# Cross sectional study of oral soft tissue lesions in kidney transplant recipients

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**Abstract**

Kidney transplantation is currently widely accepted, owing to improving quality and length of life. However, the kidney transplant recipient has to receive long-term immunosuppressive therapy in order to prevent kidney transplant rejection, which declines the immunology system. Different oral and dental problems also increase in these patients, which mostly develop as a consequence of side effects and drug interaction during immunotherapy. This study aims to determine oral soft tissue lesions and plaque index in kidney transplant recipients. The cross-sectional study was conducted from April to October 2019. Seventy-one kidney transplant recipients were examined for oral soft tissue lesion, oral hygiene, and gingival hyperplasia. Oral lesions were analyzed descriptively. Univariate and multivariate linear regression was used to assess the relationship between plaque index and different variables. Oral lesions were found in 8 kidney transplant recipients (11.3%). The most common oral lesion was oral ulcer (8.4%), followed by the median rhomboid glossitis (1.4%), and fibroma (1.4%). Gingival hyperplasia was found 1.4% in the kidney transplant recipients. Multivariate linear regression revealed that plaque index was increasing by age (regression coefficient (95% confidence interval) = 0.009 (0.003-0.018); $p$=0.041). Oral lesions were found in 11.3% of kidney transplant recipients. These lesions can be related to immunosuppressive drugs, either as side effects or as a direct consequence of the patients' immune status. A regular dental examination is necessary for early detection of the oral lesion, which allows consulting in medications adjustment and stops or relieves progression of the oral lesion.

***Keywords*****:** *Oral soft tissue lesions, Kidney transplant, Immunosuppressive drug*

## 1. Introduction

Kidney transplantation is considered to be the best treatment for end-stage renal disease patient. It is widely accepted that kidney transplantation improves quality and length of life (Al-Aradi et al., 2009). It has become a routine procedure in industrialized country owing to medically and economically effective (Haller, Gutjahr, Kramar, Harnoncourt, & Oberbauer, 2011).

However, the kidney transplant recipient has to receive long-term immunosuppressive therapy in order to prevent kidney transplant rejection (Hricik, 2015). It declines immunology system, leading to systemic complications which can be life-threatening to the patient (Andres, 2005).

Different oral and dental problems also increase in these patients, which mostly develop as a consequence of side effects and drug interaction during immunotherapy (Al-Mohaya, Darwazeh, Bin-Salih, & Al-Khudair, 2009; Seymour, Thomason, & Nolan, 1997). For example, previous studies showed oral ulcer in transplant recipients who were on immunosuppressive drugs, such as sirolimus (van Gelder, ter Meulen, Hene, Weimar, & Hoitsma, 2003); (Montalbano et al., 2004); (Sundberg, Rohr, Hartmann, Adams, & Stratta, 2004), tacrolimus (Hernandez, Jimenez, Arriba, Moreno, & Lucas, 2001); (Macario-Barrel et al., 2001) and mycophenolate mofetil (Apostolou, Tsagalis, Koutroubas, Hadjiconstantinou, & Drakopoulos, 2004); (Garrigue et al., 2001); (Schmutz, Barbaud, & Trechot, 2003).

Immunosuppressive therapy depresses the cell-mediated immune response, producing antibodies, neutrophils, monocytes, natural killer cells and complements (Burket, Greenberg, Glick, & Ship, 2008). When the general immune response of kidney transplant recipient is reduced, microbial agents of oral normal flora become opportunistic pathogens, increasing susceptibility to infections and the potential of developing lesions. Lesions in the oral cavity may arise as a direct result of immunosuppression or drug interaction (Dirschnabel et al., 2011; Lopez-Pintor, Hernandez, de Arriba, & de Andres, 2010; Rojas et al.,

2012). Most common oral complications of immunosuppression are different viral infections caused by herpes simplex virus, varicella-zoster virus, cytomegalovirus and Epstein Barr virus associated with the development of hairy leukoplakia (Al-Mohaya et al., 2009). An increased incidence of infection caused by human papillomavirus, particularly in the elderly with kidney transplants (Rose et al., 2006). Fungal infections caused by *Candida* species are prone to develop, compared with the immunocompetence (Al-Mohaya et al., 2009; Golecka, Oldakowska-Jedynak, Mierzwinska-Nastalska, & Adamczyk-Sosinska, 2006; Olczak-Kowalczyk et al., 2010). And variety of bacterial infections have been shown as well (Murphy & Gould, 1999). Gingival hyperplasia is found as a result of cyclosporine and calcium channel blockers interaction (de la Rosa-Garcia, Mondragon-Padilla, Irigoyen-Camacho, & Bustamante-Ramirez, 2005), which are extensively used in kidney transplant recipients (Lima, Benini, & Sens, 2008). Furthermore, orofacial granulomatosis is described, especially in children with solid organ transplant (Saalman, Sundell, Kullberg-Lindh, Lovsund-Johannesson, & Jontell, 2010). Malignancy such as non-Hodgkins lymphoma and squamous cell carcinoma of the lips are found as well (de la Rosa-Garcia et al., 2005; Lopez-Pintor, Hernandez, de Arriba, & de Andres, 2011; Sahebjamee et al., 2010).

In previous studies, there is a greater possibility in immunotherapy patients to develop oral lesions (Geddes et al., 2003; Živčić-Ćosić et al., 2013), so these kidney transplant recipients must undergo regular oral examination by the dentist in order to early detect, diagnose and treat any suspicious lesion. Instruction of proper oral hygiene procedures in these patients may prevent oral lesions to some extent (de la Rosa-Garcia et al., 2005). However, in Thailand, there are few studies reported oral lesions in kidney transplant recipients. Therefore, this study aims to determine oral soft tissue lesions in kidney transplant recipients.

## 2. Objectives

This study aims to determine frequencies and percentages of oral soft tissue lesions in kidney transplant recipients and assess the relationship between plaque index and different independent factors.

## 3. Materials and Methods

The cross-sectional study was conducted in 6 months (April – October 2019) after approval by the Research Ethics Committee, Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB no.88/62). Seventy-one kidney transplant recipients who had received successful kidney transplantation at least six months earlier were included in this study. All patients were 18 years of age or over. The study was performed in a follow-up visit at the Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and Chulalongkorn Memorial hospital.

The study protocol was explained to each patient. After signing informed consent, patients' demographic data and additional details regarding medical history and dental history were recorded.

The clinical oral examination consisted of oral soft tissue lesion, gingival hyperplasia and oral hygiene and was carried out by a single investigator, using mouth mirror and dental explorer. Lightweight, portable examination light was provided as recommended by the World Health Organization (WHO) (World Health Organization, 2013).

### 3.1 Oral soft tissue lesion

Oral soft tissue lesions were clinically examined based on WHO criteria (World Health Organization, 2013). The oral mucosa was evaluated in order to identify the type of lesions and their locations. Lesions of oral mucosa were photographically documented, and subjects were referred to the Dental department for further diagnostic and treatment. A biopsy was performed in the case with a doubtful diagnosis and for suspected malignancy.

### 3.2 Plaque index

The degree of oral hygiene was determined in all subjects, using Silness-Loe index (Silness and Loe, 1964). The measurement was based on recording both soft debris and mineralized deposits on the following teeth; tooth 16, 12, 24, 36, 32, and 44. The sum of 4 surfaces (buccal, lingual, mesial, and distal) of each tooth was divided by four, and the sum of 6 teeth was divided by six. Missing teeth were not substituted. The score of each surface displays below.

| Scores | Criteria |
|---|---|
| 0 | No plaque |
| 1 | A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen in situ only after application of disclosing solution or by using the probe on the tooth surface |
| 2 | Moderate accumulation of soft deposit within the gingival pocket or the tooth and gingival margin, which can be seen with the naked eye |
| 3 | An abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin |

All subjects were given the instructions on adequate oral hygiene.

3.3 Gingival hyperplasia

Gingival hyperplasia was measured per sextant using Aas index as follows below. Each sextant was graded according to the most severe site. A subject was classified as having gingival hyperplasia when at least one interdental papilla with gingival hyperplasia grade I was presented in at least one sextant.

| Grade | Criteria |
|---|---|
| 0 | No gingival enlargement |
| I | Slight or moderate gingival enlargement. The interdental papillae have assumed a more round, blunted form; the gingival margin is slightly thickened. The anatomic crowns are covered up to one-third of the vestibular surfaces. |
| II | Marked gingival enlargement. The papillae and the gingival margin cover from one-third to one-half of the vestibular surfaces. In most cases, the papillae are separated only by V-shaped cleft. |
| III | Severe gingival enlargement. The gingiva propria covers one-half to two-thirds of the vestibular surfaces and protrudes 3 to 4 mm from the surface of the teeth. |
| IV | Very severe gingival enlargement. The hyperplastic tissue covers from two-thirds to the whole of anatomic crowns in one or more regions and occlusion is rendered difficult if not prevented. |

**Statistical analysis**

All tests were performed using STATA version 15.1 (StataCorp, College Station, TX). Frequencies and percentages of oral soft tissue lesions were analyzed descriptively. Univariate and multivariate linear regression were used to assess the association between plaque index and different independent variables. Statistical significance was determined at $p<0.05$.

## 4. Results and Discussion

Seventy-one participants were from the Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University. All patients were Thai. The demographic data of kidney transplant recipients are displayed in Table 1.

Drug administration in kidney transplant recipients was in the following order: all patients were receiving immunosuppressive drugs, 44 (61.2%) were receiving tacrolimus, 19 (26.8%) were receiving cyclosporin, 53(74.6%) were receiving prednisolone. Fourteen (19.7%) and 3 (4.2%) were receiving sirolimus and everolimus, respectively.

In the oral examination, lesions were found in 8 (11.3%) kidney transplant recipients. The most common oral manifestation was an oral ulcer, 6 (8.4%). One (1.4%) median rhomboid glossitis and 1(1.4%) fibroma on the tongue were also found. Gingival hyperplasia grade II (1.4%) was found in a kidney transplant recipient who was on CSA and calcium channel blocker. Sixty-three kidney transplant recipients did not show any oral manifestation.

Plaque index in kidney transplant recipients was ranging from 0.9 to 2.8 (average 1.5±0.4). When the relationship of plaque index with different variables was assessed by univariate linear regression and selected only variable with $p<0.1$ to include in the multivariate model. The significant correlation was found in kidney transplant recipients that plaque index was increasing with age (regression coefficient (95% confidence interval) = 0.009 (0.003-0.018); $p=0.041$). Relationship between the plaque index and different variables was shown in Table 2.

**Table 1** Basic characteristics of patients in a group of KT and dialysis

| **Characteristics** | **Kidney transplant** |
|---|---|
| Gender, N (%) | |
| Male | 47 (66.2%) |
| Female | 24 (33.8%) |
| Age, mean (S.D.) | 49.7 (12.5) |
| Transplantation duration, mean (S.D.) | 100.1±82.8 |
| Education, N (%) | |
| None | 0 (0%) |
| Primary school | 6 (8.5%) |
| High school | 23 (32.4%) |
| University | 42 (59.2%) |
| Smoking, N (%) | |
| Never | 52 (73.2%) |
| Former | 18 (25.4%) |
| Smoking | 1 (1.4%) |
| Frequency of teeth cleaning, N (%) | |
| 0 | 0 (0%) |
| 1 | 7 (9.9%) |
| 2 | 64 (90.1%) |
| Toothpaste, N (%) | |
| Fluoride | 58 (81.7%) |
| Non-fluoride | 13 (18.3%) |
| Last visit to dentist, N (%) | |
| Within 6 months | 19 (26.8%) |
| Within 1 year | 11 (15.5%) |
| More than 1 year | 41 (57.7%) |
| Denture | |
| Yes | 10 (14.1%) |
| No | 61 (85.9%) |

**Table 2** Linear regression of Plaque index with different variables in kidney transplant recipients.

| **Independent variables** | **Univariate linear regression** | | **Multivariate linear regression** | |
|---|---|---|---|---|
| | **β (95% CI)** | ***p*-value** | **β (95% CI)** | ***p*-value** |
| Age | 0.010 (0.003-0.016) | **0.008** | 0.009 (0.003-0.018) | **0.041** |
| Gender | -0.131 (-0.317-0.056) | 0.167 | - | - |
| Education | -0.013 (-0.151-0.125) | 0.849 | - | - |
| Smoking | -0.062 (-0.248-0.123) | 0.506 | - | - |
| Transplant duration | 0.001 (-0.000-0.002) | 0.228 | - | - |
| Frequency of teeth cleaning | -0.288 (-0.578-0.003) | **0.052** | -0.248 (-0.609-0.112) | 0.172 |
| Fluoride toothpaste | -0.112 (-0.341-0.117) | 0.331 | - | - |

| Independent variables | Univariate linear regression | | Multivariate linear regression | |
|---|---|---|---|---|
| | β (95% CI) | *p*-value | β (95% CI) | *p*-value |
| Last visit to dentist | 0.030 (-0.075-0.134) | 0.572 | - | - |
| BUN | 0.001 (-0.005-0.007) | 0.765 | - | - |
| Creatinine | 0.009 (-0.049-0.067) | 0.756 | - | - |
| Hb | 0.012 (-0.023-0.048) | 0.484 | - | - |
| HbA1c | 0.083 (0.006-0.159) | **0.035** | 0.038 (-0.042-0.119) | 0.341 |
| LDL | -0.002 (-0.004-0.000) | 0.129 | - | - |

Abbreviations: β, regression coefficient; CI, confidence interval.

A statistical significance in univariate ($p<0.1$) and multivariate ($p<0.05$) linear regression analysis is indicated in bold.

**Discussion**

In the current study, kidney transplant recipients were male more than female. The maximum age is 79 years old. Most patients graduated from high school and university.

Oral lesions (11.3%) were found lower, compared to previous reports that the prevalence from 15.5-62% (Lopez-Pintor et al., 2010); (Gulec & Haberal, 2010); (Cebeci, Gulsahi, Kamburoglu, Orhan, & Oztas, 2009); (Avcu & Kanli, 2003); (Gaspar et al., 2015); (Mansourian, Manouchehri, Shirazian, Moslemi, & Haghpanah, 2013).

The most common oral lesion was oral ulceration (8.4%), much lower than previous studies. In patients with oral ulceration, they had received different combination of medicines: (tacrolimus, prednisolone, mycophenolate mofetil), (cyclosporin, prednisolone, mycophenolate mofetil), (tacrolimus, prednisolone, sirolimus), (everolimus and mycophenolate mofetil), (cyclosporin and mycophenolate mofetil). The oral ulcer was related to high dose immunosuppressive drugs, the withdrawal of corticoids or pharmatoxicologic problems (Hernandez et al., 2001); (Ponticelli & Passerini, 2005). There have been reports of oral ulcer in transplant recipients in relation to the immunosuppressants such as sirolimus (van Gelder et al., 2003); (Montalbano et al., 2004); (Sundberg et al., 2004), tacrolimus (Hernandez et al., 2001); (Macario-Barrel et al., 2001) and mycophenolate mofetil (Apostolou et al., 2004); (Garrigue et al., 2001); (Schmutz et al., 2003).

Fibroma was found in 1(1.4%) kidney transplant recipients which is lower than the previous study(2.8%)(Lopez-Pintor et al., 2010). The fibroma is reactive hyperplasia of fibrous connective tissue in response to irritation or trauma (Rotaru et al., 2003). In this study, lesion was found on tongue and biopsy revealed that the lesion was fibroepithelial polyp. However, there is no evidence showed that the lesion could be related to any medication or patient's immune status.

Gingival hyperplasia was found in a kidney transplant recipient who was caused by cyclosporin A and calcium channel blocker as reported in previous studies(Davidovich, Schwarz, Davidovitch, Eidelman, & Bimstein, 2005); (Lima et al., 2008); (Thomason et al., 1995). In this study, 26.8% of kidney transplant recipients received cyclosporin A, but only 1.4% of gingival hyperplasia was found, showed much lower prevalence when compared with previous studies(ranged from 8 to 85%)(Al-Mohaya et al., 2009); (Lima et al., 2008); (Allman, McWhorter, & Seale, 1994). Though the mechanism of gingival hyperplasia remains unknown, some studies reported that cyclosporin affects different signaling molecules in gingival fibroblasts (Bostrom, Bharath, Saulewicz, & Narayanan, 2005). Calcium channel blocker changes calcium ion flux which influences on collagenase, resulting in collagen production change and gingival fibroblast breakdown and finally collagen deposition in gingival tissue(Al-Mohaya et al., 2009) (Hood, 2002).

Median rhomboid glossitis, one form of erythematous candidiasis, was found in kidney transplant recipients who was on tacrolimus. Candida species are normal flora in the oral cavity can turn into opportunistic pathogens (Dongari-Bagtzoglou et al., 2009) when immune function is suppressed, and it is possible when the patient has received long-term immunosuppressive drugs. In previous studies oral

candidiasis varied from 9.4 to 46.7% (Al-Mohaya et al., 2009); (de la Rosa-Garcia et al., 2005); (Al-Mohaya, Darwazeh, & Al-Khudair, 2002); (King et al., 1994); (Gulec et al., 2003); (Tyrzyk et al., 2004).

In this study when different variable were adjusted, plaque index in kidney transplant recipients was increasingly significant correlated with age as healthy people (Holm-Pedersen, Agerbaek, & Theilade, 1975). It implies that after kidney transplantation immune system was restored by decreasing uremic toxin, causing the recovery of uremia. Moreover, another reason is that kidney transplant recipient has a much better quality of life (Al-Aradi et al., 2009).

## 5. Conclusion

All of the oral lesions found in this study can be related to immunosuppressive drugs, either as side effects or as a direct consequence of the patients' immune status. A regular professional dental examination is necessary for early detection of the oral lesion. Early detection allows consulting in medications adjustment and stops or relieves progression of the oral lesion.

For further study, bone lesions in oral and maxillofacial regions and periodontal status should be determined.

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