00%)	0 (0.00%)	NA
Pg	14 (31.1%)	6 (46.2%)	8 (25.00%)	0.165
Pm	17 (37.8%)	6 (46.2%)	11 (34.4%)	0.460
Td	18 (40.0%)	8 (61.5%)	10 (31.2%)	0.060
Tf	26 (57.8%)	11 (84.6%)	15 (46.9%)	**0.020**
Sir group	$n = 45$	$n = 7$	$n = 38$	
Aa	0 (0.00%)	0 (0.00%)	0 (0.00%)	NA
Pg	19 (42.2%)	3 (42.9%)	16 (42.1%)	0.970
Pm	20 (44.4%)	3 (42.9%)	17 (44.7%)	0.927
Td	23 (51.1%)	5 (71.4%)	18 (47.4%)	0.242
Tf	35 (77.8%)	6 (85.7%)	29 (76.3%)	0.583

*Comparisons between GO+ and GO − subjects: χ^2-test.
Significant p values are shown in bold.
GO, gingival overgrowth; Aa, *Aggregatibacter actinomycetemcomitans*; Pg, *Porphyromonas gingivalis*; Pm, *Parvimonas micra*; Td, *Treponema denticola*; Tf, *Tannerella forsythia*; CsA, cyclosporine; Tcr, tacrolimus; Sir, sirolimus; NA, not applicable.

total sample. However, no association between GO and prednisone or azathioprine use was verified in any of the multivariate final models. Similarly, the antiproliferative agent MMF, used as an adjunctive drug in some regimens, showed an association with GO in the bivariated analysis for total sample, but was not retained in the multivariate final models. It is important to notice that previous evaluations of MMF effects on GO in Sir-based immunosuppressive regimens also showed no significant associations (Cota et al. 2008).

An important pharmacological variable associated to GO in Tcr regimens was the previous exposure to CsA regimens, in accordance with previous reports (Ellis et al. 2004, Costa et al. 2006). It could be speculated that GO observed in subjects under Tcr-based regimens exposed previously to CsA could be a result of some residual effect of CsA.

Our findings showed a strong association between the concomitant use of CCB and the occurrence of GO, for all regimens evaluated. The use of CCB presented a great influence on the occurrence and severity of GO according to different authors (James et al. 2000, Ellis et al. 2004, Thomason et al. 2005, Costa et al. 2006, 2008). This fact appeared to be reinforced by studies suggesting that GO in regimens based on CsA (Greenberg et al. 2008) or Tcr (McKaig et al. 2002, Spolidorio et al. 2006, Greenberg et al. 2008) only occurred in the presence of CCB. Indeed, CCB have been implicated as independent causative agents for GO (Ellis et al. 1999, AAP 2004, Güncü et al. 2007).

Studies attempting to discriminate a pure immunosuppressant-induced GO

Table 6. Multivariate final models (logistic regression) for gingival overgrowth occurrence in the total sample and CsA, Tcr, and Sir immunosuppressive groups

Variables	Coefficient	95% confidence interval	Adjusted odds ratio (OR)	*p*
Total sample (pseudo $R^2 = 0.3794$)				
Constant	− 2.841	− 3.734 to − 1.948	–	–
% Papilla with bleeding upon stimulation	0.045	0.027 to 0.063	1.05	<0.001
Concomitant CCB use	2.079	1.106 to 3.052	7.99	<0.001
CsA group (pseudo $R^2 = 0.2910$)				
Constant	− 0.999	− 1.971 to − 0.028	–	–
Papillary bleeding index	5.886	2.276 to 9.496	359.8	0.001
Tcr group (pseudo $R^2 = 0.3873$)				
Constant	− 3.314	− 5.340 to − 1.288	–	–
CsA previous use	2.905	0.603 to 5.207	18.27	0.013
Concomitant CCB use	3.391	1.145 to 5.638	29.70	0.003
Sir group (pseudo $R^2 = 0.3165$)				
Constant	− 3.951	− 6.163 to 1.739	–	–
% Papilla with bleeding upon stimulation	0.054	0.009 to 0.099	1.06	0.018
Concomitant CCB use	2.527	0.400 to 4.654	12.51	0.020

GO, gingival overgrowth; CsA, cyclosporine; Tcr, tacrolimus; Sir, sirolimus; CCB, calcium channel blockers.

should consider excluding CCB-medicated subjects, as well as those previously using CNIs in Tcr- and Sir-based regimens. Sample size in the present study does not allow a further analysis of isolate effects of the currently main immunosuppressive agent. Thus, it can be considered a limitation. However, GO was described in the entire scenario of immunosuppressive therapies and variables were controlled in the multivariate analysis.

Some periodontal variables were reported to exacerbate the occurrence of GO, independently of the immunosuppressive regimen (Seymour et al. 2000). An association between poor plaque control and GO was suggested previously (Thomason et al. 1993, Ellis et al. 1999, Vescovi et al. 2005), although contradictory reports were also published (Wondimu et al. 1996, Romito et al. 2004, Costa et al. 2007). The lack of association between plaque scores and GO could be due to the low sensitivity of plaque measurements (Costa et al. 2007).

Indeed, the important role of dental biofilm as an aetiological co-factor for drug-induced GO appeared in the last classification of periodontal diseases (AAP 2004) and was emphasized in a recent study (Greenberg et al. 2008). Moreover, a strong association between plaque-induced inflammation and the occurrence of GO was supported by different studies (Costa et al. 2006, 2007, 2008, Cezário et al. 2008). In the present study, gingival inflammation, represented by the papillary bleeding index and the percent of papilla with bleeding upon stimulation, was confirmed as an important variable associated with GO among renal transplant recipients.

An inflammatory response induced by an altered microflora was suggested as a potential mechanism for GO (Fischer et al. 1996). The validity of plaque index as a tool for analysing the association between plaque and GO has been questioned (King et al. 1993, Romito et al. 2004), because the quality and not only the quantity of the microbiota can be related to the occurrence of GO. In fact, the microbiological profile of GO+ subjects has been poorly investigated.

Few studies investigated the oral microbiota of GO+ and GO − subjects and the results are varied (Romito et al. 2004, Saraiva et al. 2006, Spolidorio et al. 2006, Gong et al. 2008a, b). It was reported that the frequency of *Streptococcus* β-haemolytic was higher among GO − subjects (Saraiva et al. 2006), and that the frequency of *P. micra* (formerly *Micromomas micros*) was higher among GO+ subjects (Romito et al. 2004). A higher frequency of *P. gingivalis*, *T. denticola*, and *T. forsythia* was also reported for GO+ subjects (Gong et al. 2008a, b). GO+ subjects in the present study showed a higher frequency of *T. forsythia*, especially those medicated with Tcr, corroborating previous findings. It is important to observe that studies presented different methods of sample collection and analysis. This fact could have lead to some divergences.

In the present study, detection of specific periodontal pathogens was realized in saliva samples, for the reason that it is a non-invasive and appropriate method for population-based studies operating PCR (Könönen et al. 2007). This non-invasive attribute of sample collection is of particular interest for more vulnerable populations as the one in the present study, determined to be a high-risk group for oral diseases (Spolidorio et al. 2006). The use of saliva sample as an efficient and useful method for the identification of periodontal pathogens has been advocated by some authors, and positive correlations between salivary and subgingival samples have been reported (Umeda et al. 1998, Testa et al. 1999, Cortelli et al. 2005b).

However, it is important to highlight that bacterial species can present different patterns of salivary occurrence, according to specific characteristics of the population under investigation (Könönen et al. 2007). Besides, salivary samples are representative of subgingival samples in immunocompetent subjects, in a study evaluating a group of heart transplant recipients the occurrence of some periodontal pathogens differed between these two sites (Romito et al. 2004). Studies comprising renal transplant recipients under diverse immunosuppressive regimens are essential to the evaluation of bacterial occurrence patterns in different oral sites.

Conclusions

The prevalence and severity of GO were higher within immunosuppressive regimens based on CsA when compared with regimens based on Tcr and Sir, and higher within immunosuppressive regimens based on Tcr when compared with those based on Sir. The concomitant use of CCB and gingival inflammation were variables strongly associated with

GO among renal transplant recipients under immunosuppressive maintenance regimens. Previous exposure to CsA regimens was also an important variable associated to GO in Tcr-based regimens. The presence of specific periodontal pathogens seemed to be associated with GO, especially in immunosuppressive regimens based on Tcr. The adequate preventive and therapeutic management of periodontal conditions within this group of post-transplant subjects may improve gingival status and quality of life.

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Clinical Relevance

Scientific rationale for the study: There is a lack of studies comparing GO and its associated variables in post-transplant immunosuppressive regimens based on CsA, Tcr, and Sir. *Principal findings*: Overall prevalence of GO was of 34.8%. Prevalence and severity of GO was higher in regimens based on CsA (60.0%) when compared with Tcr (28.9%) and Sir (15.6%). Concomitant use of CCB and gingival bleeding as strongly associated to GO among renal transplant recipients under different immunosuppressive regimens. *Practical implications*: Integration between medical and dental team in the post-transplant maintenance is important because gingival bleeding is an important variable associated to GO.