Oct 28th, 8:00 AM - Oct 29th, 6:00 PM

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Abstract

Kidneys are visceral organs that are responsible for numerous body functions. About 90% of patients with kidney failure show oral signs and symptoms on both soft and hard dental tissues, some of them are caused by the disease, while others may be caused by the treatment.

The main aim of this paper was to present the oral health changes caused by chronic renal failure.

In order to realize the main aim, adequate literature review was conducted.

The occurrence of gingival hyperplasia due to immunosuppressive therapy is the most studied oral manifestation. It is estimated that 30% of patients who are on cyclosporine therapy show clinically significant gingival enlargement. Decreased kidney function results in an increase in levels of urea in the blood, and thus an increased level of urea in the saliva, where it is the same converts to ammonia. For this reason, uremic individuals have a characteristic halitosis (uremic fetor), which also occurs in about a third of patients on hemodialysis. Hyposalivation occurs as a result of reduced fluid intake, or as a result of secondary effects of drugs (mainly antihypertensives), as a result of the atrophy of the parenchyma of the small salivary glands or due to mouth breathing.

The knowledge of the basic anatomical and pathological characteristics of kidneys, as well as the signs and symptoms of their diseases will allow them to avoid numerous complications in everyday practice that may occur during dental interventions in such patients.
Keywords: Renal failure, chronic renal disease, uremic halitosis, oral changes

Introduction

Kidneys are visceral organs that are responsible for numerous body functions. One of the most important functions of the kidneys is the regulation of the intravascular volume and the concentration of fluids and electrolytes in the body through the production of urine. The kidneys are also involved in blood pressure regulation, detoxification from toxic substances, the secretion of hormones, the control of the acido-basic homeostasis and the concentration of electrolytes.

Urine is excreted from the kidneys into the renal pelvis through the ureters and it is then collected in the bladder. Bladder with the help of the detrusor structures is capable of loosening or expanding to accept its urine without increasing internal pressure. This means that a large volume of fluid can be collected in the bladder (700-1000 ml) without causing damage to the renal system as a result of high pressure. When urine comes out of the bladder, the urethral sphincter relaxes, the detrusor contracts and urine is excreted through the urethra into the external environment. (Fry & Wu, 1997)

Each kidney contains about 1 million cells called nephrons which represent basic renal units. Each nephron is made up of filtration components called renal capsules and tubules that extend into renal pyramids. The kidney is anatomically composed of a cortex and a medulla. The cortex contains glomerular cells, while the medulla contains the tubules. Each glomerulus is supplied with blood through the afferent arteriole. The glomeruli are protected by a capsule called Bowman's capsule. (Preuss, 1993)

The plasma filtrate first passes through the capillary endothelium, then through the basal membrane and finally between the podocytes. The changes that will occur on the membrane and which will make it more or less permeable to different substances have been detected in many glomerular diseases that lead to the occurrence of proteinuria. After the

filtrate passes the three layers or barriers, then enters the renal tubules. These tubules are composed of a single lining of epithelial cells. (Arif & Nihalani, 2013)

The main aim of this paper was to present the oral health changes caused by chronic renal failure.

For the realization of the main goal, an adequate literature review was made using the following keywords "chronic renal failure", "end-stage renal disease", "oral health", "oral changes" and "hemodialysis". Scientific literature data published dominantly in English, in professional and scientific journals from the last two decades were used.

Functions of kidneys

As aforementioned, the kidney contains numerous functional units called nephrons that produce urine through consecutive processes: 1) glomerular filtration; 2) tubular reabsorption and 3) tubular secretion. The transport system in the renal tubules has a limit in terms of substances which he can transport in one time. The transport system involves almost all natural organic and some inorganic substances. These substances are usually glucose, amino acids, small peptides and proteins, ketone bodies, calcium, phosphate. Exception regarding natural organics substances is urea. The second mechanism or mechanism based on pressure gradient refers to the filtration or control of the following electrolytes that are ions - sodium, potassium, chlorides and water. The most important substances that are secreted by tubules are hydrogen ions, sodium, creatinine, as well as some drugs such as penicillin. Renal clearance of any substance is the plasma volume from which that same substance is completely removed by the kidneys for a unit of time. In clinical practice, creatinine clearance is a measure of the glomerular filtration rate. (Roy et al, 2015; Bhaskar & Oommen, 2018)

Aldosterone is a corticosteroid hormone that is synthesized in the adrenal gland, increases potassium reabsorption and potassium secretion. Also, the antidiuretic hormone that is produced in the hypothalamus increases permeability to water through direct influence on water channels around the principal cells. (Arroyoet al, 2011)

The concentration of extracellular calcium under normal conditions is constant. The regulation of calcium in the plasma takes place through the gastro- intestinal tract, bones and kidneys. Regulation is predominantly dependent from hormones, mainly parathyroid hormones and the active form of vitamin D3. Parathyroid hormone stimulates the reabsorption of this ion in the kidney’s tubules, namely the reabsorption of calcium, as well as the release of calcium

from bones and affects the intestinal absorption of calcium. Vitamin D is formed in the skin or is ingested and then by hydroxylation passes into liver and kidneys. (Gallagher et al, 1979)

Metabolic reactions that occur in the body are extremely sensitive to the concentration of hydrogen ions. Small changes in the pH value can cause significant protein changes. There are numerous buffering mechanisms responsible for reducing changes in the pH value in the body. The most significant extracellular buffer system is the bicarbonate buffer system, which includes carbon dioxide and HCO3 ion, and the main intracellular buffers are proteins and phosphates. (Bobulescu & Moe, 2006).

The kidneys maintain a stable concentration of hydrogen ions in the plasma through excretion of hydrogen ions which are actually temporarily regulated by the bicarbonate concentration in the plasma. The kidneys excrete excess bicarbonate when the body is in a state of alkalosis or increase and create new bicarbonate when the body is in a state of acidosis. (Adamczak & Surma, 2021)

Acid-base disorders occur most often as complications, which arise as a result of various pathological processes. The body has an acute response in order to correct the existing pathological change that led to these states, using the bicarbonate system. There is also a chronic response in which includes renal and respiratory mechanisms. (Rajkumar & Pluznick, 2018)

Erythrocyte production is directly controlled by secretion of the hormone called erythropoietin. Erythropoietin is secreted in blood from a group of cells located in the kidneys. This hormone affects the bone marrow and it is stimulating- it acts on the proliferation of erythrocyte progenitor cells and their differentiation into erythrocytes. The secretion of erythropoietin increases by certain situations, like heart failure, respiratory failure, anemia, etc. Without this hormone patients develop certain types of anemia that are observed in the end-stage renal failure. (Bhoopalan et al, 2020)

Gluconeogenesis is the dominant task of the liver, but anyway the kidneys also participate in this function. The importance of the kidney's role in the function of gluconeogenesis is still unexplained, but it is concluded that the kidneys can act on homeostasis of glucose and may lead to hypoglycemia. (Kaneko et al, 2018)

Chronic renal failure

Unlike acute renal failure, chronic renal insufficiency is a slowly progressive condition characterized by an irreversible reduction of the glomerular filtration rate. As chronic renal

failure progresses it actually begins with asymptomatic increased kidney function, which leads to end-stage kidney failure. Until the moment of manifestation of symptoms and reduction renal function, other systems can be affected by changes. The patients develop symptoms that are directly related to kidney dysfunction. End-stage kidney failure, also known as uremic syndrome, is the ultimate stage of chronic renal failure. Uremia is defined as asymptomatic renal failure followed by metabolic changes and complications.

There are three modalities in the treatment of renal failure, the first step of treatment is essentially conservative therapy. The second type of treatment is actually dialysis, which is intended for the terminal stage of renal failure. And the third option is transplantation of kidneys.

Conservative medical treatment consists of dietary changes which refer to restriction of salt and water intake, restriction of protein intake to reduce uremia, then sodium restriction-chloride and potassium chloride as well as avoiding magnesium, phosphorus and aluminum. These patients are usually prescribed loop diuretics as well as thiazide diuretics in order to be able to maintain an adequate balance of fluids and calcium-carbonate in order to control serum calcium and phosphate levels. It is sodium bicarbonate reserved for control of metabolic acidosis and administered intravenously. (Kim & Jung, 2020)

If an adequate therapeutic response is not achieved, these patients are referred to dialysis. Dialysis is actually a mechanism through which they are removed. The liquid is the waste products as well as electrolytes, acids and bases by way of diffusion and osmosis across a semipermeable membrane. There are two forms of dialysis - hemodialysis and peritoneal dialysis. The complications that are associated with hemodialysis are thrombosis, infections, hypotension, dyspnea, hemorrhage, hepatitis B and C, as well as hypertrophic cardiomyopathy which represents one of the most common causes of death in dialysis patients. (Vadakkedath & Kandi, 2017)

Complications such as thrombosis, hypotension, dyspnea and hemorrhage that may occur can also affect the dental interventions, so they represent risk factors for deterioration of the patient's condition. In these patients it is necessary to decide on this condition and to take preventive measures in order not to disturb the general health condition in this person. The appearance of hepatitis B and C, as infectious diseases, also belong to the group of diseases with dental risk, due to the need to take appropriate measures to prevent the potential risk of spreading the infection. (Bello et al, 2017)

Complications in end-stage renal failure patients

1. Volume

Patients in the end stage of renal failure do not produce urine, which means that fluid balance in these patients depends on dialysis and from fluid restriction. If these patients develop hypervolemia then they can serious complications such as pulmonary edema, hypertension, congestive heart failure and peripheral edema. Also, if there is too much liquid removed during dialysis then hypovolemia, hypotension, orthostasis and syncope can occur. Ideally patients should be normovolemic. During dental treatment, continuous monitoring of blood pressure is necessary if possible. The pressure should be measured on the arm where it is not placed in the arteriovenous fistula. (Claure-Del Granado & Mehta, 2016)

2. Electrolytes

In patients in the terminal stage of kidney disease, changes in potassium, magnesium, phosphorus and calcium levels. Because of this they are checked for basal metabolism during dialysis. Because hyperkalemia can cause arrhythmias and heart blocks, hyperkalemia is one of the indications for emergency dialysis. Hypomagnesemia is manifested as generalized muscle weakness, which can lead to respiratory collapse, hypotension and bradycardia. Hypokalemia and hyperphosphatemia are common in patients with renal failure, as a result of increased excretion of phosphates and vitamin D production. (Yamada & Inaba, 2021)

Patients who are in the end stage of renal failure are under high risk of developing metabolic acidosis, because their organism is not capable of clearance of accumulated hydrogen ions. The organism compensates for this through hyperventilation. When the compensatory mechanism will no longer function patients develop lethargy, confusion, nausea and vomiting. This can lead to cardiovascular collapse, coma and death. (Kim, 2021)

3. Anemia

Anemia is common in end-stage renal insufficiency and occurs as a result of hemolysis, which is associated with hemodialysis and also due to the lack of erythropoietin production. These patients should have a blood test before any dental intervention in order to check the status of hemoglobin and hematocrit. A lot of patients with renal failure also have comorbid diseases such as coronary disease and diabetes. Anemia combined with stressful clinical treatment (like dental treatment) may increase myocardial oxygen demand that can cause

cardiac arrest. Medicines for reducing stress such as nitric oxide or oxygen, as well as local anesthesia should be administered even for minor procedures. Any kind of major dental procedure imposes the need for sedation or with receiving sedatives. However, before these drugs are administered, it is must be done consultation with anesthesiologist. (Babitt & Lin, 2012)

4. Hemorrhage (bleeding)

Hemorrhage most often occurs as a result of the use of heparin during dialysis or as a result of kidney dysfunction associated with lack of coagulation factors as a result of uremia. The half-life of heparin is approximately 3-4 hours. For these reasons any dental treatment should be coordinated on days when the dialysis is not performed. This will reduce the side effects of heparin. The patients who are on hemodialysis, with kidney failure before they are undergoing any surgical procedure or dental intervention should have their prothrombin time, partial thromboplastin time, uremia and creatinine status checked. (Shen & Winkelmayer, 2012; Ribic & Crowther, 2016)

5. Infections

In patients with end-stage renal failure, the possibility of the occurrence of infections is high, especially in those patients who have kidney transplant as response to immunosuppressive drugs. If infection occurs, these patients should be hospitalized, they should be treated with surgical drainage of the abscess, to remove the source of infection and anyway to administer intravenous antibiotics. Dentists should avoid treating these infections with oral antibiotics because the infections can be expanded very quickly. Many authors recommend using them prophylactically antibiotics to prevent infection in dialysis patients before a routine dental procedure. (Cawcutt, & Zimmer, 2019)

6. Clearance of drugs

Since many drugs are metabolized and excreted by the kidneys, dosing of these drugs is based on the half-life of the drug and their active metabolites. Potassium should be avoided to prevent hyperkalemia. Other medicines such as clindamycin or erythromycin that are metabolized in the liver may be administered to these patients. Non-steroidal anti-inflammatory drugs because of their nephrotoxic effect should be avoided in renal insufficiency. Local anesthetics may be used in these patients. (Hartmann et al, 2010)

Vasoconstrictors should be used with caution due to hypertension associated with renal failure. Many narcotics can be administered to patients with end-stage renal disease, but should be used carefully. (Domi et al, 2016)

Influence of end-stage renal insufficiency on oral health

About 90% of patients with kidney failure show oral signs and symptoms on both soft and hard dental tissues, some of them are caused by the disease, while others may be caused by the treatment. (Oyetola et al, 2015) Decreased kidney function results in an increase in levels of urea in the blood, and thus an increased level of urea in the saliva, where it is the same converts to ammonia. For this reason, uremic individuals have a characteristic halitosis (uremic fetor), which also occurs in about a third of patients on hemodialysis. This halitosis is manifested as perception of an unpleasant, metallic taste in the mouth. Apart from urea, there can be other changes in the composition of saliva such as an increase in the concentration of phosphates and proteins and changes in the pH of saliva. Also, these patients can also have sensory disturbances, such as changes in taste perception, especially for sweet and sour. (Lasisi, et al, 2016). These phenomena are due to high levels of urea, the presence of dimethyl- and trimethyl-amines or low levels of zinc (due to malabsorption resulting from gastrointestinal disorders. There may also be burning sensation on the lips and tongue, of neuropathic origin. (Gardeitchik et al, 2012)

Hyposalivation occurs as a result of reduced fluid intake or as a result of secondary effects of drugs (mainly antihypertensives), as a result of the atrophy of the parenchyma of the small salivary glands or due to mouth breathing. The present anemia that occurs as a consequence of reduced synthesis of erythropoietin, which can be clinically observed skin and the mucous membrane. Uremic stomatitis is clinically characterized by the presence of erythematous lesions that may be localized or generalized. Special therapeutic modalities are not required, all that is required is that normalizes blood urea. Also patients should use mild antiseptics or hydrogen peroxide. (Laheij et al.(2022)

Regarding the dental anomalies in these patients, the eruption delayed teeth in children. Another sign that is often found in children is the presence of hypoplasia of enamel, due to changes in the metabolism of calcium and phosphates. In adults reduction of the pulp chamber is often observed. In patients with kidney diseases, non-carious loss of dental tissues occurs much more often. This is due to the presence of nausea, esophageal regurgitation or bulimia

nerviosa (in patients who do not like the restrictive diet, which is part of the treatment).(Nrmala, 2019)

In patients with kidney diseases, there is a higher incidence of periodontal disease, bone loss, gingival recession and deep periodontal pockets. Osteodystrophy occurs in these patients. This is a late sign of renal failure disease and because of these changes occur in the metabolism of calcium and phosphorus, abnormal metabolism of vitamin D and the compensatory hyperactivity of parathyroid glands (that is, due to secondary hyperparathyroidism). This condition is characterized by the following signs: bone demineralization, decreased trabeculation, reduced cortical bone thickness, metastatic calcifications of soft tissues, fibrocystic lesions or giant lesions cells, osteolytic areas of bones, fracture of the jaws (spontaneous or after dental procedures), abnormal healing of the alveolus and bone in completeness after tooth extraction, as well as increased tooth mobility as a consequence of loss in alveolar bone. (Jain & Kabi, 2013)

Bleeding tendency in these patients may to be due to factors in depending on the disease, as well as changes in platelet aggregation or because of the renal anemia (which occurs secondary to deficient erythropoiesis) or in turn, as a result of dialysis, which leads to a decrease in the number of platelets due to mechanical damage or due to the use of heparin. Because of these, frequent occurrence of ecchymoses occurs in hemodialysis patients, such as petechiae and hemorrhage of the oral mucosa. Oral hygiene in patients who are on hemodialysis is usually poor, so that calculus deposits and dental plaque are increased. (Kaw & Malhotra, 2006)

To kidney transplant patients immunosuppressive therapy is prescribed and thus they become more susceptible to infections and development of malignant neoplasms. Furthermore, they often face the secondary effects of immunosuppressive drugs - excessive obesity.

The fungal infections, the lesions are mainly associated with Candida albicans. The most common clinical manifestation is angular cheilitis, although other forms of candidiasis: pseudomembranous, erythematous and chronic atrophic candidiasis. However, such conditions are rare due to the fact that in these patients antimycotic drugs are prescribed systemically. Herpes group of viruses, in particular cytomegalovirus (CMV) and herpes simplex virus (HSV), are often associated with immunosuppressive patients after organ transplantation. Because of this immunosuppression, HSV reactivation occurs quite often, and the condition is characterized by the onset of recurrent, severe and long-lasting infections. In case of recurrent HSV infections in these patients, doses of 400 mg of Acyclovir may be administered orally, 3 times a day for 10 or more days (usually more than 2 weeks). (de la Rosa García, et al, 2006)

The occurrence of gingival hyperplasia due to immunosuppressive therapy is the most studied oral manifestation. It is estimated that 30% of patients who are on cyclosporine therapy show clinically significant gingival enlargement. When patients are treated with a combination of cyclosporine and nifedipine the prevalence of gingival enlargement increases to 50%. This effect occurs within 3 months of treatment. Age is an important factor in the occurrence of this side effect, because children are more susceptible than adults. The gingival enlargement usually affects the attached gingiva, but it can also extend occlusally, interfering with occlusion and mastication. This type of increase, which usually starts at the level of the interdental papillae, is more common in the frontal regions. (Rapone et al, 2019)

The most important characteristics in these patients are the existence of a tendency to bleeding, hypertension, anemia, drug intolerance, increased susceptibility to infections and the presence of several manifestations related to the disease or the treatment of the disease. There is also an increased susceptibility to infection endocarditis and vascular infections caused by bacteria of oral origin in patients undergoing hemodialysis. Valvulopathies, especially cardiac valvular calcifications as a consequence of hyperparathyroidism are common in this case population. Antibiotic prophylaxis is suggested in this condition. A lot of antibiotics are actively metabolized in the kidneys, so adaptation to dose by amount or by frequency is needed. Penicillin (and its derivatives, such as amoxicillin), and cephalosporins are the preferred antibiotics for these patients. In the case of non-narcotic analgesics, paracetamol is the best choice. It is desirable to avoid remaining non-steroidal anti-inflammatory drugs, because they cause hypertension. Benzodiazepines may be prescribed without dose adjustment. (Rajani & Klein, 2020)

In the presence of gingival enlargement, especially if it is extreme, it is necessary to perform surgical treatment (gingivectomy). The clinical decision to perform the intervention is based mainly if there is a presence of functional discomfort and esthetic change. The change in immunosuppressive therapy is an alternative to surgical treatment, but this is not always possible. (Agrawal, 2015).

In case of need dental treatment in patients on conservative renal treatment adequate communication with a nephrologist is recommended, in order for dentists to be aware of the stage of the disease and its treatment. Before any invasive dental procedure an examination should be done for the existence of any hematological problems. The possibility of any secondary infection should also be carried. Recommendation for the use of drugs, those that are nephrotoxic must be avoided (tetracyclines, aminoglycosides), while some of them need to be adjusted the dose.

In cases of peritoneal dialysis, a catheter is placed in the abdominal wall and inserted into the peritoneum through which access is gained to the body, in order to remove the nitrogen and other metabolic toxic products. This type of dialysis can be done at home, but it must be done every day. No special measures are required for these patient's dental treatment, in addition to the above mentioned. (Constantinidis et al, 2018)

A patient with kidney disease during hemodialysis. In hemodialysis, the process filtering is done with a machine (dialyzer), outside the patient's body. This procedure is done three times a week. In order to remove the blood from the body and to doors, it is necessary to have vascular access. Permanent vascular access is obtained by surgically connecting an artery and a vein, with the help of a blood vessel (arteriovenous shunt) or through a synthetic bridge (arteriovenous graft). In the hemodialysis process, the patient's blood is anticoagulated with heparin. For this reason, when performing dental treatment there is a risk of bleeding and they must not be performed on the day of hemodialysis. If it is necessary to perform an emergency dental intervention, protamine sulfate is used (which is a heparin antagonist) to block the anticoagulant effect. In these patients there is also a risk of infection due to the vascular access and transmission of HBV, HCV and HIV. (Sulejmanagić et al, 2005)

As it is known, these patients are immunosuppressed with drugs. Maintaining proper oral health is especially important because oral infections in transplant patients can affect the acceptance of the transplanted organ. They usually receive corticosteroids, calcineurin inhibitors and lymphocytes proliferation inhibitors. Long-term treatment with high doses of corticosteroids leads to suppression of adrenal functions, which can lead to an acute complication, referred to as adrenal crisis, when exposed to stressful situations (illness, infection, surgical and dental interventions). Also, this chronic excess of corticosteroids can cause Cushing's syndrome. To minimize the risk of adrenal crisis in patients receiving highdoses of corticosteroids who are exposed to a surgical and dental procedure, they should take double doses of corticosteroids on the day of intervention. This procedure is not necessary if the patient is treated with low doses (less than 7.5 mg of prednisolone) or if the patient is on conservative treatment. However, the risk of developing an adrenal crisis while oral surgery under local anesthesia is done is very low and a larger part of the dental treatments can be performed without the addition of corticosteroids. (Roberts & Fishman, 2021)

Conclusion

The knowledge of the basic anatomical characteristics and pathological changes of kidneys, as well as the signs and symptoms of their diseases allow them to avoid numerous complications in everyday practice that may occur during dental interventions in such patients.

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