Review Article

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Oral Manifestations of Children with Chronic Kidney Disease: A Review Article

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Abstract

Chronic kidney disease occurs due to a progressive and irreversible decline in the total number of functioning nephrons, which causes a decline in the glomerular filtration rate. It is considered a major public health problem affecting the young population with a rapidly increasing global burden. Children suffering from chronic kidney disease have many oral manifestations resulting from the medical condition itself, the type of treatment administered, or both. Oral manifestations include a uremic odor, uremic stomatitis, glossitis, and gingival enlargement secondary to drug therapy. Other manifestations include enamel hypoplasia, increased dental calculus deposition, and xerostomia. Oral health care is important in the management of CKD. Negligence of oral health in children with CKD is due to poor dental awareness among the children and health care personnel which leads to poor quality of life for these children. This article reviews the oral and dental manifestations of chronic kidney disease to guide dentists in their management of these patients. Treatment planning should be done after consultation with nephrologists regarding specific precautions for each patient.

Keywords Oral health, Hemodialysis, Dental caries, Developmental defects of enamel

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Introduction

Chronic kidney disease (CKD) is a multi-symptomatic condition that occurs primarily due to a decrease in the number of active nephrons. The process of diagnosis of CKD depends on several factors such as anatomical and/or functional renal abnormalities together with glomerular filtration rate (GFR) below 60 ml/min/1.7 m^2. [1] Even though the prevalence of this disease is lower in children than adults, CKD is a significant problem in the young population. It is regarded as a public health problem that highly influences the quality of life of affected children. [2]

If CKD is left untreated, it can lead to the development of end-stage renal failure (ESRF) which can only be managed by renal replacement therapy (RRT) in the form of hemodialysis (HD), peritoneal dialysis (PD), or renal transplantation. CKD is a devastating disease, and the mortality rate for children with ESRF on renal dialysis is between 30-150 times more than that of the general pediatric population. [2], [3]

Children suffering from CKD have many oral manifestations resulting from the medical condition itself, the type of treatment administered, or both. Oral manifestations include a uremic odor, gingival enlargement secondary to drug therapy, enamel hypoplasia, dental calculus, and xerostomia. Children also suffer from dysgeusia, uremic stomatitis, mucositis, glossitis, and gingival inflammation. Oral health care is important in the management of CKD. Poor oral health in children with CKD is an important factor contributing to the development of systemic infection and inflammation. [4]

Review of Current Literature

Normal kidney functions

The kidneys are composed of functional units called nephrons. Each kidney contains about 1 million active nephrons and the nephron contains a filtrating body, the glomerulus, and a long tubule. The final parts of these tubules are interconnected to form the collecting ducts, which open into the renal pelvis. The kidneys play a central role in the excretory, metabolic, and endocrine functions of the body. These functions expose the kidneys to the internal environment of the whole body and in turn increase the sensitivity of the body to any changes in kidney function. The kidneys also play a role in the endocrine system of the body by secreting renin, the active form of vitamin D, and erythropoietin. These hormones are important in maintaining blood pressure, calcium metabolism, and the synthesis of red blood cells respectively. [5], [6]

Definition of chronic kidney disease

CKD is defined as kidney damage that persists for more than 3 months evident by GFR of less than 60 ml/min/1.73 m^2, albuminuria of at least 30 mg per 24 hours, or markers of kidney damage (hematuria or structural abnormalities such as polycystic or dysplastic kidneys). [6]

Epidemiology

CKD has lately become one of the leading causes of suffering and death. In 2017, it was estimated that around 843.6 million individuals worldwide were indeed suffering from CKD. [7] The global burden of CKD is rapidly increasing and is projected to become the 5th most common cause of years of life lost worldwide by 2040, with the burden of CKD increasing faster in low and middle-income countries. [8]

Since CKD is most often asymptomatic initially, it is difficult to obtain reliable data on the early stages of pediatric CKD, so incidence and prevalence are very likely to be underestimated. Epidemiological data for CKD in children are scarce. Due to the lack of disease awareness, access to diagnosis, and data acquisition, the prevalence of kidney diseases in low-resource settings is even less well-identified. [9]

Diagnosis and etiology

Diagnosis of CKD starts with identifying the possible etiology of the disease as there are different causes for CKD in children. Etiologies for CKD may be systemic or local. Possible systemic etiologies are hypertension, diabetes, vasculitis, amyloidosis, autoimmune disorders like systemic lupus erythematosus, scleroderma, chronic infections, malignancy, and genetic disorders like sickle cell anemia. Local causes may be hereditary conditions like cystinosis and nephrocalcinosis or congenital conditions such as polycystic kidney disease, obstructive uropathy, reflux nephropathy, and renal hypoplasia/ dysplasia/aplasia. [10]

Additionally, local acquired causes may be expected such as nephrolithiasis, pyelonephritis, recurrent urinary tract infections, and prior exposure to potential nephrotoxins (nonsteroidal anti-inflammatory drugs [NSAIDs], antibiotic therapies such as gentamicin, and chemotherapies). [10], [11]

Diagnosis of CKD is confirmed by laboratory work such as serum chemistry profile, urine studies, and measurement of GFR. Children with CKD will show high levels of urea, blood urea nitrogen (BUN), and creatinine. Also, hyperkalemia, hypocalcemia, hypoalbuminemia, and low levels of bicarbonate are found. Urine analysis of children with CKD will show signs of proteinuria and sedimentation of red and white blood cells. [12]

Staging of CKD [10]

CKD is classified into five stages according to the National Kidney Foundation guidelines. Staging is based on GFR, albuminuria, and the etiology of CKD. According to these guidelines, staging is classified as follows:

- G1 is (GFR ≥ 90 ml/min/1.73 m^2)
- G2 is (GFR between 60 and 89 ml/min/1.73 m^2)
- G3 is (GFR 30–59 ml/ min/1.73 m^2)
- G4 is (GFR 15–29 ml/min/1.73 m^2)
- G5 is (GFR < 15 ml/min/1.73 m^2)

Albuminuria should ideally be quantified by a urine albumin-to-creatinine ratio (ACR). Albuminuria staging is classified as:

- A1 (urine ACR <30 mg/g or <3 mg/mmol)
- A2 (urine ACR 30-300 mg/g or <3-30 mg/mmol)
- A3 (urine ACR >300 mg/g or >30 mg/mmol)

Systemic manifestations of CKD

CKD is recognized as a major public health problem as it is associated with several adverse clinical conditions that increase in prevalence with lower kidney function. The damage to the kidneys results in these complications: cardiovascular disorders, chronic pulmonary disease, electrolyte disturbances, endocrinal disturbances, and increased risk of infections and cancers. These conditions contribute to high morbidity, mortality, and poor quality of life. [3], [12], [13]

Destruction of the renal tubular system and fibrosis of interstitial tissues lead to decreased erythropoietin production and decreased bone marrow stimulation resulting in reduced red blood cell production and anemia. Anemia in children with CKD can manifest as weakness, fatigue, dizziness, and difficulty in concentration. The damage to kidneys affects their filtration functions and as a result, the accumulation of toxic substances such as urea, guanidine, and indoxyl sulfate, destroys red blood cells and development of anemia due to the decreased survival rate of cells. Uremic syndrome also occurs due to the accumulation of uremic toxins and is manifested by anorexia, fatigue, peripheral neuropathy, leg cramps, nausea and vomiting, insulin resistance, muscle wasting, platelet dysfunction, and pruritis. [3], [10], [13]

The kidneys are responsible for the production of the active form of vitamin D, and when the kidneys are damaged there will be a vitamin D deficiency. This deficiency causes decreased absorption of calcium ions from intestines which leads to hypocalcemia and secondary hyperparathyroidism. The decrease in GFR following kidney damage results in decreased excretion of phosphate (hyperphosphatemia) which further leads to secondary hyperparathyroidism as a result of serum phosphate binding calcium and decreasing blood calcium. The disturbance in calcium and phosphate which represent essential minerals of calcified body tissues results in a condition known as chronic kidney disease – mineral and bone disorder (CKD-MBD). These changes affect bone remodeling and somatic growth. [3], [10], [12], [13]

The most common complication in children with CKD is cardiovascular disease. Children may suffer from variable manifestations such as atherosclerosis, cardiomyopathy, valvular disease, left ventricular hypertrophy, and dysrhythmias. Reduced GFR also leads to decreased excretion of potassium (hyperkalemia) which causes cardiac dysrhythmia. Also, the decreased excretion of salt and water leads to systemic volume overload,

hypertension, and pitting edema. [3], [10], [12], [13]

CKD is also characterized by reduced excretion of ammonium which leads to metabolic acidosis, skeletal muscle catabolism, insensitivity to endocrine hormones, bone disease, and acceleration of the progression of CKD. Children also suffer from growth impairment which occurs most frequently in infants due to malnutrition, metabolic acidosis, mineral and bone disorders, anemia, and fluid and electrolyte abnormalities. However, later on after early childhood, growth failure is mainly due to disturbances in growth hormone and its main mediator, insulin-like growth factor-I. [3], [13], [14]

Treatment options

Treatment for children with CKD includes dietary changes, management of systemic complications, and RRT such as HD, PD, or renal transplantation. Dietary changes and fluid restrictions are necessary to accommodate the defective excretory function of kidneys. Children also follow a dietary restriction of potassium and sodium for the management of hyperkalemia and hypertension. [15]

In dialysis therapy, blood is cleared from metabolic waste products such as urea, and excess fluid is removed from the children's body to restore circulatory volume by utilizing the use of a semipermeable membrane. Children also receive a variety of medications to manage complications from CKD. For example, treatment with recombinant human growth hormone for growth impairment, treatment with phosphate binders for hyperphosphatemia and CKD-MBD, treatment with recombinant human erythropoietin for defective erythropoiesis, different supplements for electrolyte disturbances, and treatment with antihypertensive drugs (e.g., calcium channel blockers and renin-angiotensin-aldosterone system inhibitors) for hypertension. [13]

Kidney transplantation is the gold standard treatment for children with CKD as it provides improved survival and better quality of life. However, the availability of matched kidneys from living/deceased donors is limited, and children will have to strictly adhere to immunosuppressive medications with possible side effects that can lead to unpleasant symptoms. [16]

Oral manifestations of CKD

Oral health is defined as a multifaceted status. It includes the ability to speak, smile, smell, taste, touch, chew, swallow, and convey different emotions through facial expressions with confidence and without pain, discomfort, and disease of the craniofacial complex. Other attributes of oral health include that it is a fundamental element of physical and mental health. It exists along a continuum influenced by the values and attitudes of people and communities. It reflects the physiological, psychological, and social attributes that are essential to the quality of life, and it is influenced by the person's changing expectations, experiences, perceptions, and

ability to adapt to different circumstances. [17]

Children with CKD suffer from a variety of oral manifestations caused by the condition itself, its treatment, or a combination of both. These changes are not specific to CKD but occur due to uremic, metabolic, and immunological disturbances associated with CKD. Changes affect both soft and hard tissues and vary according to the stage of disease. [4], [15], [18], [19], [20]

Soft tissue manifestations include pallor of the oral mucosa, atrophy of tongue papillae, gingivitis, periodontitis, uremic stomatitis, recurrent ulcers, and increased bleeding tendency evident by easily bleeding gums, petechiae, and ecchymosis. Children with CKD receiving immunosuppressive drugs suffer from an increased risk of opportunistic infections and candidiasis. Furthermore, children receiving calcium channel blockers as an antihypertensive drug or cyclosporine as an immunosuppressive drug suffer from drug-induced gingival enlargement. For children receiving multiple blood transfusions or on HD, transmission of bloodborne infections like acquired immunodeficiency syndrome (AIDS) and hepatitis is highly likely, and these children will present with oral manifestations of blood-borne infections along with their CKD. As a result of drug reactions like diuretics and beta blockers, children may present with white patches characteristic of lichenoid disease. [4], [15], [20], [21], [22], [23]

The effect on hard tissues includes developmental defects of tooth structure due to disturbance in calcium and phosphate levels, which would be more evident in children with early onset of CKD-MBD. Other symptoms include xerostomia, uremic breath (halitosis), and altered taste (dysgeusia). CKD-MBD can be reflected in oral health and is evident by radiographic manifestations such as pulp narrowing and calcifications, osteolytic brown tumors of hyperparathyroidism, loss of lamina dura, and decreased bone trabeculation (ground glass appearance). [4], [15], [19], [20], [24]

Dental caries

Dental caries is a multifactorial disease involving the interaction between the host, cariogenic bacteria, and the environment. Changes in the dental biofilm lead to nourishment of acidogenic and aciduric bacteria which ferment carbohydrates retained in the oral cavity into acids. The accumulation of acids within the biofilm gradually decreases oral pH which results in the demineralization of tooth structure once the pH is below critical levels of the tooth surface. [25]

The prevalence of dental caries in patients with CKD has been a topic of controversy in literature. Previous studies reported a low prevalence of dental caries and attributed this finding to the presence of high salivary urea levels which leads to alkaline salivary pH (urea is hydrolyzed into ammonia and carbon dioxide). The alkaline pH of saliva allows acid neutralization and protection of teeth against demineralization.

It was also found that high levels of phosphate in saliva, as a result of systemic hyperphosphatemia, would increase the buffering capacity of saliva and promote remineralization of incipient carious lesions. However, other studies reported high caries prevalence in patients with CKD as they usually consume a high carbohydrate diet (sweets, soft drinks, and processed food) to compensate for protein intake restriction. Also, due to their chronic medical condition, their oral health was neglected. Along with the diminished protective effect of saliva as patients with CKD suffer from xerostomia as a complication of their systemic condition. [4], [22], [26], [27], [28], [29], [30]

Periodontitis

Periodontitis is chronic inflammation of the supporting tissues of teeth (gingiva, periodontal ligament, and bone) induced by bacteria. The presence of excessive loads of bacteria and improper immune responses disturb the homeostasis of periodontium. The increased prevalence of periodontitis in patients with CKD has been reported in the literature and a proportional relationship between the severity of CKD, length of RRT, and severity of periodontitis has also been discussed. [31], [32], [33]

Ammonia, which is a product of urea and amino acid metabolism, is potentially cytotoxic to gingival tissues. Ammonia increases the permeability of the sulcular epithelium to other toxic or antigenic substances which causes gingivitis. It also favors the formation of dental calculus. Systemic uremia following CKD influences the immune system through abnormal neutrophil activity, impaired immune cell development and maturation, dysregulation of cytokines, increased levels of oxidative stress, along defective barrier immunity. These immune system changes contribute to the development of a state of maladaptive, uncontrolled, and persistent inflammation in patients with CKD. Moreover, patients with CKD are in a state of immunosuppression making them susceptible to infections. [31], [32], [33]

The interplay between periodontal disease and CKD has been investigated in previous studies. Bacteria responsible for periodontal disease escape the immune system and cause protracted inflammation which in turn contributes to systemic inflammation and exacerbates the progression of CKD and its complications. On the other hand, CKD-induced impairment of immunity leads to the colonization of bacteria and causes persistent, protracted inflammation of the periodontium. Also, patients with CKD undergoing HD receive repeated systemic anticoagulants which predispose gingival bleeding and facilitate bacterial colonization. [31] Furthermore, metabolic acidosis is a constant complication for patients on dialysis, and it can cause periodontal bone loss. Gingivitis and periodontitis can also occur due to xerostomia as the protective effect of saliva is diminished with CKD-induced reduction of salivary flow. [18], [31]

Dental calculus is formed as calcified depositions on the tooth surface, the depositions originate from interactions

between salivary calcium and phosphate and the dental plaque found on teeth. In patients with CKD, the oral equilibrium is disturbed, and this is evident by higher phosphate levels in saliva, lower magnesium levels, and high urea concentration in saliva responsible for changing the salivary pH from neutral to alkaline. The alkalinity of saliva favors the deposition of minerals, while the decreased levels of magnesium contribute to more calcification. Moreover, the alkaline pH of the oral environment provides more favorable growth conditions for periodontal pathogenic bacteria. These changes along with oral health neglect in patients with CKD, favor increased calculus deposition and periodontal breakdown. [29], [32], [34]

It has been discussed in the literature that patients with CKD suffering from periodontitis showed high levels of C-reactive protein in their serum and saliva which is indicative of chronic inflammation and results in the worsening of the patients' health. In addition, studies have reported increased levels of Cystatin C in both the serum and saliva of patients with CKD suffering from periodontitis. Cystatin C is an important serum biomarker used for the diagnosis of CKD. Increased levels of Cystatin C will negatively affect both renal function and oral health. [33]

Periodontal disease is believed to be associated with cardiovascular disease which can further lead to systemic atherosclerosis. Intervention studies in CKD patients have reported that treatment of periodontitis improved serum inflammatory biomarkers and decreased systemic inflammation which supports the belief that improvement of oral health leads to improved systemic health. [31]

Developmental defects of enamel

Enamel is a unique calcified hard tissue that is formed by ameloblasts that are sensitive to changes in their environment. The quality of formed enamel is dependent on the bioavailability of minerals (calcium and phosphate) during the mineralization stage, while the quantity of enamel is affected by the amount of enamel matrix proteins produced by ameloblasts. Dysfunction of ameloblasts during any stage of development will result in what is known as developmental defects of enamel (DDE). [20]

Children with CKD present with disturbances in calcium and phosphate metabolism in their bodies, which reflects in the mineralization of hard tissues like enamel. Thus, CKD patients show DDE with variable presentation ranging from demarcated opacities, diffuse opacities, hypoplasia, and discolorations. Intrinsic staining is generally a result of the adsorption of pathological pigments onto the dentine matrix. Brown discoloration can be seen when uremia is present during the development of the dentitions. However, extrinsic staining occurs as children are treated for anemia with ferrous sulfate in syrup form, which causes the black-brown extrinsic staining on the teeth. The severity of DDE depends on the timing, severity, and

duration of disruption during tooth development. [20]

Soft tissue lesions

CKD is responsible for the development of oral soft tissue complications. These complications include the appearance of mucosal pallor due to patients developing anemia. The presence of candidiasis, coated tongue, petechiae, and ecchymosis was also reported in previous studies. [35]

Xerostomia

Generally, the normal salivary flow rate ranges between 0.3-0.5 ml/min. In patients with CKD, hyposalivation is often encountered due to decreased saliva production below 0.1 ml/min. Several causes of xerostomia in CKD have been studied in literature, yet, the definitive cause is still unknown. [36] **Postorino *et al.*** [37] reported the presence of salivary gland fibrosis and atrophy in ESRF patients which manifested clinically in xerostomia.

It was also reported that xerostomia in HD patients was due to the administration of multiple drugs which exert their anticholinergic activity on muscarinic acetylcholine receptor M3 or act centrally on brain centers to reduce fluid secretions. Patients on HD are also advised to limit fluid intake which may contribute to reduced salivary production. [38] Another study by **Szulimowska *et al.*** [36] suggested the involvement of salivary cytokines, chemokines, and growth factors with salivary gland dysfunction as these molecules are produced as a result of persistent inflammation in salivary glands affecting the function of acinar cells.

Saliva plays an important role in the health and functions of the oral cavity. It acts as a lubricant to facilitate mastication, swallowing, and speech. It also provides protection and lubrication for the soft tissues. Saliva plays a protective and antimicrobial role against bacteria responsible for caries and periodontal disease. Saliva is saturated with calcium, phosphate, and fluoride which allows remineralization of incipient carious lesions. The buffering capacity of saliva maintains the oral pH at 7.4 by neutralizing bacterial acids to protect teeth against demineralization. [39]

Xerostomia is associated with multiple consequences that affect the quality of life of children with CKD, including difficulty in mastication, swallowing, and speech. The diminished lubricant effect of saliva causes dryness of mucosa and oral soreness. Furthermore, children suffer from an increased risk of opportunistic infections, candidiasis, altered taste, and increased plaque retention. [38]

Conclusion

Children with CKD suffer from a variety of oral manifestations. These changes occur due to uremic, metabolic, and immunological disturbances associated with CKD. Changes affect both soft and hard tissues and vary according to the stage of disease. Poor oral health in children with

CKD is an important factor contributing to the development of systemic infection and inflammation.

Conflict of Interest

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