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ORIGINAL ARTICLE

Oral manifestations of allograft recipients immediately before and after kidney transplantation

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ABSTRACT

Objective: To identify the oral lesions of individuals with kidney disease immediately before and shortly after kidney transplantation, taking into account the immunosuppressive regimen, antiviral prophylaxis and type of transplantation.

Methods: A prospective observational cohort study was carried from January 2017 to January 2018. Eighty individuals aged 18 years or older who were admitted for kidney transplantation were eligible to participate. Clinical data regarding medical history, immunosuppressive therapy, antiviral prophylaxis, laboratorial data and oral examination were performed by the same trained researcher, in three different moments: 24 hours before transplantation (1st time point), 15–20 days (2nd time point) and 45–60 days (3rd time point) after transplantation.

Results: In the first, second and third time points, it was found that 3.7% (3/80), 23.7% (18/76) and 25.7% (19/74) of the participants showed oral soft tissue lesions. Ulcers and candidiasis were the most frequent oral lesions, and they were associated with the use of everolimus ($p = .005$) and azathioprine ($p = .034$), respectively. Less patients reported xerostomia after transplantation than before ($p < .001$).

Conclusions: Oral lesions are common in the short term after renal transplantation and are particularly related to both toxicities of immunosuppressive drugs and immunosuppression.

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Kidney transplantation; oral lesions; immunosuppressive agents; candidiasis; stomatitis

Introduction

Kidney transplantation is the preferred treatment for end-stage renal disease. Despite the improvements of immunosuppressive strategies, occurred in the last years, numerous complications have still been reported since the first renal transplantation in 1954. These complications are classified as pathological or surgical. Most pathological complications include rejection, infection and cardiovascular events, whereas surgical complications mainly involve vascular and urological problems [1].

Among the pathological complications, according to the literature, oral lesions are mainly related to drug-induced immunosuppression [2]. The prevalence of oral lesions in renal recipients varies from 28% to 60% and different types of lesions have been described depending on where the study was conducted, immunosuppressive regimen used and time elapsed since transplantation [3–11]. The majority of studies evaluated oral lesions after more than 6 months after transplantation. At this stage the patient is clinically stable and on maintenance immunosuppressive therapy [2,6,7]. The mainly oral lesions described in these studies include gingival overgrowth, ranging from 3.2% to 74.1% [2–6]; candidiasis, ranging from 2.2% to 33.1% [2,4–11]; oral HSV lesions, ranging from 2% to 7.8% [2,6–8,12]; hairy leukoplakia, ranging from 5.3% to 12.2% [2,5,7]; oral warts, ranging from 3% to 7% [7]; and oral ulcers, which affects around 2.5% of the renal transplant recipients (RTRs) [6,7].

We have found no cohort study in the literature assessing oral lesions in the short term after renal transplantation. In this context, and considering that advanced immunosuppressive and prophylactic therapeutic regimens have been recently introduced [1,7], the aim of this study is to identify the oral lesions of individuals with kidney disease immediately before and shortly after kidney transplantation (after 15–20 days and then after 45–60 days), taking into account the immunosuppressive regimen, antiviral prophylaxis and type of transplantation.

Materials and methods

We performed a prospective observational cohort study, between January 2017 and January 2018, in two kidney transplant centres in Brazil. Individuals aged 18 years or older who were admitted for kidney transplantation were eligible

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to participate. Exclusion criteria included multiple organ transplantation and previous renal transplant. The study was approved by the institutional review boards of the participating clinical centres, and all participants provided written informed consent.

Data collection was performed through face-to-face interview, medical record abstraction, and physical and laboratory examination. Complete blood count (CBC) were obtained at the same day of physical examination, in three consecutive periods of time as follows: up to 24 hours before transplantation (1st time point), 15–20 days (2nd time point) and 45–60 days after renal transplantation (3rd time point). Figure 1 illustrates the flow of participants through the study.

All participants in this research who underwent living donor transplantation were admitted to the hospital 24 hours before the surgery. As soon as they were admitted, the nursing staff informed the researcher (DS), who went to the hospital, applied the informed consent form and started collecting all research data. Patients receiving deceased donor kidney were called by the hospital up to 2 hours before transplantation. In this case, the nursing staff notified the researcher, who immediately went to the hospital to include the patient in the research. All included patients were re-evaluated by the same researcher at the 2nd and 3rd time points.

Oral physical examination was carried out in a consulting room by using mouth mirrors and portable light source, with the patient sitting on a chair with the head slightly tilted back or lying on a bed. All participants were examined for presence of oral lesions, and a presumptive diagnosis was established according to clinically accepted criteria [13]. The final diagnoses were established based on clinical characteristics and PCR confirmation for HSV. Evaluation of xerostomia was performed by asking the patient to answer two objective questions (i.e. yes or no): 1. Do you feel dry mouth along the day? 2. Do you feel dry mouth during meals? Two positive responses indicated xerostomia.

McNemar's statistical test was used to compare the prevalence of oral lesions during the observation period and Fisher's exact or χ^2 test to analyze for immunosuppressive drugs or removable denture with presence of oral lesions. Student's *t*-test was used to compare age between patients with or without lesion. The resulting data were analyzed by using the SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). All tests were performed considering a significance level of 0.05.

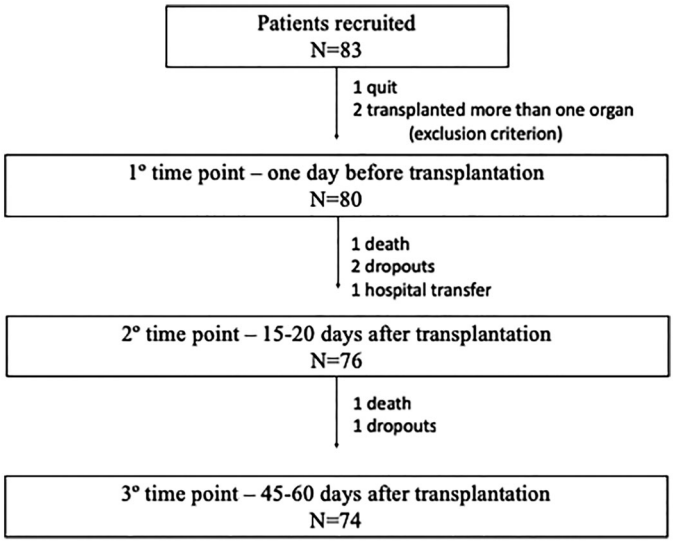

Figure 1. Flowchart of the study.

Results

Eighty eligible participants were evaluated in the 1st time point, 76 were evaluated in the 2nd time point (because one died, one was transferred to another hospital and two quit the study), and 74 patients were evaluated in the 3rd time point (because one quit the study and another died). The mean waiting time for kidney transplantation was 38.3 ± 36.9 months, ranging from 1 to 180 months. Table 1 summarizes demographic and baseline data of the participants.

All patients underwent induced immunosuppression treatment with polyclonal antibodies at the time of transplantation, and soon after the surgery they started receiving immunosuppressive drugs (Table 2). In addition to the immunosuppressive regimen, all participants received antibiotic prophylaxis with cefazolin before transplantation and Bactrim (sulphamethoxazole + trimethoprim, 400 mg/80 mg per day) immediately after it for pneumonia prophylaxis. Nine patients (9/80, 11.3%) received IV ganciclovir for prophylaxis of cytomegalovirus. Most patients (74/80, 92.5%)

Table 1. Demographic and baseline data.

Variable	*N* = 80	100%
Age	43.2 + 11.6	
Gender		
Male	43	53.8
Female	37	46.3
Race		
Caucasian	31	38.8
African	21	26.3
Mixed race	28	35.0
Smoking habit		
Present	4	5.0
Absent	55	68.7
Past	21	26.3
Removable denture		
Total	10	12.5
Partial	10	12.5
No use	60	75.0
Dialysis		
Hemodialysis	71	88.7
Peritoneal	3	3.7
Absent	6	7.6
Donor		
Living	45	56.3
Deceased	35	43.7
Underlying disease		
Hypertension	23	28.7
Diabetes Mellitus	11	13.7
Polycystic kidneys	6	7.5
Systemic lupus	2	2.5
Alport's Syndrome	2	2.5
Hydronephrosis	1	1.3
IgA Nephropathy	4	5.0
Focal segmental glomerulosclerosis	6	7.5
Unique kidney	2	2.5
Congenital defect of urethra	2	2.5
Recurrent urinary tract infection	1	1.3
Renal calculus	3	3.7
Glomerulonephritis	5	6.3
Undetermined	12	15.0

used gastroprotective drugs, 35 subjects (35/80, 47.7%) used antihypertensive drugs, 9 (9/80, 11.2%) used oral antihyperglycemic agents, 4 (4/80, 5%) were taking benzodiazepines. All of these medications were used by participants before and after kidney transplantation

The frequency of oral lesions increased along the study. Before transplantation, in the 1st time point, 3.8% (3/80) of the patients presented at least one oral soft tissue lesion, such as candidiasis, herpes labialis and leukoplakia, whereas 28/80 (35%) reported xerostomia. In the 2nd time point, 23.7% (18/76) of the patients presented oral lesions, and 10.7% (8/75) reported xerostomia. In the 3rd time point, the prevalence of soft tissue oral lesions was 25.7% (19/74), and 8.2% (6/73) of the participants reporting xerostomia. The number of people with oral lesions in the second and third evaluations was significantly higher than in the first one ($p < .001$). But there was no statistical significant difference between number of participants with oral lesions at second (23.7%) and at third period (25.7%) of observation. We have observed a statistically significant reduction in the cases of xerostomia between the initial and final examination ($p < .001$). Table 3 summarizes the oral lesions and immunosuppressive regimen used by renal transplant recipients. We found a positive association between the use of azathioprine and candidiasis ($p = .034$), and between the use of everolimus and oral ulcer (0.005) (Table 4).

The use of removable prostheses was not associated with new lesions after transplantation at either the 2nd (Fisher's exact test, $p = .221$) or 3rd (Pearson's chi-square test, $p = .935$) time point. Age was not associated with the presence of lesions. Patients with oral lesions had a mean age of 45.6 ± 11.6 years old, whereas those without oral lesions had a mean age of 42.4 ± 11.7 years, (Student's t-test, $p = .247$).

Oral ulcers and candidiasis were the most frequent lesions after transplantation. In total, 10 participants had oral ulcers in the post-transplant period. Table 5 resumes clinical and laboratorial data as well as the presumptive diagnosis of the oral ulcerative lesions.

The two cases of ulcers seen at 2nd time point and five cases seen at 3rd time point, in patients using everolimus, received the presumptive diagnosis of mTORI-associated stomatitis (mIAS). These ulcers were extremely painful, discrete, ovoid or irregular, superficial, well-demarcated with a greyish white pseudomembrane or erythematous halo, measuring about 4 mm in diameter (Figure 2).

We found a positive association between oral ulcer and the use of everolimus ($p = .005$), since of the 16 participants who used everolimus, 37.5% (6/16) presented ulcers, whereas of the 59 patients who did not used any mTOR inhibitors drug, 6.7% (4/59) had ulcerations in the oral mucosa.

Oral candidiasis was diagnosed in 10 of the 80 participants, of whom one was seen in the 1st time point, seven were observed in the 2nd time point and two in the 3rd time point. Among the 10 cases of candidiasis, six were pseudomembranous, 3 were erythematous candidiasis and 1 was classified as angular cheilitis. Of the six cases of pseudomembranous candidiasis, one affected the soft palate and oropharynx and the

Table 2. Immunosuppressive therapy.

Therapy	$N = 75$[a]	100%
Tacrolimus		
Yes	69	92
No	6	8
Cyclosporine		
Yes	6	8
No	69	92
Mycophenolate sodium		
Yes	31	41.3
No	44	58.7
Azathioprine		
Yes	28	37.3
No	47	62.7
Everolimus		
Yes	16	21.3
No	59	78.7
Immunosuppressive regimen		
Tacrolimus + Azathioprine + Prednisone	22	29.3
Cyclosporine + Azathioprine + Prednisone	6	8
Tacrolimus + Everolimus + Prednisone	16	21.3
Tacrolimus + Mycophenolate sodium + Prednisone	31	41.4

[a]In the second evaluation period, one patient was not receiving the immunosuppressive treatment because he was in the intensive care unit with herpes simplex infection and pneumonia.

Table 3. Oral lesions in renal transplant recipients.

Oral lesions	Absolute number of participants	1st time point	2nd time point[a]	3rd time point[a]	Immunosuppressive regimens
Ulceration	10	–	5	8	Tac + Aza + Pred ($n = 2$) Tac + Eve + Pred ($n = 6$) Tac + Myc + Pred ($n = 2$)
Candidiasis	10	1	8	5	Tac + Aza + Pred ($n = 6$) Cyc + Aza + Pred ($n = 1$) Tac + Myc + Pred ($n = 3$)
Herpetic stomatitis	5	1	3	3	Tac + Aza + Pred ($n = 2$) Tac + Eve + Pred ($n = 2$) Tac + Myc + Pred ($n = 1$)
Leukoplakia	1	1	1[b]	1	Tac + Myc + Pred ($n = 1$)
Mucoceles	2	–	1	1	Tac + Aza + Pred ($n = 2$)
Fistula	1	–	1[b]	–	Tac + Myc + Pred ($n = 1$)
Oral papilloma	1	–	–	1	Tac + Myc + Pred ($n = 1$)
Total Prevalence of participants with oral lesions		3.8% (3/80)	23.7% (18/76)	25.7% (19/74)	

Aza: Azathioprine; Cy c: Cyclosporine; Eve: Everolimus; Myc: Mycophenolate sodium; Pred: Prednisone; Tac: tacrolimus. Total prevalence represents the number of patients affected, regardless of the number of lesions they presented.
[a]Data lost due to death or withdrawal. The same patient could present the same lesion in different periods.
[b]The same patient presented fistula and leukoplakia in 2nd time point.

Table 4. Association between immunosuppressive drug and ulceration, candidiasis and HSV lesions.

		Ulceration			Candidiasis			Herpes labialis[b]		
Therapy	Lesion	Yes *n* (%)	No *n* (%)	p^a	Yes *n* (%)	No *n* (%)	p^a	Yes *n* (%)	No *n* (%)	p^a
Tacrolimus	Yes	10 (100)	59 (90.8)	.999	9 (90)	60 (92.3)	.999	4 (100)	65 (91.5)	.999
	No	0 (0)	6 (9.2)		1 (10)	5 (7.7)		0 (0)	6 (8.5)	
Cyclosporine	Yes	0 (0)	6 (9.2)	.999	1 (10)	5 (7.7)	.999	0 (0)	6 (8.5)	.999
	No	10 (100)	59 (90.8)		9 (90)	60 (92.3)		4 (100)	65 (91.5)	
Mycophenolate sodium	Yes	3 (30)	29 (44.6)	.502	3 (30)	29 (44.6)	.502	1 (25)	31 (43.7)	.632
	No	7 (70)	36 (55.4)		7 (70)	36 (55.4)		3 (75)	40 (56.3)	
Azathioprine	Yes	2 (20)	26 (40)	.304	7 (70)	21 (32.3)	.034	1 (25)	27 (38)	.999
	No	8 (80)	39 (60)		3 (30)	44 (67.7)		3 (75)	44 (62)	
Everolimus	Yes	6 (60)	10 (15.4)	.005	0 (0)	16 (24.6)	.107	2 (50)	14 (19.7)	.198
	No	4 (40)	55 (84.6)		10 (100)	49 (75.4)		2 (50)	57 (80.3)	
Total		10 (100)	65 (100)		10 (100)	65 (100)		4 (100)	71 (100)	

The data correspond to all lesions observed in the post-transplantation period (2nd and 3rd time points).
[a]Fisher's exact test.
[b]One patient died before establishing the immunosuppressive regimen. Thus, 4 patients were included in the statistical tests.

Table 5. Laboratorial and clinical data of the participants with oral ulcerations in the 2nd and 3rd time points.

Participant	Neutropenia	Systemic CMV disease	History of local trauma	Everolimus use	Presumptive diagnosis
2nd time point					
#6	+	+	−	−	Neutropenic ulcer
#16	−	−	−	+	mIAS
#23	−	−	−	+	mIAS
#47	−	−	+	−	Traumatic ulcer
#53	−	−	+	−	Traumatic ulcer
3rd time point					
#4	−	−	−	+	mIAS
#6	+	+	−	−	Neutropenic ulcer
#7	−	−	−	+	mIAS
#11	−	−	−	+	mIAS
#20	−	−	−	+	mIAS
#23	−	−	−	+	mIAS
#53	−	+	−	−	CMV-induced ulcer
#66	−	−	+	−	Traumatic ulcer

mIAS: mTOR inhibitor-associated stomatitis.
Patients #6, #23 and #53 had ulcers in both time points.

others were limited to oral cavity (Figure 2(B)). Three patients showing erythematous candidiasis were removable denture wearers. In all, 20 patients (25%, 20/80) were using removable denture and three had erythematous candidiasis. Considering all types of candidiasis, lesions were more prevalent in patients taking azathioprine ($p = .034$). Of the 28 patients taking azathioprine, seven (25%) showed oral candidiasis, whereas of the 47 patients who did not take azathioprine, three (6.3%) had oral candidiasis (Table 4).

In total, five participants presented herpesvirus (HSV) oral lesions. One of them was diagnosed in the 1st time point, three participants in the 2nd time point, and one new patient was diagnosed at the 3rd time point (Figure 2(D)). In three patients, the lesions were self-limiting, and in two patients lesions were involving oropharynx.

Discussion

Our results have shown that 36.2% of the renal transplant recipients (RTRs) undergoing graft-preserving immunosuppressive therapy presented some oral soft tissue lesions in the short-term, that is, up to 60 days after renal transplantation. The present study is unique as each patient was followed at three different times.

Most studies in the literature have evaluated RTRs receiving long-term immunosuppressive therapy, reporting wide variations in the frequency of individuals with oral lesions and in their type, including gingival enlargement, oral candidiasis and hairy leukoplakia [3,6,7,10]. The percentage of RTRs developing lesions varies from 24% in Iran to 81% in Brazil [2,3,5,6,9,12].

Ulcers and candidiasis were the most frequently observed oral lesions in the present study, and we have found an association between presence of oral ulcers and use of everolimus ($p < .005$). Aphthous-like stomatitis has been identified as one of the most common dose-limiting toxicities associated with mTOR inhibitor therapy in cancer patients [14–16]. Since Sonis and colleagues [17] proposed the term *mTORI-associated stomatitis* (mIAS) it has become the preferred descriptor of the mTOR inhibitor-associated toxicity.

A few reports of mIAS in RTRs have been published. Differential diagnosis of mIAS includes traumatic ulceration, neutropenic ulcers and recurrent aphthous stomatitis. It seems that the frequency and severity of stomatitis appear to be associated with higher doses and IV administration of mTOR inhibitor. Ulcers generally improve over time, but some patients require dose reduction and/or interruption along with intensive supportive care measures.

Oral ulcerations secondary to mycophenolate mofetil therapy have also been described in RTRs [18–20]. In this present study, of the 10 participants with oral ulcers, three was undergoing mycophenolate mofetil therapy. In these patients

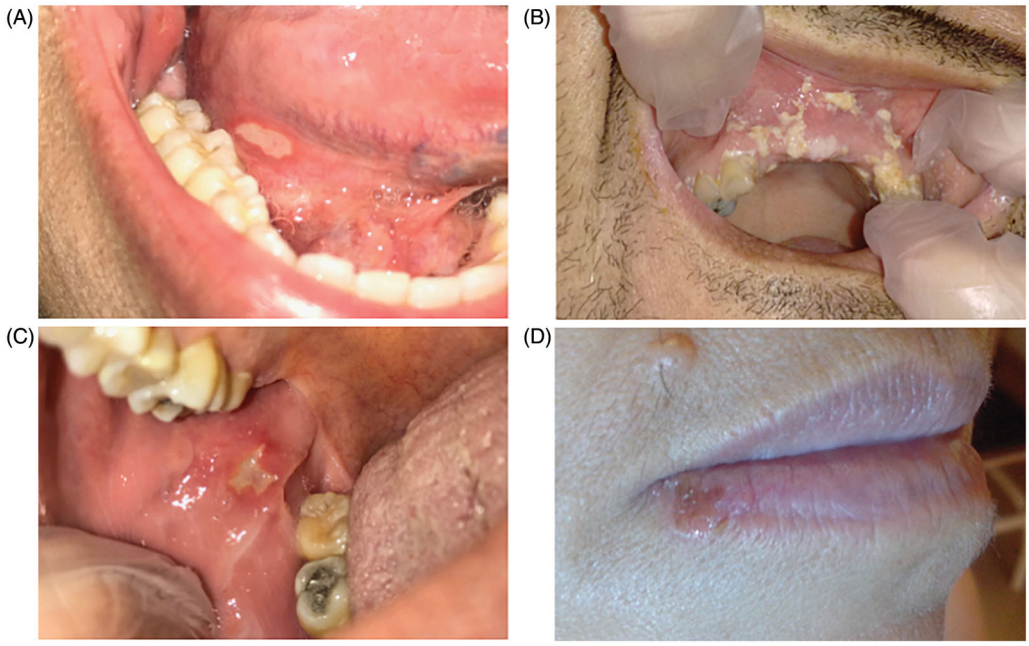

Figure 2. (A) Ulcerative lesion on the floor of mouth, 48 days after renal transplantation, associated to everolimus use. (B) Pseudomembranous candidiasis in the alveolar ridge, 18 days after renal transplantation. (C) Painful ulcerative lesion in the buccal mucosa, 50 days after renal transplantation, under tacrolimus, everolimus and prednisone. (D) Herpes labialis, 17 days after renal transplantation.

history of trauma and neutropenia were identified. This overlap of factors did not allow us to associate these ulcers with mycophenolate use. The biopsy at this point would not be enlightening either. For such cases, it is ideal to follow the patient and if trauma and neutropenia have been resolved and the ulcer persists, reduction or replacement of MMF should be considered.

We have established the presumptive diagnosis of oral ulcers by taking into account clinical characteristics, time of evolution, type of lesion (i.e. single or multiple), size of lesion and symptoms, in addition to ruling out any association with trauma, neutropenia and systemic CMV disease. We were unable to perform biopsies at the time of data collection. This is certainly a weakness of our study. Anyway, even with histopathological analysis establishing the cause of the oral ulcer always poses a challenge to the stomatologist. The benefit of biopsy would be related to confirmation of hypothesis of ulcerated lesions caused by CMV. According to Peterson and colleagues [21], clinical similarities between mIAS and recurrent aphthous stomatitis and difficulty in differentiating one from the other is likely to result in overestimation of the true incidence of mIAS in RTRs.

We have observed high prevalence of oral candidiasis, that was seen in 10 participants along the study, agreeing with other authors [3,8,9,11]. Candidiasis was more prevalent in patients taking azathioprine, supporting results found by Gupta et al. [22]. Previous studies showed that corticosteroids also influence the prevalence of candidiasis [5]. Da Silva et al. [12] reported that the concomitant use of azathioprine and corticosteroids potentiates the immunosuppressive effect and may increase the risk of oral candidiasis, and these data are corroborated by our findings.

López-Pintor et al. [10] reported that severe candidiasis is more frequent in the immediate post-transplant period. However, in our study, only one patient showed oropharyngeal pseudomembranous candidiasis, during the immediate post-transplant period. The remaining nine cases were limited to oral cavity.

In the 3rd time point, 4% of participants had oral HSV lesions. The literature shows that the long-term prevalence of oral HSV lesions in RTRs ranges from 0% to 11.3% in the post-transplant period [2,6–8,12,23–25], being the most common viral infection found in these individuals [26]. In our study, two patients presented extensive herpetic stomatitis in the lower and upper lips and nose, including oropharynx in one case.

A higher risk of reactivation of HSV-1 was found to be related to renal allograft recipients who were under a CsA-based immunosuppressive regimen [24]. Nine of our patients received prophylaxis for CMV with IV ganciclovir and one of them presented herpes labialis after transplantation. The incidence of HSV reactivation is lower in the 'cytomegalovirus prophylaxis era' [27], as confirmed by other studies [2,6,8,25,28]. In our sample, only six patients used CsA in the immunosuppressive regimen. All cases of HSV oral lesions affected patients under tacrolimus and prednisone regimens associated with azathioprine, everolimus or mycophenolate sodium.

Xerostomia is a common finding in patients with advanced chronic renal disease, which explains the high prevalence of this symptom in our patients during the 1st time point, that is, immediately before transplantation [29,30]. After transplantation, only one participant still complained of xerostomia during the study period.

We did not analyze the possible relationship of comorbidities and other drugs that patients used, with oral lesions. But we believe this weakness of the study did not compromise our conclusions especially because we compared the oral conditions of the same patient immediately before and at two moments after transplantation.

In summary, oral lesions, especially candidiasis and oral ulcers, are common in the short-term after renal transplantation and are mainly related to the immunosuppression and toxicity of immunosuppressive drugs. Our data suggest that ulcerations are associated with the use of everolimus and candidiasis is associated with azathioprine. Our results emphasize the importance of oral health care provider in the multidisciplinary transplant team before and immediately after organ transplant.

Ethical approval

All the procedures performed in studies involving human participants were in accordance with the ethical standards set by institutional and/or national research committees and with the 1964 Helsinki declaration, including its later amendments or comparable ethical Standards. This study was approved by the Research Ethics Committee of the University of São Paulo School of Dentistry according to protocol number 1.824.857.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Disclosure statement

The authors declare no conflicts of interest.

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