

Comparison of Oral Lesion Prevalence Between Renal Transplant Patients and Dialysis Patients

Arash Mansourian¹, Amin Manouchehri², Shiva Shirazian³, Elham Moslemi^{✉3}, Golnaz Haghpanah⁴

¹Associated Professor, Dental Research Center Dentistry Research Institute, Department of Oral Medicine, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran

²Associated Professor, Department of Nephrology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

³Assistant Professor, Department of Oral Medicine, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran

⁴Dentist

Abstract

Objective: Renal transplantation is performed in patients with end stage renal disease as the best treatment plan. However, different complications may occur in these patients due to the direct consequences of the renal disease or drug-induced suppression of the body immune system. The main objective of the present study was to compare different oral lesions in patients receiving renal transplantation with the patients undergoing dialysis referred to two hospitals in Tehran, Iran.

Materials and Methods: In this cross-sectional study, 93 renal transplant patients who had received renal transplant at least 6 months prior to our study, were selected from their records at the hospitals. Furthermore, 93 candidates of renal transplantation were selected as the control group. The patients in both case and control groups underwent oral examinations and the results were analyzed by chi-square test and Spearman correlation coefficient.

Results: At least one oral lesion was found in 30 (32.2%) patients in the renal transplant group and 8 (8.6%) patients in the control subjects. The difference between the two groups was statistically significant ($p < 0.0001$). The most prevalent lesion was xerostomia observed in 20 patients of the renal transplant group and 4 patients in the control group. The odds ratio of cyclosporine and amlodipine and the effect of these in increasing the risk of oral lesions was 1.21 and 1.02, respectively in renal transplant recipients.

Conclusion: The results of the study showed that renal transplantation significantly increases the risk of related oral lesions. Therefore, renal transplant recipients must undergo regular oral examinations in order to find any suspicious lesion(s) as soon as possible to treat them.

Key Words: Oral Manifestation, Renal Failure, transplantation

✉ Corresponding author:

E. Moslemi, Department of Oral Medicine, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran

dr.emoslemi@yahoo.com

Received: 28 May 2013

Accepted: 5 October 2013

Journal of Dentistry, Tehran University of Medical Sciences, Tehran, Iran (2013; Vol. 10, No. 6)

INTRODUCTION

Renal transplantation is the best treatment plan in patients with end stage renal disease. Dialysis is also available as an alternative and effective lifesaving treatment in end stage renal

failure. Patients who received renal transplant have a better life in comparison to dialysis patients as a longer lifespan and less comorbidity [1,2]. However, there are still some concerns about the survival rate.

The increase of life expectancy in renal transplant patients has an impact on oral and dental health services. Different oral and dental problems arise in these patients, most of which develop as a consequence of drug-induced immunosuppression [3, 4]. Immunosuppressant treatment depresses the cell-mediated immune response, producing antibodies, monocytes, neutrophils, natural killer cells and complement [5]. For the clinician, this means a greater risk of oral infection and other associated complications. When the immune system suppress, microbial agents of normal oral flora have an opportunity to become pathogen and make infection and destruction in the oral cavity. Oral lesions may also develop as a result of side effects and drug interactions during immunosuppressive therapy. But there are little studies about oral lesions in renal transplant patients [6]. The oral manifestations associated with immunosuppressive drugs are gingival hyperplasia, xerostomia, dental caries, periodontal diseases, dental anomalies, opportunistic infections such as oral candidiasis and hairy leukoplakia, squamous cell carcinoma of the lips and non-Hodgkins lymphoma [7-9]. Gingival enlargement may be caused by cyclosporine and calcium channel blocker application that begins initially from the interdental papilla and anterior labial regions [10-12]. Depending on the high prevalence of oral manifestations after renal transplantation, the patients must undergo regular oral examinations by dentists in order to diagnose and treat any suspicious lesion. Establishment of proper oral hygiene procedures in these patients may prevent oral lesions to some extent [7]. Reports on the prevalence of oral mucosal lesions in renal transplant patients are scarce. Rosa-Garcia and colleagues (2005) found that 60% of renal transplant patients had at least one oral lesion [7]. Gulec and Haberal (2006) reported the prevalence of some oral lesions such as gingival hyperplasia and oral candidiasis in renal transplant recipients [13]. Although there are a few studies that reported

oral lesions in renal transplant patients in Iran, there is no comparison between the prevalence of oral lesions in dialysis patients and recipient renal transplant patients. So the objective of the present study was to compare the prevalence of different oral lesions in patients receiving renal transplant and candidates of renal transplantations in two centers in Tehran, Iran.

MATERIALS AND METHODS

This cross-sectional study was performed on 93 patients who had received renal transplantation in 2 hospitals in Tehran from 2001 to 2008. The inclusion criteria included receiving transplants at least six months prior to the study. The subjects were selected from their records at the hospital centers, and information on age, gender, date of receiving transplant, dialysis duration and patient medications were extracted from the patients' medical records. All patients were invited to come to the dental unit of Imam Khomeini hospital at the specified visit time by calling them. Oral examination was done on the dental unit and oral lesions were diagnosed clinically by an oral medicine specialist. Xerostomia was diagnosed objectively by the "tongue-blade" test; sticking a tongue-blade on the oral mucosal surfaces indicates that the mucosa is not sufficiently moisturized by the saliva and also subjectively by the patients complaints of difficulty in chewing, swallowing, speaking and denture retention. Candidiasis was diagnosed clinically by the appearance and symptoms. Pseudo membranous candidiasis was diagnosed based on whitish or yellowish plaques throughout the oral mucosa that could be easily scraped off. Erythematous candidiasis was diagnosed if the burning mouth sensation was accompanied by a diffuse loss of filiform papillae of the dorsal tongue, resulting in a red-dened "bald" appearance of the tongue. The diagnosis of recurrent aphthous stomatitis was made by clinical presentation and squamous papilloma was confirmed by biopsy.

Ninety-three candidates for renal transplantation were selected as the case group. The patients in both case and control groups underwent oral examinations and the results were analyzed by chi-square test to compare oral manifestations in both groups and Spearman correlation coefficient to determine the relationship between related drugs and oral manifestations. A p value less than 0.05 was considered as significant.

RESULTS

Ninety-three renal transplant recipients, of which 52 were men (55.9%) and 41 were women (44.1%) with a mean age of 40.6 ± 13.8 (range 14-66) years were examined. In addition, 93 patients (59 men, 63.4%) with a mean age of 50.03 ± 15.1 (range 11-80) years who received dialysis were recruited as the control group. The mean time after receiving renal transplantation was 3.30 ± 2.45 (range 1-8) years. In the control group, the mean duration of being on dialysis was 5.70 ± 4.40 (range 1-25) years.

The mean time from the diagnosis of end stage renal failure in the case group was 1.84 ± 1.86 years before renal transplantation and in the control group it was 5.7 ± 6.6 years. Table 1 shows characteristics of renal transplant recipients and dialysis patients.

Drug administration in renal transplantation patients was in the following order: all the patients were receiving corticosteroids. 97.80%, 29% and 17.2% of them were receiving cyclosporine, amlodipine and azathioprine, respectively. In the control group, the most administered drug was aprex (95%).

On oral examination, at least one lesion was found in 30 (32.2%) patients of the renal transplant group and 8 (8.6%) patients in the control group. The most common oral manifestation was xerostomia being observed in 20 (21.5%) patients in the case group and 4 (4.3%) patients of controls (Table 2).

Pseudo-membranous candidiasis was observed equally in both groups. Gingival enlargement was reported in three renal transplant cases (3.3%) and one of the controls (1.1%).

Table 1. Basic Characteristics of Renal Transplant Recipients and Dialysis Patients

Variables	Renal Transplant	Dialysis Patients
Age	Mean \pm Std. Dev. 40.6 \pm 13.8	Mean \pm Std. Dev. 50.03 \pm 15.1
Gender	M=55.9% F=44.1%	M=63.4% F=36.6%
Transplant Duration	Mean \pm Std. Dev. 3.3 \pm 2.45	-
Dialysis Duration	-	Mean \pm Std. Dev. 5.7 \pm 6.6

Table 2. Frequency of Oral Lesions in Renal Transplant Recipients and Dialysis Patients

Oral Lesions	Transplant Recipients	Dialysis Patients
Xerostomia	20(21.5%)	4(4.3%)
Minor Aphthous	5(5.4%)	-
Squamous Papilloma	-	1(1.1%)
Gingival Enlargement	3(3.2%)	1(1.1%)
Candidiasis	2(2.2%)	2(2.2%)

Minor aphthous was found in five (5.4%) patients of the case group and squamous papilloma was detected in one patient of the control group (1.1%). Sixty patients in the case group (67.7%) and 85 patients in the control group (91.4%) did not show any oral manifestation. The difference between the two groups was analyzed by chi-square test and it was statistically significant ($p < 0.0001$). The odds ratio of different offending medications and the effect of these in increasing the risk of oral lesions in renal transplant recipients is shown in Table 3.

DISCUSSION

Endodontic the prevalence of oral lesions was higher in renal transplant patients compared with the dialysis group. One of the possible causes may be immunosuppressive drugs. In general, 32.3% of renal transplant recipients and 8.6% of the control subjects exhibited oral lesions. This rate was four times higher in renal transplant recipients. In addition, according to statistical analysis, the difference between the two groups was significant.

In the present study, xerostomia was the most common oral lesion in both groups. Dirschnabel and associates (2011) also showed that the most prevalent oral lesion was xerostomia [14]. The reasons for xerostomia are dehydration, mouth breathing and side effects of the related drugs after renal transplantation such as cyclosporine and nifedipin [15].

Symptoms of xerostomia are burning sensation of the oral mucosa, difficulty in swallowing, mastication and speaking, dysgeusia and an increased prevalence of dental caries.

Therefore, it is essential for patients to maintain meticulous oral hygiene. Patients require more frequent dental visits and must work closely with their dentists to maintain optimal dental health. Our study showed the presence of xerostomia in 4.3% of dialysis patients and 21.5% of renal transplant recipients. This frequency is lower than the study conducted by Kho and associates (32.9%) as well as the study performed by Udayakumar and colleagues (31%) [16,17]. Gingival enlargement (GE) was another oral lesion in 3.2% of renal transplant recipients and 1.1% of dialysis patients. It may be caused by cyclosporine that was reported in most of the previous studies [8]. Additionally, most of the studies explained the synergistic effect of calcium channel blocker in the development of GE. Clinically, GE begins initially from the interdental papilla and anterior labial regions. Usually it is limited to the attached gingiva, but it can extend coronally and interfere with occlusion, mastication and speaking [18]. In this study, 97.8% of the patients were taking cyclosporine. But the frequency of GE was lower compared to the previous studies [3.2%]. Saheb-jamee and associates (2009) found GE in 7% of their patients. In addition, it was found in 7.25% of the patients in a study carried out by Cezario and colleagues [8,19]. There are very different reports about GE in various studies. King and colleagues reported higher percentage of GE in renal transplant recipients in contrast of this study [20]. Interestingly, Al-Mohayaa and colleagues reported GE in 74% of their renal transplant patients [3].

Table 3. Odds Ratio of Oral Manifestations in Renal Transplant Recipients with Effective Offending Medications

Generic Name	Name Trade	Odds Ratio
Cyclosporine	Iminural	1.21
Amlodipine	Amlodipine	1.02
Azathioprine	Imuran	0.27
Sirolimus	Rapamune	0.96
ATG (Antithymocyte Globulin)	Atgam	0.99
ALG (Antilymphocyte Globulin)	Atgam	0.99

Regarding the great number of medications taken by the patients and the low frequency of GE in this study, it was impossible to evaluate the effects of each drug on GE. Furthermore, GE may be caused by the synergistic effect of cyclosporine and calcium channel blockers. Hypertension is one of the most common side effects of immunosuppressive drugs such as cyclosporine; so calcium channel blockers can be effective in these patients. They can cause GE independently; however, in combination with calcineurin inhibitors like cyclosporine or tacrolimus, they may have synergistic effects on gingival tissues [19]. The mechanism of action of calcium channel blockers is reducing free calcium in the cytoplasm by blocking calcium channels. Synthesis and the releasing process of collagenase and metalloproteinases from gingival fibroblast are calcium-dependent stages. Furthermore, administration of these drugs inhibits collagenolysis by interrupting the synthesis and release of collagenase. Imbalance between production and break-down of collagen could be one of the GE development-related mechanisms in kidney transplant recipients [8]. So calcium channel blockers and cyclosporine act in a parallel way to cause GE. Al-Mohaya and associates have proposed the elevated level of blood glucose as another influential factor in the development of GE in kidney transplant recipients. The presence of diabetes mellitus as an underlying disease in some of these patients is expectable [3]. In addition, the individuals' genetic potentials against long-term drug metabolites, the degree of gingival sensitivity to drugs, and previous gingival conditions such as inflammation are the other potential variables in the incitement of GE in different individuals [21].

The lower frequency of GE in this study compared to others may be attributed to pretransplant examinations, control of oral conditions and encouraging patients to use oral hygiene aids. The results of this study displayed minor aphthous stomatitis in 5.4% of renal transplant

recipients as well as pseudomembranous candidiasis in 2.2% of them. Sahebamee and colleagues reported oral candidiasis in 16% of their patients [8]. In spite of the great discrepancy in the frequency of oral candidiasis between these two mentioned studies, the majority of oral candidiasis was caused by the pseudomembranous type. Al-Mohaya et al. found oral candidiasis in 15.5% of the renal allograft recipients [3]. Gupta and colleagues also reported it in 10.5% of their patients [22]. Regarding the complexity of oral candidiasis pathogenesis, consuming high doses of immunosuppressive drugs in the first three months after renal transplantation may predispose patients to opportunistic infections. Also, reduction of salivary flow as a side effect of antihypertensive drugs is one of the risk factors for oral candidiasis in renal transplant recipients. Reduction of salivary flow causes a reduction in salivary proteins like immune globulins and the absence of the washing potential of saliva causes decreasing resistance to different infections in the oral cavity [23]. Xerostomia, minor aphthous ulcers, GE and candidiasis are the most common oral lesions that were found in renal transplant patients. As these lesions may have various effects on different aspects of life in these patients, it seems necessary that an oral medicine specialist should be present in the team of renal transplant clinicians.

CONCLUSION

Kidney transplantation significantly increases the risk of oral lesions. Therefore, it is recommended that any oral lesion should be eliminated before transplantation and the patients should undergo regular oral examinations in order to diagnose any suspicious lesions.

REFERENCES

- 1- Favi E, Salerno MP, Romagnoli J, Castagneto M, Citterio F. Significant improvement in patient survival after renal transplantation in the last decade. *Transplant Proc.* 2011 Jan-Feb;43(1):285-7.

- 2- Abecassis M, Bartlett ST, Collins AJ, Davis CL, Delmonico FL, Friedewald JJ et al. Kidney transplantation as primary therapy for end-stage renal disease: A National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. Clin J Am Soc Nephrol. 2008 Mar;3(2):471-80.
- 3- Al-Mohaya MA, Darwazah AM, Bin-Salih S, Al-Khudair W. Oral lesions in Saudia renal transplant patients. Saudia J Kidney Dis Transpl. 2009 Jan;20(1):20-9.
- 4- Seymour RA, Thomason JM, Nolan A. Oral lesions in organ transplant patients. J Oral Pathol Med. 1997 Aug;26(7):297-304.
- 5- Greenberg M, Glick M, Ship J. Burket's oral medicine. 11th ed. Hamilton: BC Decker Inc; 2008. 19:461-468.
- 6- Lopez-Pintor RM, Hernandez G, de Arriba L, de Andres A. Comparison of oral lesion prevalence in renal transplant patients under immunosuppressive therapy and healthy controls. Oral Dis. 2010 Jan;16(1):89-95.
- 7- de la Rosa-Garcia E, Mondragon-Padilla A, Irigoyen-Camacho ME, Bustamante-Ramirez MA. Oral lesions in a group of kidney transplant patients. Med Oral Pathol Oral Cir Bucal. 2005 May-Jul;10(3):196-204.
- 8- Sahebamee M, Shakur Shahabi M, Nikoobakht MR, Momen Beitollahi J, Mansourian A. Oral lesions in kidney transplant patients. Iran J Kidney Dis. 2010 Jul;4(3):232-6.
- 9- Galili D, Kaufman E, Leviner E, Lowental U. The attitude of chronic hemodialysis patients towards dental treatment. Oral Surg Oral Med Oral Pathol. 1983 Dec;56(6):602-4.
- 10- Lima RB, Benini V, Sens TA. Gingival overgrowth in renal transplant recipients: a study concerning prevalence, severity, periodontal, and predisposing factors. Transplant Proc. 2008 Jun;40(5):1425-28.
- 11- Kennedy DS, Linden GJ. Resolution of gingival overgrowth following change from cyclosporine to tacrolimus therapy in a renal transplant patient. J Ir Dent Assoc. 2000;46(1):3-4.
- Kerr AR. Update on renal disease for the dental practitioner. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001 Jul;92(1):9-16.
- 12- Gulec AT, Haberal M. Lip and oral mucosal lesions in 100 renal transplant recipients. J Am Acad Dermatol. 2006 Jan;62(1):96-101.
- 13- Dirschnabel AJ, Martins Ade S, Dantas SA, Ribas Mde O, Gregio AM, Alanis LR, et al. Clinical oral findings in dialysis and kidney transplant patients. Quintessence Int. 2011 Feb;42(2):127-33.
- 14- Porter SR, Scully C, Hegarty AM. An update of the etiology and management of xerostomia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004 Jan;97(1):28-46.
- 15- Kho HS, Lee SW, Chung SC, Kim YK. Oral manifestations and salivary flow rate, pH, and buffer capacity in patients with end-stage renal disease undergoing hemodialysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999 Sep;88(3):316-9.
- 16- Udayakumar P, Balasubramanian S, Ramalingam KS, Lakshmi C, Srinivas CR, Mathew AC. Cutaneous manifestations in patients with chronic renal failure on hemodialysis. Indian J Dermatol Venereol Leprol. 2010 Mar-Apr;72(2):119-25.
- 17- Ciavarella D, Guiglia R, Guiglia R, Campisi G, Di Cosola M, Di Liberto C, Sabatucci A, et al. Update on gingival overgrowth by cyclosporine A in renal transplant. Med Oral Pathol Oral Cir Bucal. 2007 Jan;12(1):E19-25.
- 18- Cezario ES, Cota LO, Ferreira SD, Siqueira FM, Soares RV, Zenobio EG et al. Gingival overgrowth in renal transplant subjects medicated with Tacrolimus in the absence of calcium channel blockers. Transplantation. 2008 Jan;85(2):232-6.
- 19- King GN, Healy CM, Glover MT, Kwan JT, Williams DM, Leigh IM, et al. Prevalence and risk factors associated with leukoplakia, hairy leukoplakia, erythematous candidiasis and gingival hyperplasia in renal transplant recipients. Oral Surg Oral Med Oral Pathol. 1994 Dec;78(6):718-26.

20- Kataoka M, Kido J, Shinohara Y, Nagata T. Drug- induced gingival overgrowth- a review. *Biol Pharm Bull.* 2005 Oct;28(10):1817-21.

21- Gupta KL, Ghosh AK, Kochhar R, Jha V,

Chakraarti A, Sakhuja V. Esophageal candidiasis after renal transplantation: comparative study in patients on different immunosuppressive protocols. *Am J Gastroenterol.* 1994 Jul;89(7):1062-5.