Prevalence of Oral Candidiasis in Chronic Renal Failure and Renal Transplant Pediatric Patients

Victoria Olivas-Escárcega * / Ma. del Socorro Ruiz-Rodríguez** / Ma. del Pilar Fonseca-Leal *** / Miguel Ángel Santos-Díaz**** / Antonio Gordillo-Moscoso***** / Juan Francisco Hernández-Sierra***** / Amaury de J. Pozos-Guillén******

The objective of this study was to evaluate the prevalence and risk factors associated with candidiasis in chronic renal failure (CRF) and renal transplant (RT) patients. A cross-sectional study was made of 66 patients who were divided into 2 groups: group A (33 patients), RT patients, and group B (33 patients), who had been diagnosed with CRF. Data with respect to demographics, treatment type and duration, clinical laboratory results for blood leucocytes, oral hygiene, and diagnosis of oral candidiasis were collected. Risk factors associated with candidiasis were evaluated. Among the 66 patients, 21 showed microbiologic evidence of oral candidiasis; 12 of these were from the RT group and 9 were from the CRF patients. Children who were renally compromised (RT and CRF) presented a frequency of oral candidiasis of 31.82%, with no difference between study groups. C. albicans was the most frequently isolated species from RT and CRF patients. Duration of therapy and oral hygiene were the variables associated with the presence of oral candidiasis.

Key words: candidiasis, chronic renal failure, renal transplant patients.
J Clin Pediatr Dent 32(4): 313–318, 2008

INTRODUCTION

During the last two decades, advances in pediatric nephrology have resulted in a significant increase in the number of children being treated for kidney disease. Many complications observed previously can now be prevented or effectively treated. These therapeutic advances have introduced new problems, including concerns for oral health.

Chronic renal failure (CRF) is a progressive and irreversible decline in the total number of functioning nephrons, with a concomitant decline in the glomerular filtration rate. It is accompanied by clinical and laboratory changes mainly related to the kidney`s inability to excrete breakdown products of body metabolism and fulfil their endocrine functions with secretion of active vitamin D and erythropoietin.[1] Data on epidemiology are available in many countries. The reported incidence of patients with chronic renal failure is 337, 90, 107, and 95 per million population in the US, Australia, New Zealand, and the UK, respectively. Approximately 8 million people in the United States are affected with some type of renal disease.[2] Incidence increases with age, and males are more commonly affected than females. Incidence also varies with ethnicity.[3] In Mexico, renal diseases are the ninth cause of death in the general population, with a rate of 10.37 per 100,000 inhabitants (SSA, 2000). The incidence of CRF continues to rise worldwide, and, as a consequence, increasing numbers of individuals with such disease will probably continue to require oral care. Patients with renal disease present oral manifestations. These include ammonia-like odor, dysgeusia (impaired taste), stomatitis, xerostomia, parotitis,[4-7] demineralization of mandible and maxilla, loss of trabeculation and lamina dura, metastatic calcification,[6] dental pulp mineralization and gingival

* Victoria Olivas-Escárcega, DDS, Resident, Pediatric Dentistry Postgraduate Program, Facultad de Estomatología, the Universidad Autónoma de San Luis Potosí, México.
** Ma. del Socorro Ruiz-Rodríguez, DDS, MS, Profesor and head, Pediatric Dentistry Postgraduate Program, Facultad de Estomatología, the Universidad Autónoma de San Luis Potosí, México.
*** Ma. del Pilar Fonseca-Leal, MD, MS, Associate professor, Department of Pediatric Nephrology, Hospital Central "Dr. Ignacio Morones Prieto, the Universidad Autónoma de San Luis Potosí, México.
**** Miguel Ángel Santos-Díaz, MD, MS, Associate professor, Department of Pediatrics, Hospital Central "Dr. Ignacio Morones Prieto, the Universidad Autónoma de San Luis Potosí, México.
***** Antonio Gordillo-Moscoso, MD, PhD, Associate professor, Clinical Epidemiology Postgraduate Program, Facultad de Medicina, the Universidad Autónoma de San Luis Potosí, México.
****** Juan Francisco Hernández-Sierra, MD, MS, Associate professor, Clinical Epidemiology Postgraduate Program, Facultad de Medicina, Universidad Autónoma de San Luis Potosí, México.
******* Amaury de J. Pozos-Guillén, DDS, PhD, Pediatric Dentistry Postgraduate Program, Facultad de Estomatología, Universidad Autónoma de San Luis Potosí, México.

Send all correspondence to: Dr. Amaury de Jesús Pozos Guillén, Facultad de Estomatología, UASLP, Av. Dr. Manuel Nava #2 Zona Universitaria, C.P. 78290; San Luis Potosí, S.L.P. México.
Tel: (444) 8262357 ext 106
Fax: (444) 8139743
E-mail: apozos@uaslp.mx

enlargement secondary to drug therapy,[8] and mucosal lesions (particularly ulcerations, and leukoplakia). The prevalence of dental caries is low (due to raised pH). Urea is present in the saliva, and there is greater concentration of salivary proteins, potassium, and sodium.[9] Anomalies of developing teeth, such as enamel hypoplasia, may be present.[10-12]

Although the care of children with end-stage renal disease has improved, renal transplantation remains the optimum treatment for these patients.[13] Significant progress has been achieved during the past 2 decades in grafting and in patient survival after renal transplantation. This is due, in part, to improvements in surgical and tissue-matching techniques; in addition to advances in antirejection drug therapy.[14] Renal transplant (RT) patients are usually conditioned with immunosuppressive agents such as corticosteroids, cyclosporine, azathioprine, and antilymphocyte monoclonal antibodies. Immunosuppressive treatment used for prevention of rejection renders transplant patients susceptible to infection.[13-18] Among the different types of infections that may occur in RT patients, those caused by fungi are associated with the highest mortality rate. Because of the chronic and extensive immunosuppressive therapy, organ transplant patients generally are expected to have a higher prevalence of oral candidal carriage and to be more susceptible to oral candidiasis.[15]

Candida albicans and related species are highly successful, opportunistic pathogens that reside in a benign state as commensals in the oral cavity. However, among the immunocompromised population, a drastic increase in the incidence of oral candidiasis has been observed.[19] Angular cheilitis has been described in up to 4% of hemodialysis and renal allograft recipients. Other oral candidal lesions such as pseudomembranous, erithematous, and chronic atrophic candidiasis have been reported in allograft recipients.[16,20]

The objective of this study was to evaluate the prevalence and risk factors associated with candidiasis in chronic renal failure and renal transplant pediatric patients.

MATERIAL AND METHODS

Subjects were recruited from the Clinic for Pediatric Dentistry Postgraduate Program, Facultad de Estomatologia, San Luis Potosi University, General Hospital "Dr. Ignacio Morones Prieto" and General Hospital Number 1, Instituto Mexicano del Seguro Social, San Luis Potosí, Mexico. The study was approved by the Ethics Committee. The objective of the study was explained to either the parents or legal guardians, and written informed consent was obtained. A cross-sectional study was made of 66 patients who were divided into 2 groups: group A (33 patients) RT patients, and group B (33 patients), who had been diagnosed with CRF. Inclusion criteria were as follows: patients with renal transplants or chronic renal failure, of both sexes, and between 2 and 20 years of age. Data with respect to demographics, treatment type and duration, clinical laboratory results for blood leucocytes, oral hygiene, and diagnosis of oral candidiasis were collected. Previously, studies had been done to assess the reproducibility of recording the clinical diagnosis of oral candidiasis. The kappa value for interexaminer agreement was 0.90, and the reproducibility for laboratory identification was 1.00 (kappa value).

For isolation of the *Candida* species, oral samples were obtained from the mid-dorsum of the tongue and floor of the mouth with a sterile swab, immediately inoculated into Sabouraud`s Dextrose Agar (SDA; Difco Laboratories, Detroit, MI, USA) plates, incubated at 37^{O}C for 48 to 72 hours, and evaluated daily for growth of yeast colonies. Colonies growing on original cultures were tested for germ-tube formation, chlamydospore production, and ability to grow at 45^{O}C. Isolated yeast colonies were streaked on Tween 80-oxgall-caffeic acid (TOC) agar (Remel, Lenexa, KS, USA), then the plates were incubated at 37^{O}C for 3 hours for evaluation of germ-tube formation, followed by incubation at room temperature for 2 to 3 days in the dark. Germ-tube and chlamydospore production was observed using phase contrast light microscopy. The identification of the *Candida* species was characterized for substrate assimilation profiles using the API 20C system (bioMérieux Vitek, Hazelwood, MO, USA).

For the statistical analysis, the data were analyzed by a nonparametric statistical test. The chi-square and Fisher exact tests were used where appropriate. The potential effect of risk factors associated with candidiasis was controlled using logistic regression analysis. A probability value of $<.05$ was considered statistically significant. The R version 1.6.2 statistical program was used to analyze the data.[21]

RESULTS

A total of 66 patients were studied. Group A (RT) included 20 males (61%) and 13 females (39%) ranging in age from 8 to 20 years, with mean age of 16.3; group B (CRF) included 19 males (58%) and 14 females (42%) ranging in age from 2 to 20 years, with mean age of 15.1. Serum urea and creatinine concentrations were 63.0 ± 2.4 mg/dL and 2.90 ± 3.8 mg/dL, respectively, for group A and 117.21 ± 43.5 mg/dL and 7.22 ± 7.4 mg/dL, respectively, for group B. These clinical laboratory results revealed significant differences between groups ($P < .05$). The mean duration of renal transplant was 31 months, ranging from 0.5 to 71 months. Twenty-four patients had a cadaver renal transplant, whereas living donors were used for transplantation in 9 patients. In the CRF group, hemodialysis (11 patients) and peritoneal dialysis (22 patients) were the modalities of therapy, with a mean duration of 25 months, ranging from 1 to 108 months. Thirty-seven patients (56.06%) were taking some medications. Table 1 presents the medications used by the CRF and RT patients.

The mouth of each patient was evaluated by the main examiner for oral manifestations. Candidiasis, enamel hypoplasia, and gingivitis were the most common manifestations in both groups. Caries was found in 42.42% of RT patients and 45.45% of CRF patients. Other findings were gingival enlargement, ulcerations and leukoplakia (Table 2).

Among the 66 patients, 21 (31.82%) showed microbiologic evidence of oral candidiasis; 12 (36.36%) of these were

Table 1. Medication used by patients with renal transplant and chronic renal failure

Medications used	RT Frequency (%)	CRF Frequency (%)
No medication	0 (0.00)	29 (87.88)
CsA, Pd, Aza	20 (60.61)	1 (3.03)
CsA, Pd, Micofenolato mofetil	7 (21.21)	0 (0.00)
CsA, Pd	1 (3.03)	2 (6.06)
CsA, Tacrolimus, Pd	2 (6.06)	0 (0.00)
CsA, Pd, AZA Mycostatin	1 (3.03)	0 (0.00)
Tacrolimus, Pd, Mycostatine	1 (3.03)	0 (0.00)
Tacrolimus, Pd	1 (3.03)	0 (0.00)
Nifedipine	0 (0.00)	1 (3.03)

RT: renal transplant patients; CRF: chronic renal failure patients; CsA: cyclosporine; Pd: prednisone; Aza: azathioprine.

Table 2. Oral manifestations of hard and soft tissues in renal transplant and chronic renal failure patients

	RT Frequency (%)	CRF Frequency (%)	P value
Hard tissue manifestations			
Enamel hypoplasia	32 (96.97)	32 (96.97)	NS
Caries	14 (42.42)	15 (45.45)	NS
Soft tissue manifestations			
Gingivitis	31 (93.94)	22 (66.67)	0.005*
Candidiasis	12 (36.36)	9 (27.27)	NS
Gingival enlargement	24 (72.73)	1 (3.03)	<.001*
Ulcerations	9 (27.27)	8 (24.24)	NS
Leukoplakia	4 (12.12)	4 (12.12)	NS

RT: renal transplant patients; CRF: chronic renal failure patients.
*Statistically significant (X2, Fisher exact tests); NS: not significant

from the RT group and 9 (27.27%) were CRF patients. There was no difference in candidiasis prevalence between groups.

The majority of the isolates consisted of *C. albicans* (13 cases; 62%). Other less frequently encountered species were 3 cases of *C. sp* (14%), 2 cases of *C. parapsilosis* (9.5%), and *C. krusei, T. candida, T. beigelli*, with 1 case each (Table 3). The prevalence of oral candidiasis colonization in RT and CRF patients was not influenced by age or gender.

Oral hygiene was found to be poor in 23 patients (70%) of the RT group and 22 patients (67%) of the CRF group. Twenty patients (95.2%) of both groups with positive candidiasis had poor hygiene (Table 4).

We also evaluated the possible influence of some risk factors for the development of oral candidiasis in these groups of patients. Logistic regression analysis confirmed that duration of therapy and oral hygiene were variables associated with the presence of candidiasis with an odds ratio (OR) of 1.043 ($CI_{95\%}$ 1.001-1.07) and OR of 3.98 ($CI_{95\%}$ 2.90-5.47), respectively.

DISCUSSION

The systemic condition of patients with renal failure and renal transplants exhibits oral manifestations, and it has specific implications for dental treatment.[6] The oral manifestations involve both soft and hard tissues and affect teeth, bone, and mucosa.[3,22,23] The prolonged duration of the disease process and extended life maintained by transplantation and combinations of drugs result in several secondary problems both before treatment and as a consequence of the drug therapy that helps keep patients alive.[7]

The treatment of CRF includes dietary changes, correction of systemic complications, and dialysis or a renal graft. RT patients are usually conditioned with immunosuppressive agents. This therapy is required to minimize the risk of allograft rejection. Commonly used agents are corticosteroids, azathioprine, cyclosporine, and tacrolimus. Patients of this study were treated with these agents and other non-immunosuppressors agents such as micophenolate mofetil, mycostatin, and nifedipine. These agents reduce the patient's immune response and increase the risk of developing infections.[14,15,18] *Candida*, mainly *Candida albicans*, is part of the normal flora of the mouth and is found in more than 40% of the symptom-free population. It has been estimated that about 6% of patients in third-world countries develop systemic fungal infection after renal transplantation.[24] RT patients have a higher prevalence of oral candidal carriage and are more susceptible to oral candidiasis than healthy subjects. Few studies have reported the prevalence of oral candidiasis in RT patients.[15,16] The majority of the studies report the detection of *Candida* in both healthy and HIV-infected populations. Studies have shown candidiasis to be one of the most common oral infections in children.[19,25] King *et al*,[16] in a study evaluating the prevalence of oral lesions in RT patients found a prevalence of oral candidiasis in 9.4%. Gülec et al[26] reported a prevalence of 25.5%. Al-Mohaya *et al* [15] found that 15.5% of RT patients showed clinical and microbiologic evidence of oral candidiasis, with the *C. albicans* species being isolated with the most frequency. This finding was similar to our study, in which *C. albicans* was

Table 3. Candida species recovered in patients with renal transplant and chronic renal failure

Species	RT Frequency	CRF Frequency	Total frequency (%)
C. albicans	9	4	13 (62)
C. sp	1	2	3 (14)
C. parapsilosis	0	2	2 (9.5)
C. krusei	0	1	1 (4.7)
T. candida	1	0	1 (4.7)
T. beigelli	1	0	1 (4.7)
Total frequency (%)	12 (31.82)	9 (27.27)	21 (31.82)

RT: renal transplant patients; CRF: chronic renal failure patients.

Table 4. Relation of candidiasis and oral hygiene in patients with renal transplant and chronic renal failure

Oral hygiene	Positive candidiasis Frequency (%)	Negative candidiasis Frequency (%)	Total
Good	1 (4.8)	20 (44.4)	21 (31.8)
Poor	20 (95.2)	25 (55.6)	45 (68.2)
Total	21 (100)	45 (100)	66 (100)

isolated in 62% of the patients in both groups. *C. albicans* is the most commonly isolated species reported in the literature from both RT patients and healthy subjects.

The present investigation showed that the oral cavity of 36.36% of RT patients and 27.27% of CRF patients were colonized with *Candida*; although the difference was not statistically significant. This prevalence may be explained partially by the oral hygiene: the prevalence of candidiasis was 95.2% in patients with poor hygiene in both groups. Apparently, the type of immunosuppressive medication has no influence on the predisposition to oral candidiasis. Similar findings were reported by Klassen and Krasco,[20] who found that renal patients had worse oral hygiene than the healthy control patients. However, duration of therapy independent of immunosuppression type was associated with the presence of candidiasis.

Other oral manifestations found in this study were gingivitis, which was associated with poor plaque control, and gingival enlargement, inasmuch as 94% of RT patients used cyclosporine and nifedipine therapeutically. Of the latter, 73% showed gingival enlargement. In the literature, the reported prevalence of gingival enlargement ranges between 13% and 85% in adult RT patients.[27] Another factor associated with gingival enlargement is inadequate oral hygiene and plaque accumulation. In our study, 68% of patients showed poor hygiene. The prevalence of caries was 43% in both groups. Some studies report that the prevalence of dental caries in patients with CRF is low,[9,21,28] likely because of increased pH of the oral cavity. This occurs because salivary urea is split to form ammonia, which may raise the pH above the critical level for demineralization of dental enamel. The increased salivary phosphate concentration could contribute to the higher buffer capacity.[9] These salivary changes might explain the low caries incidence in these patients despite their poor oral hygiene. Enamel hypoplasia, the most common abnormality in the development and mineralization of human teeth, was found in up to 95% of patients. The prevalence of enamel hypoplasia has been reported in various studies. In patients with renal disease, it varies from 31% to 83%, depending on the racial, ethnic, nutritional, and socioeconomic status of the child, type of classification system used, and method of examination.[12,21,29]

The 36% and 27% prevalence of oral candidiasis among RT patients and CRF patients, respectively, represents a significant finding because this prevalence is higher than that reported by others.[15,16,26] This high prevalence confirms the importance of regular and careful screening in these patients and the development of dental education programs.

Children with renal disease require close monitoring by their pediatric dentist in close collaboration with the pediatric nephrologist. The dentist should regularly see patients who have been prescribed drugs known to be associated with oral manifestations. Close cooperation with the prescribing physician is vital because renal failure alters the disposition—even the pharmacological properties—of some drugs.[22] Dental evaluation should focus on the identification and removal of potential sources of infection. Untreated dental infection in immunosuppressed individuals could contribute to morbidity and transplant rejection. For successful treatment of patients with renal disease, a multidisciplinary approach is essential.

CONCLUSIONS

Children who are renally compromised (RT and CRF) presented a frequency of oral candidiasis of 31.82%. There was no difference between study groups. *C. albicans* was the most frequently isolated species from RT and CRF patients. Duration of therapy and oral hygiene were variables associated with the presence of oral candidiasis.

ACKNOWLEDGMENTS

Special thanks to Ma. Blanca Ortiz and Ma. Magdalena Castillo for their time and effort in assisting this study. We would like to thank Norman Wahl, for his assistance in editing this manuscript.

REFERENCES

1. Fogo A, Kon W. Pathophysiology of progressive chronic renal disease. In: Avner ED, Harmon WE, Niaudet P, editors. Textbook of pediatric nephrology. 5th ed. Philadelphia: Lippincott Williams & Wilkins, p. 1267–1480, 2004.
2. De Rossi SS, Glick M. Dental considerations for the patient with renal disease receiving hemodialysis. J Am Dent Assoc, 127: 211–9, 1996.
3. Proctor R, Kumar N, Stein A, Moles D, Porter S. Oral and dental aspects of chronic renal failure. J Dent Res, 84: 199–208, 2005.
4. Davidovich E, Schwarz Z, Davidovitch M, Eidelman E, Bimstein E. Oral findings and periodontal status in children, adolescents and young adults suffering from renal failure. J Clin Periodontol, 32: 1076–82, 2005.
5. Davidovich E, Davidovits M, Eidelman E, Schwarz Z, Bimstein E. Pathophysiology, therapy, and oral implications of renal failure in children and adolescents: an update. Pediatr Dent. 27: 98–106, 2005.
6. Sowell SB. Dental care for patients with renal failure and renal transplants. J Am Dent Assoc, 104: 171–7, 1982.
7. Lucas VS, Roberts GJ. Oro-dental health in children with chronic renal failure and after renal transplantation: a clinical review. Pediatr Nephrol, 20: 1388–94, 2005.
8. Somacarrera ML, Hernandez G, Acero J, Moskow BS. Factors related to the incidence and severity of cyclosporin-induced gingival overgrowth in transplant patients: a longitudinal study. J Periodontol, 65: 671–5, 1994.
9. 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, 88: 316–9, 1999.
10. Nikiforuk G, Fraser D. The etiology of enamel hypoplasia: a unifying concept. J Pediatr, 98: 888–93, 1981.
11. Koch MJ, Bührer R, Pioch T, Schärer K. Enamel hypoplasia of primary teeth in chronic renal failure. Pediatr Nephrol, 13: 68–72, 1999.
12. Ibarra-Santana C, Ruiz-Rodríguez MS, Fonseca-Leal MP, Gutiérrez-Cantú FJ, Pozos-Guillen AJ. Enamel hypoplasia in children with renal disease in a fluoridated area. J Clin Pediatr Dent, 31: 274–8, 2007.
13. Bereket G, Fine RN. Pediatric renal transplantation. Pediatr Clin North Am, 42: 1603–28, 1995.
14. Peddi VR, Whiting J, Weiskittel PD, Alexander JW, First MR. Characteristics of long-term renal transplant survivors. Am J Kidney Dis, 32: 101–6, 1998.
15. Al-Mohaya MA, Darwazeh A, Al-Khudair W. Oral fungal colonization and oral candidiasis in renal transplant patients: the relationship to Miswak use. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 93: 455–60, 2002.

16. King GN, Healy CM, Glover MT, 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, 78: 718–26, 1994.
17. Greenspan D, Greenspan JS, De Souza YG, Levy JA, Ungar AM. Oral leukoplakia in a HIV-negative renal transplant recipient. J Oral Pathol Med, 18: 32–4, 1989.
18. Seymour RA, Thomason JM, Nolan A. Oral lesions in organ transplant patients. J Oral Pathol Med, 26: 297–304, 1997.
19. Jabra-Risk MA, Torres SR, Rambob I, Meiller TF, Grossman LK, Minah G. Prevalence of oral *Candida* species in a North American pediatric population. J Clin Pediatr Dent, 31: 260–3, 2007.
20. Klassen JT, Krasko BM. The dental health status of dialysis patients. J Can Dent Assoc, 68: 34–8, 2002.
21. Ihaka R, Gentleman R. R: a language for data analysis and graphics. J Comp Graph Stat, 5: 299–314, 1991.
22. Nunn JH, Sharp J, Lambert HJ, Plant ND, Coulthard MG. Oral health in children with renal disease. Pediatr Nephrol, 14: 997–1001, 2000.
23. Al-Nowaiser A, Roberts GJ, Trompeter RS, Wilson M, Lucas VS. Oral health in children with chronic renal failure. Pediatr Nephrol, 18: 39–45, 2003.
24. Chugh KS, Sakhuja V, Jain S, Talwar P, Minz M, Joshi K, Indudhara R. High mortality in systemic fungal infections following renal transplantation in third-world countries. Nephrol Dial Transplant, 8: 168–72, 1993.
25. Brown DM, Jabra-Rizk MA, Falkler WA Jr, Baqui AA, Meiller TF. Identification of *Candida dubliniensis* in a study of HIV seropositive pediatric dental patients. Pediatr Dent, 22: 234–8, 2000.
26. Güleç AT, Demirbilek M, Seçkin D, et al. Superficial fungal infections in 102 renal transplant recipients: a case-control study. J Am Acad Dermatol, 49: 187–92, 2003.
27. Friskopp J, Klintmalm G. Gingival enlargement: a comparison between cyclosporine and azathioprine treated renal allograft recipients. Swed Dent J, 10: 85–92, 1986.
28. Al Nowaiser A, Lucas VS, Wilson M, Roberts GJ, Trompeter RS. Oral health and caries related microflora in children during the first three months following renal transplantation. Int J Paediatr Dent, 14: 118–26, 2004.
29. Slayton RL, Warren JJ, Kanellis MJ, Levy SM, Islam M. Prevalence of enamel hypoplasia and isolated opacities in the primary dentition. Pediatr Dent, 23: 32–6, 2001.