



REVIEW

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Oral disorders in patients with chronic renal failure.

Narrative review.

Abstract: Chronic renal failure (CRF) is one of the best known renal diseases. It is characterized by a deterioration in the overall renal function and is associated with other conditions such as hypertension, diabetes mellitus, uropathy, chronic glomerulonephritis and autoimmune diseases. Patients with CRF show alterations of the masticatory system that are specific to the disease and other type of disorders as a result of treatment. Oral health in dialysis and transplant patients tends to be poor, which makes them more likely to develop pathological conditions in the oral cavity, potentially increasing morbidity, mortality and affecting the quality of life of patients. Among the lesions we can find dysgeusia, periodontitis, candidiasis, gingival bleeding, petechiae, and joint alterations. Gingivitis and xerostomia associated to long-term use medications can cause oral lesions. Children with CRF show two oral conditions of interest: high incidence of dental anomalies and low caries activity. In patients receiving a kidney transplant, previous dental treatment is critical because the immune status of the patient will be affected not only by the toxemia, but by the immunosuppressive drugs used to prevent transplant rejection. Therefore, the dentist plays an important role in training parents and/or guardians, doctors and paramedics on the treatment of oral lesions in these patients.

Keywords: *Chronic renal failure, Oral manifestations, Transplantation, Dialysis, Immunosuppression.*

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INTRODUCTION.

Chronic renal failure (CRF) is defined as a progressive loss of the ability of the kidneys to purify solutes, concentrate urine and preserve electrolytes with the subsequent deterioration of their function¹⁻⁴.

Renal alterations lead to a general deterioration of health characterized by a physiological imbalance that strongly influences the quality of life of people with the disorder. Some medical treatments have been implemented in order to improve the health of the patient. However, alterations caused by CRF,

and sometimes by the medications given to treat it, result in alterations in various systems, including the stomatognathic system^{2,3}.

End-stage renal disease (ESRD) is the final stage of the disorder and patients must be treated with hemodialysis, affecting their quality of life and causing alterations in different parts of the body, including oral manifestations^{5,6}.

Patients with CRF may develop oral lesions, which often affect the normal functioning of the oral cavity resulting in infectious complications caused by

microorganisms that, otherwise, routinely interact with the host^{3,7}. Most CRF patients have a poor oral hygiene, which can further result in a more serious complication of the systemic disease^{2,6}.

Regular dental care in patients with well-controlled renal disorders usually occurs smoothly. The oral cavity usually reflects how well the kidney disease is controlled; therefore, the most severe oral problems can be found in poorly controlled patients⁸⁻¹³.

Given the characteristics of this type of patients, it is necessary to determine their oral health conditions in order for the dentist to plan the treatment course most suitable for them, to provide higher quality care and improve the patient's overall health conditions.

The aim of this article is to review the most common oral disorders reported in the literature and their dental management in relation to patients with chronic renal failure.

CHRONIC RENAL FAILURE: DIAGNOSIS AND MANAGEMENT.

Chronic renal failure is defined as an almost always irreversible, slow and progressive loss of kidney function as a result of diseases that cause a diffuse bilateral destruction of the renal parenchymal. Its clinical manifestation involves specific symptoms of the disease and manifestations caused by the loss of kidney function^{2,6,8}.

Incidence of CRF is approximately 200 cases per million people in Western countries. Males are the most affected and the mean age of patients is 55 years^{1,2,7,14-16}.

Incidence of kidney disease in children includes tubular dysfunction, tubular acidosis, chronic renal failure, kidney stones, among others^{17,18}.

In Chile, epidemiological indicators show a prevalence of 2.7% of CRF in the general population and an increase in the number of patients receiving chronic hemodialysis, from 12.7 patients per million people in 1980 to 903 in 2010¹¹.

Indicators of public health at global and national levels show an alarming and progressive increase in the number of patients with chronic renal disease. These are associated with a high prevalence of diseases such as diabetes mellitus (in 40-60%), hypertension (in 15-30%), primary and secondary glomerulonephritis (less than 10%) and polycystic kidney disease (in 3.2%). In the case of diabetic patients CRF is a result of high blood glucose levels, which are highly toxic to the nephrons. This condition is called diabetic nephropathy³. It may also be caused by immunological diseases such as systemic lupus erythematosus and neoplastic disorders^{7,9-11}.

Kidney failure can take two forms: acute and chronic. Acute renal failure (ARF) has an abrupt onset and is potentially reversible. The first sign of a possible ARF is oliguria, but it must be taken into account that up to 50% of patients with this condition may have normal or even higher levels of diuresis. Chronic renal failure progresses slowly over a period of at least three months and can lead to permanent kidney failure. The main consequence of the loss of renal function is the difficulty to remove excess water and waste products from metabolism such as urea, uric acid, and creatinine³.

CRF is a stage in which an endogenous irreversible loss of kidney function has occurred serious enough to make the patient permanently dependent on renal replacement therapy: dialysis or transplantation, in order to prevent that uremia put his or her life in danger. Patients with kidney disease are more susceptible to infection due to general weakness and depression of their immune response^{6-8,12}.

Dialysis is an artificial mechanism that cleans the blood of waste nitrogen and other toxic products of metabolism. In hemodialysis (HD), blood filtering is performed by a machine (dialyzer) equipped with a semipermeable membrane that allows the flow of excess fluids and waste products. Most HD patients must undergo the procedure at least three times a week^{7,12}.

As the disease may not show symptoms, it is likely that physicians first detect the condition through routine blood and urine tests. The National Kidney Foundation³

(NKF) recommends three simple tests to detect kidney disease:

- Measuring blood pressure.
- Testing for protein or albumin in the urine.
- Calculation of glomerular filtration rate (GFR) based on serum creatinine measurement.

The measurement of blood urea nitrogen level provides additional information. If blood and urine tests indicate that there is reduced renal function, physicians may suggest other tests to help identify the cause of the problem such as ultrasound, computed tomography or magnetic resonance imaging, and kidney tissue biopsies if necessary.

Clinical manifestations of CRF involve changes in the cardiovascular, hematopoietic, muscular, endocrine, genitourinary, pulmonary, dermatological, and gastrointestinal systems, as well as changes in blood chemistry, bone metabolism and oral health¹³.

This condition often occurs as a syndrome characterized by nausea, morning vomiting, loss of appetite, fatigue, weakness, intolerance to temperature changes, altered mental status and irritability. Neurological disorders and other characteristic abnormalities such as discoloration of the skin and ammonia breath odor may be also present^{2,11,19}.

In CRF uremic poisoning has a special effect on platelets and lymphocytes, making patients susceptible to bleeding, showing poor humoral and cellular defense^{2,20}.

Decreased cellular immune function and chemotactic defects induced by uremia predispose patients to infection, which is the second leading cause of death in these patients²¹.

Cyclosporine-A (CsA) is one of the drugs used to prevent rejection of kidney transplants. It is a cyclic polypeptide calcineurin inhibitor. Its use prevents the appearance of genes of various cytokines whose activity is critical for T cell activation, including interleukins W and 4 , interferon gamma, tumor necrosis factor alpha and others, thereby preventing lymphocyte proliferation. This drug is used alone or in combination with other immunosup-

pressive drugs^{20,22-24}.

In patients receiving immunosuppressive therapy, the response mediated by immune cells is depressed, increasing the likelihood that oral pathogens will cause local destruction and opportunistic infections due to the inability of the immune system to suppress and destroy these pathogens^{1,22}.

In renal transplant patients different oral lesions are observed, including gingival enlargement. The condition in turn is exacerbated by poor oral hygiene^{22,25}. Gingival enlargement is a well known side effect of cyclosporin and calcium channel blockers. Both drugs are widely used in transplant patients^{1,23}.

ORAL DISORDERS

About 90% of patients with renal failure have oral symptoms that affect both bone and soft tissue. These may be caused by dialysis, kidney transplantation and etiologic factors of CRF^{2,3,7,8,26,27}.

CRF patients have medical, psychological and socio-economic characteristics that may predispose them to dental problems. Oral health in dialysis and transplant patients tends to be poor, and they are more likely to develop diseases of the oral cavity, potentially increasing morbidity, mortality and affecting the quality of life of patients^{1,14}. When pediatric patients suffer from renal disease they will have oral manifestations of the condition that will depend on the type of kidney disease, medication administered, specific conditions of the host and the age of the patient at the onset of the disease²⁸.

The following dental alterations are described in the literature:

a) **Dysgeusia and cacogeusia:** There may be an unpleasant metallic or salty taste in the mouth as a result of the increase in urea concentration in saliva and its subsequent transformation into ammonia, which occurs in about one third of individuals undergoing hemodialysis. In addition, there are decreasing levels of calcium and magnesium^{2,3,7,13,15,21}.

b) **Xerostomia:** As a result of the restriction on fluid

intake, side effects of medications (primarily antihypertensive drugs), possible disruption of the salivary glands, and secondary oral breathing problems due to lung perfusion^{12,15,28}. However, decreased salivary flow was not observed in studies conducted in post-dialysis patients when compared to healthy subjects because once the procedure is over water balance is normal levels⁷.

c) Coated tongue: As a result of fluid intake restriction, and poor oral hygiene⁶.

d) Mucosal pallor: Because patients suffer from anemia generated by the decline in erythropoietin production in the kidney. This can mask diseases such as gingivitis and even periodontitis^{2,29}.

e) Gingival bleeding: As a result of platelet dysfunction, thrombocytopenia and thrombasthenia, or both, as well as a result of the effects of anticoagulants in patients undergoing hemodialysis. Gums and mucous can become purple due to deficiency in coagulation factor VIII, spontaneous gingival bleeding and intraoral edema^{3,29}.

Petechiae and bruising appear as a consequence of the bleeding caused by antithrombotic drugs².

f) Patients with chronic kidney disease suffer from inflammation caused by multiple processes, such as transient infections, comorbidities and intermittent dialysis. Chronic periodontitis is a persistent, continuous and local source of inflammation, thereby contributing to systemic inflammation^{10,28,30-32}.

There is some controversy in the literature regarding gingival inflammation in patients with CRF. On the one hand, some studies report a low incidence of gingivitis, which is explained in terms of immunosuppression and uremia, which could inhibit the inflammatory response to plaque accumulation. On the other hand, some studies report the opposite, as multiple lines of epidemiologic evidence indicate that the prevalence of periodontal disease is higher in patients with CRF. It is also possible to observe an increase in the prevalence and severity of gingivitis and destructive periodontal disease in CRF patients on dialysis^{10,13,29}.

According to the study by Yeras *et al.*³³, periodontal

disease was detected in 72.0% of in patients receiving hemodialysis treatment.

Gingival enlargement is related to consumption of cyclosporin in the case of kidney transplants. It mainly affects the surface of the interdental papilla, although larger areas may also be affected, including the gingival, lingual margins and palatal surfaces. Treatment often requires surgical resection. Tacrolimus, another drug used for this purpose, has not been associated with gingival enlargement^{3,28,32}.

g) Tartar: Patients with CRF are susceptible to develop dental calculus due to increased levels of urea in saliva, phosphorus and large amounts of calcium carbonate that some patients take as part of their treatment^{6,9,15}. A study conducted in 180 patients in Iran showed a 100% prevalence of oral abnormalities, being the most common: tartar, high DMF and plaque indexes and gingivorrhagia³⁴. Several studies in Brazil, Canada, Jordan, Israel, Spain, Taiwan, Turkey and the United States have reported an increase in plaque levels in patients on dialysis³².

h) Reduction in the occurrence of dental caries: It is known that urea is released in patients with severe renal impairment, which dissociates into ammonia and carbon dioxide. Ammonia causes an increased oral pH, which "protects" teeth^{14,28}. Some studies have observed children with CRF and a high percentage of caries. It is explained as a consequence of the reduced thickness of the enamel as well as its lower quality because of hypoplasia. In turn, the observed decrease in salivary flow significantly affects the cleaning of the oral cavity³.

i) Severe erosion on the lingual surfaces of the teeth: Frequent gastroesophageal reflux and vomiting induced by uremia, drugs, dialysis and the consumption of sweets high in sugar to mask taste disturbance could precipitate this condition^{7,28,35}.

j) Alterations in the dentinal tubules: narrowing and enlargement of pulp giving rise to prominent pulp calcifications, dental taurodontism, enamel hypoplasia, delayed growth and tooth eruption^{3,15,28}.

Defects in the development of enamel result from al-

terations in the metabolism of calcium and phosphate, and coincide with the onset of renal disease and its severity. When there is enamel hypoplasia there is also hypocalcemia; a decrease in serum levels of 1.25 dihydroxycholecalciferol and increased serum levels of inorganic phosphate and parathyroid hormone are also observed. Enamel hypoplasia is also found in patients with nephrocalcinosis and hypokalemia. It should be mentioned that the prolonged use of corticosteroids to control the disease produces an alteration in calcium deposits in the body^{15,28}. The first visible sign of kidney disease in the oral cavity is enamel hypoplasia due to the alteration in the dental mineralization. Seventy-seven per cent of the population with chronic renal failure have enamel hypoplasia^{3,28}.

k) Musculoskeletal disorders: temporomandibular joint (TMJ), bone demineralization, increased trabecular bone and difficulty in uptake and metabolism of calcium and serum phosphorus^{2,27,36}.

l) Renal osteodystrophy: Characterized by fractures, bone pain, morphological changes (micrognathia, malocclusion and facial dysmorphism, dolichocephaly, frontal bossing, nasal backs flattened with wide alar base, severe maxillary hyperplasia, severe labial incompetence and wide bands of exposed mucosa). Subperiosteal bone resorption or altered bone density characterized by large radiolucent areas and lobular form both in upper and lower jaw can be observed radiographically^{13,15}.

m) Uremic stomatitis, white plates distributed mainly in oral mucosa, tongue, and floor of the mouth are clinically observed. It may be accompanied by unpleasant taste, oral pain and burning sensation. They can be classified into Type I uremic stomatitis, that causes redness and thickening of the mucous membranes, which are covered with a rough, sticky, grey exudate. In type II an apparent mucosal ulceration can be observed^{3,28,29}.

Among the different types of serious systemic infections that may follow post-renal transplant are those caused by fungi, which usually lead to a high mortality rate due to opportunistic infections. Prolonged immuno-

suppression caused by the consumption of medications (cyclosporine) may result in other negative effects such as oral candidiasis, hairy leukoplakia, squamous cell carcinoma of the lip, Non-Hodgkin lymphoma and herpes simplex infections^{1,15,22,37,38}.

Both oral diseases and dental management can produce bacteremia. It can lead to significant morbidity and potential mortality in patients with renal failure and on dialysis treatment^{8,15}.

CLINICAL MANAGEMENT.

Currently there is no validation protocol for comprehensive oral health care in patients with CRF and its relationship with other medical interventions². The dentist must be familiar with the implications of kidney failure in the body and specifically in the oral structures. Consultation with the nephrologist is going to provide important information on the status of the disease, type of treatment, the best dental care and possible complications^{7,21}.

Children with chronic renal failure have two oral conditions of interest: a high incidence of dental anomalies and low caries activity. In pediatric patients with systemic involvement interconsultation with the dentist should be established as early as possible, because in this way the specialist can instruct the mother in areas such as hygiene care, risk factors for dental caries, use of preventive systems, among others. In the study by Acosta *et al.*²⁸, forty-four per cent of children with CRF had never visited the dentist.

According to the clinical condition of the patient a dental program for periodontal care must be established and strictly followed every 3 months^{7,20,39}.

In dialysis patients the most effective dental care is performed the day after dialysis when there is an electrolyte balance. Surgical procedures should be performed at least 8 hours after completion of dialysis^{7,20,24}.

The main considerations for the management of these patients are:

a) Bleeding: A meticulous surgical technique must be used, wound closure as main concern and the use of es-

Table 1. Medication guide for patients with end-stage renal disease⁷.

Drug	Elimination metabolism	Adjustment method and posology
Antimicrobial	Clindamycin	H
	Metronidazole	H
	Doxycycline	H (R)
	Metronidazole	R
	Ketoconazole	H
	Cefadroxil	R
	Azithromycin	H
Analgesic	Paracetamol	H
Anesthetics	Mepivacaine	H
	Lidocaine	H

R: Renal excretion. H: Hepatic metabolism. The letter in parentheses is the least important path of excretion, but equally significant.

sential and of traditional elements such as oxidized re-generated cellulose (Surgicel) and microfibrillar collagen to prevent bleeding complications^{7,21}.

b) Hypertension: For this it is necessary to control the blood pressure of the patient at the beginning and end of the session⁷.

c) Use of medication: CRF produces abnormal excretion of some drugs, abnormal metabolism of others, so dentists must consult before prescribing any medication or adjust the doses of antibiotics, analgesics and local anaesthetics (Table 1). Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen and diclofenac, have a high degree of binding to plasma proteins and are mainly metabolized by the liver. These drugs should be avoided if possible at all stages of CRF, unless they have specific and monitored indication because of their nephrotoxic potential. They have the ability to accelerate the progression of kidney damage and entry into dialysis treatment, or accelerate loss of valuable residual renal function in these patients^{7,22}.

It is critical to eliminate any infection in the oral cavity as soon as possible. The dentist should consider antibiotic prophylaxis with amoxicillin or clindamycin to treat bleeding and/or if there is risk of septicemia (extractions, periodontal treatment, endodontic treatment and periapical surgery, or placement of orthodontic appliances, etc.)^{20-22,39}.

Importantly, patients with renal impairment should be administered no fluoride, as they have retention of fluoride. The dentist should indicate the use of alcohol-free rinses and artificial saliva in patients who have not received transplant to alleviate the effects of xerostomia⁷.

Dental management of a patient with end-stage renal function involves important biological and psychological considerations, because the patient's attitude may interfere with complex dental procedures, such as prosthetic treatments^{2,22}.

In patients who have received a kidney transplant, previous dental treatment is crucial to avoid the complications of immunosuppressive treatment and associated toxemia^{33,39}. As in other transplant patients, it is necessary to insist on monitoring oral hygiene to reduce the frequency and severity of gingival hyperplasia and other oral complications. Promoting good dental hygiene reduces the risk of oral infections that may predispose a patient to sepsis, endocarditis and possible obstruction of vascular access for hemodialysis, or catheters for peritoneal dialysis²².

All this reinforces the importance of teamwork to prevent the occurrence of oral lesions, performing preventive and educational treatments to patients, especially when it comes to oral hygiene. When the physician notes oral alterations that may imply a systemic involvement, an interconsultation should immediately be arranged. Thorough knowledge of oral changes in patients with CRF is essen-

tial for the diagnosis of the underlying disease and for preventing bacteremia and further complications^{8,28,40}.

CONCLUSION.

Patients with CRF suffer from a variety of disorders or alterations of their masticatory apparatus, as well as others that are consequences of the therapies to which they are sub-

jected. About 90% of patients with CRF suffer from at least one hard and/or soft oral tissue lesion.

Gingival enlargement, dry mouth, metallic taste, changes in enamel development, periodontitis, decreased tooth decay, are some of the manifestations that can be observed. The dentist is a central part of the team to provide proper care and ensure a better quality of life for these patients.

Alteraciones bucodentales en pacientes con insuficiencia renal crónica. Revisión narrativa.

Resumen: La insuficiencia renal crónica (IRC) es una de las nefropatías más conocidas, caracterizada por la disminución del estado de la función renal global. Se encuentra asociada a patologías como la hipertensión arterial, diabetes mellitus, las uropatías, glomerulonefritis crónica y enfermedades autoinmunes. Los pacientes con IRC presentan alteraciones del aparato masticatorio, que son propias de la enfermedad, y otras como consecuencia de su tratamiento. La salud bucal en los pacientes de diálisis y trasplantados tiende a ser pobre, siendo más propensos a desarrollar condiciones patológicas en la cavidad oral y con un potencial impacto sobre la morbilidad, mortalidad y calidad de vida del paciente. Entre las lesiones podemos encontrar disgeusia, periodontitis, can-

didiasis, sangramiento gingival, petequias, alteraciones a nivel articular, entre otras. La gingivitis y xerostomía asociadas a medicamentos de uso obligatorio pueden generar lesiones orales. Los niños con IRC exhiben dos condiciones orales de interés: alta incidencia de anomalías dentarias y baja actividad cariosa. En el paciente que recibirá un trasplante renal, el tratamiento dental previo es primordial, pues el estado inmune del paciente no sólo se verá afectado por la toxemia, sino por los fármacos inmunodepresores que se usan para evitar el rechazo de órganos implantados. Por lo anterior, el odontólogo juega un papel importante en la instrucción a padres y/o representantes, médicos y paramédicos para el control y tratamiento de lesiones en boca de estos pacientes.

Palabras clave: *Insuficiencia renal crónica, Manifestaciones bucales, Trasplante, Diálisis, Inmunosupresión.*

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