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# Developmental Defects of Enamel and Dental Caries in Pediatric Patients with Chronic Kidney Disease–Mineral Bone Disorders

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**Abstract:** Chronic kidney disease (CKD) is an extremely widespread pathology characterized by numerous metabolic alterations, including impairments of calcium–phosphorus and of vitamin D metabolisms, which lead to a condition known as CKD–mineral and bone disorders (CKD-MBDs). In CKD children, this pathological condition induces anomalies in physiological growth processes, alterations in bone morphology, renal osteodystrophy and rickets. CKD-MBDs are not only associated with systemic complications but also show dental and maxillofacial manifestations in children. In fact, children affected by CKD-MBDs present defects in enamel development and dental anomalies when compared to healthy children. Therefore, the aims of this narrative review are to focus on the hard dental tissues and to investigate the possible correlation between the CKD-MBDs in children and the presence of developmental defects of enamel. In addition, the possible risk and protective factors of dental caries in CKD pediatric patients are analyzed. The review describes, with a multidisciplinary nephrological–dental approach, the pathogenic mechanisms that can cause anomalies in dental structure in CKD pediatric patients.

**Keywords:** chronic kidney disease; renal osteodystrophy; rickets; vitamin D deficiency; dental anomalies; maxillofacial manifestations; developmental defects of enamel; dental caries



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## 1. Introduction: Epidemiology of CKD in Pediatric Patients and Main Complications of CKD in Pediatric Patients

Chronic kidney disease (CKD) is an extremely widespread pathology characterized by the progressive loss of renal function and is closely related to cardiovascular diseases, which represent its main cause of morbidity and mortality [1]. In particular, CKD is defined by "Kidney Disease: Improving Global Outcomes" (KDIGO) as an alteration of renal structure and/or function that persists for at least 3 months and which has implications for the individual's health [2]. The most recent epidemiological estimates suggest a global prevalence of 13.4% for CKD and it is estimated that this prevalence is destined to increase due to the growing spread of its risk factors, including arterial hypertension and diabetes mellitus and increasingly widespread unhealthy lifestyles [3]. CKD belongs to the non-communicable diseases and mainly affects the older population; in fact, CKD prevalence seems to increase proportionally together with advancing age [4], even though there are many children who are affected by this pathology.

The data on CKD prevalence in children are insufficient. Its global prevalence ranges from 15 to 74.7 cases/million children [5]. In Europe, it has been estimated that its incidence in children is approximately 11–12 per million of the age-related population (pmarp) for stages 3–5, and approximately 8 pmarp for stages 4–5 [6].

The main causes of CKD in the pediatric population are congenital anomalies of the kidneys and the urinary tract. In fact, these represent up to 40–50% of all causes of CKD in children. These congenital anomalies provoke CKD, characterized by a slower progression to end-stage kidney disease (ESKD) and a higher risk of polyuria when compared to CKD in adults [5,7]. The second most common cause of CKD in children are hereditary nephropathies, which together with the congenital anomalies of the kidneys and of the urinary tract, represent 2/3 of all the CKD causes in children living in developed countries. On the other hand, the acquired causes are predominant in developing countries [6].

One of the main problems of CKD in children is that it may alter their physiological growth processes. In fact, children affected by CKD are often characterized by short stature due to substantial alterations in growth processes. The risk of growth retardation is greater the younger the child with CKD is. The causes that lead to the alteration of growth processes are various. These include an electrolyte imbalance, metabolic acidosis, mineral and bone disorder (MBDs), anemia, inflammation processes and CKD-associated growth hormone (GH) insensitivity [8]. In particular, the CKD-MBDs, characterized by a reduced renal excretion of phosphate and an impaired gastrointestinal and renal reabsorption of calcium may result in a condition called renal osteodystrophy (ROD), as we will see in detail later. The latter is related to an alteration in bone metabolism that induces growth defects in children [9,10].

Another possible cause of short stature in CKD children is also malnutrition [11]. Indeed, a deficiency in protein, energy and micro-nutrient intake (like vitamin D) due to vomiting, anorexia, gastroesophageal reflux and the dysregulation of the hunger and satiety mechanisms are deeply associated with growth disorders [12].

These changes involving bone metabolism can not only alter a child's growth process but also their oral health. Consequently, the aims of this narrative review are to focus on the hard dental tissues and to investigate the possible correlation between the CKD-MBDs in children and the presence of the developmental defects of enamel. In addition, the possible risk and protective factors of dental caries in CKD pediatric patients are analyzed. The review describes, with a multidisciplinary nephrological–dental approach, the pathogenic mechanisms (in particular the alteration of calcium–phosphorus and of vitamin D metabolisms) that can cause anomalies of dental structure in CKD pediatric patients.

## 2. CKD and Calcium–Phosphorus Metabolism in Pediatric Patients

One of the main comorbidities of CKD is CKD-MBDs (Figure 1) [13]. This condition is an important cause of morbidity and is associated with a reduction in the patient's quality of life and an increased risk of cardiovascular mortality [14]. CKD-MBD is a systemic disorder involving a change in mineral and bone metabolism due to CKD and which may manifest as follows: (i) alterations in calcium, phosphorus, parathyroid hormone (PTH) or vitamin D metabolism; (ii) alterations in bone turnover and mineralization and/or (iii) the hyper-calcification of vessels or other soft tissues [15].

The pathogenesis of this disorder is very complex and involves numerous factors. First of all, in CKD, there is an increase in phosphorus in the blood levels, due to its reduced excretion. Hyperphosphatemia, in turn, involves the activation of a mechanism that begins with the increase in the levels of a factor called fibroblast growth factor 23 (FGF23). This is mainly responsible for controlling plasma levels of phosphate and reduces their tubular reabsorption; consequently, it increases their urinary excretion [16]. Therefore, the FGF23

activation in the early stages of the disease attenuates hyperphosphatemia. On the other hand, the increase in FGF23 levels has a further consequence; that is the reduction in the 1α-hydroxylase activity, which, as we will see in the next paragraph, is responsible for the activation of vitamin D. Vitamin D deficiency is in turn responsible for the reduction in calcium intestinal absorption [17]. The reduction in circulating calcium levels stimulates the parathyroid glands, which increase the release of PTH; the latter is implicated in the renal excretion increase in phosphates, and, at the same time, is responsible for bone calcium reabsorption. As a consequence, PTH stimulates the activity of osteoclasts that cause bone demineralization, thus promoting the release of calcium but, at the same time, compromising the bone structure and increasing the risk of fractures [18,19]. This complex mechanism is known as secondary hyperparathyroidism and is responsible for all the alterations that involve calcium–phosphorus metabolism.

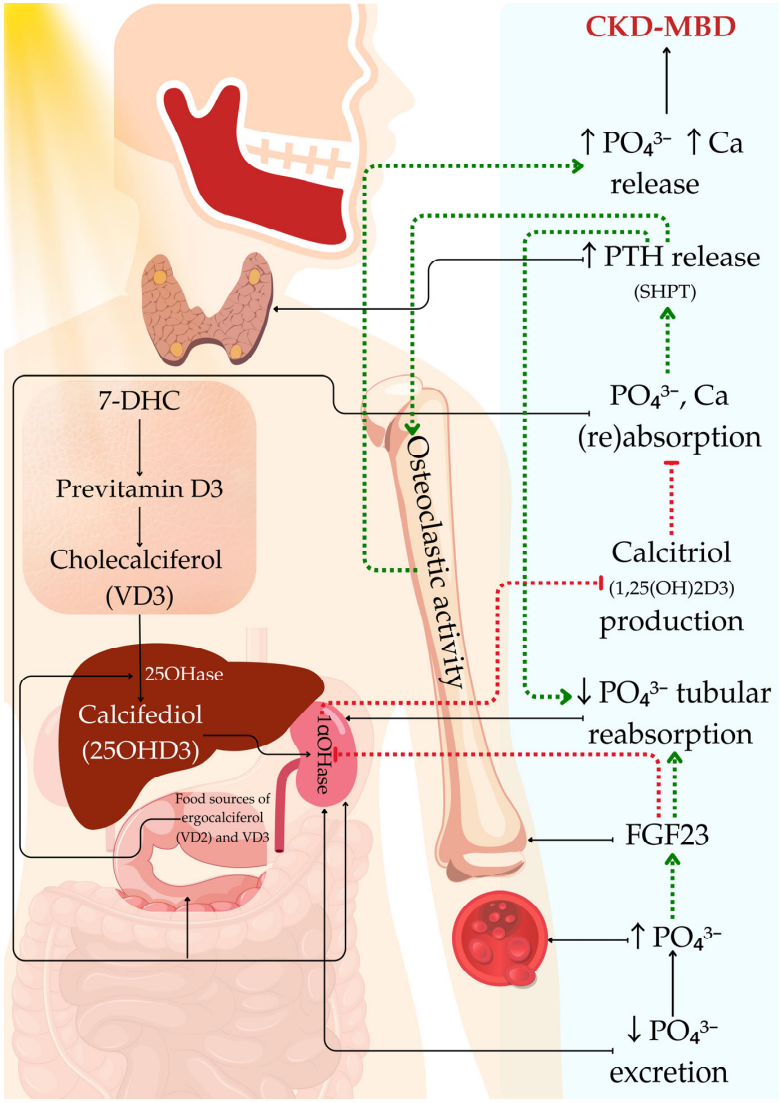


**Figure 1.** Molecular mechanisms underlying chronic kidney disease–mineral bone disorders. Abbreviations: Ca, calcium; CKD-MBD, chronic kidney disease–mineral bone disorders; FGF23, fibroblast growth factor 23; $PO_4^{3-}$, phosphate; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism; VD2, vitamin D2; VD3, vitamin D3; 1αOHase, 1α-hydroxylase; 1,25(OH)2D3, 1,25-dihydroxycholecalciferol; 7-DHC, 7-dehydrocholesterol; 25OHase, 25-hydroxylase; 25OHD3, 25-hydroxycholecalciferol. The arrows indicate a sequence of events: ↑ (short), increase; ↓ (short), decrease; → (long), succession of events; ⟶, organ where the event occurs; ⇢, activation; ⇢|, inhibition.

In this context, it is essential to mention the klotho factor. This factor is present in two forms that perform different functions; as a transmembrane protein, it acts as a receptor for FGF23, while as a soluble protein, within the proximal tubule of the nephron, it inhibits the excretion of phosphorus, modulating the activity of Na-coupled Pi transporters [20]. In the course of CKD, a deficiency of the klotho factor occurs, thus losing the protective effect against the calcification of soft tissues and the preservation of the residual renal function [21].

Childhood is a crucial time for the correct development of the skeletal system. CKD children, especially when diagnosed before the age of three, are more likely to experience growth retardation and bone deformities [22]. One of the main causes of these abnormalities is the imbalance of the calcium–phosphorus metabolism, strongly implicated in the growth process, which can cause harmful outcomes in children [23]. In fact, CKD-MBDs in children negatively impact bone strength, mineralization and structure, leading to bone pain, deformities, growth retardation and an increased risk of fractures [24–26].

Several studies demonstrate that secondary hyperparathyroidism is strongly implicated in growth retardation in children, although a direct correlation between PTH levels and growth rate has not been described [27,28]. In fact, although the normal ranges of serum PTH in children are controversial, it has been shown that high levels of PTH are related to a slowing of skeletal growth in CKD children [29,30]. These effects are not attributable to the direct action of PTH on skeletal growth but rather to the pivotal role that this hormone plays in the etiopathogenesis of ROD [28].

ROD is described as the presence of alterations in bone morphology associated with CKD. Its signs and symptoms include bone fractures and deformities, pain, cardiovascular events and soft tissue calcification, while in children these may present as growth failure and skeletal deformities [31,32]. Despite current therapies aimed at rebalancing calcium–phosphorus metabolism, the incidence of bone fractures is from 2 to 3 times higher in children with CKD than in children without CKD [30,32].

## 3. Vitamin D and CKD in Pediatric Patients

Vitamin D deficiency in CKD is extremely common, both in adults and children. In fact, a significant association between the reduction in glomerular filtration rate and vitamin D deficiency has been widely demonstrated in children [33,34].

Vitamin D is a pro-hormone essential for human life, mainly involved in calcium–phosphorus metabolism. Vitamin D exists in two main forms: ergocalciferol (vitamin D2), which is mainly found in food sources (such as mushrooms, oily fish, egg yolk and offal), and cholecalciferol (vitamin D3), which is produced in the skin by an endogenous photochemical reaction starting from 7-dehydrocholesterol. Vitamin D, still inactive, initially reaches the liver, where it undergoes a hydroxylation at the carbon 25 position, by 25-hydroxylase, to become 25-hydroxyvitamin D. Finally, it is transported to the kidney, where it undergoes a second hydroxylation, by 1α-hydroxylase, which converts it to the active form, 1,25-dihydroxyvitamin D [35].

Many studies suggest that CKD patients are at high risk of developing vitamin D deficiency for various causes, even in the early stages of the disease. First of all, vitamin D deficiency in CKD patients can be induced by reducing food intake due to a lack of appetite, a depressive state, dietary restrictions and gastrointestinal alterations that alter the absorption of dietary vitamin D [36]. Furthermore, proteinuria has been described as one of the main factors influencing vitamin D levels in CKD patients. In fact, it has been shown that patients with proteinuria showed significantly lower vitamin D values due to its increased urinary excretion of the vitamin D-binding protein. This protein is responsible

for transporting 25-hydroxyvitamin D to the proximal tubule to undergo its activation by the kidney, causing a reduction in active vitamin D levels [37].

Moreover, a reduction in renal mass limits the amount of 1α-hydroxylase available for the production of active vitamin D. The progressive reduction in glomerular filtration rate (GFR) can also limit the availability of 25(OH)D to 1α-hydroxylase, causing a reduction in the production of active vitamin D [38].

Another factor that can induce vitamin D deficiency in CKD patients is the rise in FGF23 serum levels that increases with the decline of GFR, which directly suppresses the activity of 1α-hydroxylase [17].

Finally, uremia, which occurs in the CKD terminal stages, may alter the physiological response of the skin to UVB radiation, which is essential for the production of vitamin D [39].

Vitamin D's main function is to regulate calcium–phosphorus metabolism. In particular, vitamin D stimulates the intestinal absorption of calcium and phosphorus, stimulates the mobilization of calcium in the bones and increases the renal reabsorption of calcium in the distal tubule [40]. Moreover, vitamin D is essential for numerous biological processes and is not only related to the skeletal system. In fact, a vitamin D deficiency not only alters the skeletal processes but also endothelial function, renin–angiotensin–aldosterone system (RAAS) regulation, redox balance and immune system activity [35].

For all these fundamental functions, a deficiency can cause serious damage, especially in the pediatric population. Vitamin D deficiency is one of the most common causes of rickets in children. Rickets is a condition that can be described as a defect in the mineralization of the epiphyseal plates, which are the growth plates at the ends of the bones. It can manifest itself through irritability, a retardation of the child's growth or, in the most severe cases, with a sudden death [41]. Due to its enormous importance in calcium–phosphorus metabolism, a long-term deficiency of vitamin D can cause a reduction in serum calcium levels, causing an inhibition of the bone mineralization process, essential for the skeletal growth of the child [42,43]. Rickets is frequently found in children aged between 6 months and 2 years, where is may alter the structure of the skull, cause changes in the rib cage, deformations of the upper and lower limbs (bowed legs, knock knees, increased risk of fractures) or alterations in the spinal column (hyperkyphosis) [44].

However, vitamin D is not only essential for proper skeletal bone health. In fact, vitamin D deficiency in children has been associated with an increased risk of developing autoimmune diseases, obesity, diabetes mellitus, cardiovascular diseases, periodontal disease and cancer, including colon, prostate and breast cancer, in adulthood [45].

## 4. Alteration of Calcium–Phosphorus Metabolism and Oral–Maxillofacial Manifestations in Pediatric CKD Patients

CKD in pediatric patients can determine a series of oral manifestations that differ in relation to the age of onset (newborn, child or adolescent), the stage of CKD and the type of treatment (conservative or substitutive) (Figure 2).

The relationship between CKD and oral health is intricate. The oral–maxillofacial manifestations of CKD-MBDs are heterogeneous because they include alterations of both oral soft tissues and hard tissues and up to 90% of CKD patients exhibit signs of oral disease [46]. Moreover, CKD-MBDs can also have an impact on the jaw and alveolar bone metabolism [46] and can alter the turnover and the structural and mechanical properties of the maxillary cortical bone [47].

The CKD oral manifestations can be classified into the following catergories: gingivitis/periodontitis, gingival overgrowth, calculus formation and accumulation, leukoplakia, halitosis, xerostomia, dysgeusia, anomalies of dental structure, anomalies of dental erup-

tion timing, alterations of craniofacial growth, pallor of the oral mucosa, candidiasis and uremic stomatitis [48–50]. During ROD and in hyperparathyroidism associated with CKD, widespread jaw enlargement, a ground-glass appearance of the bone, hypercementosis, bone resorption with the loss of the lamina dura, delayed tooth eruption, dental spacing, tooth mobility, propensity for mandibular and maxillary fractures [51], bone demineralization, decreased bone trabeculation, radiolucent giant cell lesions, radiolucent fibrocystic lesions, abnormal bone healing after tooth extraction, lytic areas of bone [52] and brown tumors can be observed [53], while in ESKD, there is a predisposition to the atrophy of the alveolar bone and the narrowing of the dental pulp chamber [54].

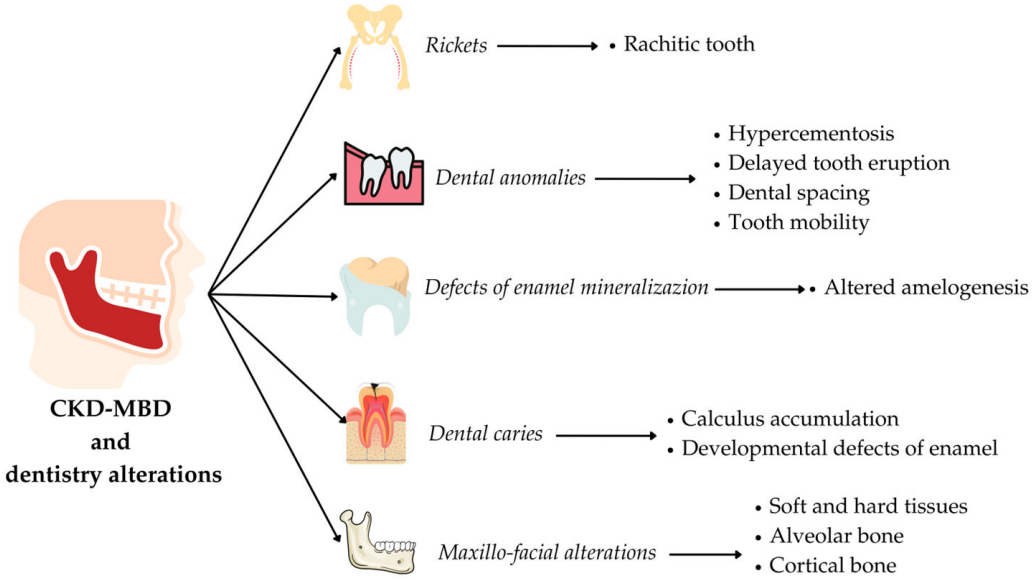


**Figure 2.** CKD-MBDs and dentistry alterations in CKD pediatric patients. Abbreviation: CKD-MBD, chronic kidney disease–mineral bone disorders.

Furthermore, several studies have highlighted how, during CKD, there is an alteration of the oral microbiota, which can be the cause of numerous pathological manifestations affecting the oral cavity, including periodontal disease and dental caries [55–57]. In particular, the chronic low-grade inflammation, characteristic of CKD patients, could alter the activity of the patient's immune system, increasing their susceptibility to oral infections [58]. In fact, the oral microbiota of CKD patients could be colonized by pathogenic bacteria (like *Enterobacteriaceae*, *Streptococcus*, *Fusobacterium* and *Staphylococcus*) and this oral dysbiosis could cause a translocation of oral pathogenic bacteria into the bloodstream, exacerbating systemic inflammation in CKD patients [59].

### *4.1. Alteration of Enamel Mineralization*

Developmental defects of enamel (DDEs) may be caused by an oral manifestation of CKD [60]. In fact, several cross-sectional studies carried out in CKD pediatric patients observe a high frequency of DDEs compared to healthy children [61–64].

The frequency rate of DDEs varies in a wide range depending on the study examined: 83% diffuse opacities and 22% enamel hypoplasia [65], 57% DDEs [66], while 88.8% DDEs in kidney transplant recipients (KTR), 80% in CKD stage 4–5 and 66.7% in CKD stage 1–3 [62] was also observed.

In a study by Tuma et al. conducted on 120 children and adolescents (mean age 12.78 ± 3.9 years) who underwent a kidney transplant procedure, it was observed that 86.7% showed an oral manifestation directly related to CKD and 40.8% showed DDEs [67].

DDEs are structural anomalies of the enamel and are defined as disturbances in hard tissue matrices and their mineralization during odontogenesis (specifically during amelogenesis). Amelogenesis is a process that begins at approximately 3–4 months of intrauterine life for deciduous teeth and from birth for permanent teeth [68].

The quality–quantity of formed enamel is dependent on amelogenesis and can be altered by different pathogenic noxae that can act in the different stages of enamel formation and can determine DDEs. A scoping review of the literature identified 114 factors potentially involved in acquired DDEs and classified them into three sections, corresponding to prenatal, neonatal and postnatal periods. Renal dysfunction, hypocalcemia and vitamin D deficiency are highlighted among the general risk factors of postnatal periods [69].

This association between CKD and pre-eruptive DDEs may be explained by the numerous metabolic or pathophysiological mechanisms of CKD related to hypocalcemia, decreased serum levels of 1,25-dihydroxycholecalciferol and elevated levels of serum phosphate, the parathyroid hormone and fluoride, which negatively influence the amelogenesis stage [60,62].

Amelogenesis is a phase of odontogenesis in which ameloblasts, specialized cells, participate, and it is divided into three stages: (a) ameloblast secretion, (b) mineralization, (c) maturing [69]. During the secretory phase, differentiated ameloblasts secrete an extracellular enamel protein matrix that acts as a scaffold for the deposition of hydroxyapatite crystals, consisting mainly of calcium and phosphate (with traces of fluoride, if present) that form the enamel prisms [70]. Once the maturation phase is complete, enamel becomes the most mineralized tissue in the human body, but there is differences between permanent and primary dentition. In fact, the primary enamel structure shows a lower level of $Ca^{2+}$ and Pi than permanent dentition [71]. An alteration of calcium–phosphorus metabolism at the systemic level, such as in CKD, could negatively influence the mineralization and maturation of enamel by altering the bioavailability and deposition of calcium and phosphate ions in the matrix and thus lead to DDEs [69]. Furthermore, CKD could alter the removal of inorganic fluoride to the extent of increasing serum fluoride levels which could cause fluorosis [72].

The tooth mineralization process occurs parallel to skeletal mineralization. Therefore, as skeletal alterations can be present in CKD pediatric patients, at the same time, alterations can occur in the tooth mineralization. Vitamin D plays a key role in the mineralization and development of bones and teeth [73] and when its levels are severely compromised (<10 ng/mL) it causes hypocalcemia and hypophosphatemia with secondary hyperparathyroidism (driven by hypocalcemia), altering the bioavailability of $Ca^{2+}$ and Pi ions, which is essential for tooth mineralization [74].

Furthermore, the vitamin D–vitamin D receptors (VDR) complex modulates the transcription of genes encoding the various structural proteins of the unmineralized extracellular matrix: amelogenins, enamelin (synthesized ameloblasts), dentin syaloglycoproteins and dentin phosphoproteins (synthesized by odontoblasts) [75].

In this way, a vitamin D deficiency in children during the period of bone development can cause rickets and during the period of tooth development can cause alterations in tooth mineralization, namely a “rachitic tooth” [76]. In “rachitic tooth”, besides the anomalies of enamel mineralization, dentin hypomineralization [75] and varying degrees of interglobular dentine [77] are also evident. In the “rachitic tooth”, alterations of the pulp chamber with unusual pulpal horn extensions can also be observed [78].

Vitamin D deficiency can influence the mineralization phases of primary and permanent dentition, affecting specific teeth according to the timing of mineralization which differs for each tooth [68]. Furthermore, maternal vitamin D deficiency during pregnancy

can influence the prenatal serum-circulating vitamin D levels of the fetus and cause enamel defects in the newborn [79].

Enamel alterations are an important oral manifestation of CKD because they cause permanent damage [60]. In fact, when the formation and mineralization of the enamel is fulfilled, it will not have regenerative capacity [70] because the "enamel organ" is lost upon tooth eruption [76].

DDEs show as intrinsic discolorations (opacity of enamel, lack of translucence of enamel, localized areas of discolored enamel with a color that can vary from white-yellow-brown), irregular areas (pits, grooves and thin or missing enamel) and misshapen tooth crowns [48]. In a study by Nunn et al. conducted on children and adolescents (aged 2–16) with CKD, it was highlighted that enamel defects were common, with a higher prevalence of diffuse opacities (83%) and enamel hypoplasia (22%) [65]. Enamel alterations are irreversible and can be classified as quantitative defects (enamel hypoplasia: enamel with reduced thickness and normal consistency) or qualitative defects (enamel hypomineralization: enamel with normal thickness but altered appearance) [80].

Alterations in the enamel structure can affect different teeth, both deciduous and permanent, and can have different degrees of severity and incidence in relation to the time of tooth formation [81] to the early management of the renal disease, which minimizes metabolic disturbances and dental decalcification [50], and to the age of CKD onset. In fact, the earlier the onset of CKD occurs, the more severe the DDEs will be [65].

In a study conducted on CKD mouse models with micro-computed tomography (μCT), alterations were observed in CKD mice not only in the enamel (30% decrease in molar enamel volume), but also in the dentin/cementum (7% increase in molar dentin/cementum volume) and in the dental pulp (30% decrease in the pulp with evidence of pulp calcification) compared to the control group [82].

It is important to consider that the tooth surface (enamel) of the dental elements is continuously subjected to demineralization–remineralization dynamics. Demineralization is the process of removing mineral ions from hydroxyapatite (HA) crystals of hard tissues, while remineralization is restoring these mineral ions again to the HA crystals. Remineralization is guaranteed by saliva and its mineral component (calcium, phosphorus, fluoride) [70]. An alteration of calcium–phosphorus metabolism at the systemic level in CKD may influence salivary calcium and phosphorus levels [59]. Hypocalcemia may decrease salivary calcium levels, as found in CKD patients compared to healthy subjects [83]. Therefore, it might alter the re-mineralization mechanism of the enamel, whereas hyperphosphatemia and uremia might increase salivary phosphate concentrations that may facilitate the re-mineralization of incipient carious lesions [84].

Finally, it is worth remembering that another enamel anomaly can be observed in nephropathic patients as the enamel-renal syndrome (MacGibbon syndrome). This syndrome is a rare genetic disorder transmitted through an autosomal recessive mode and it is characterized by hypoplastic amelogenesis imperfecta, affecting both deciduous and permanent teeth, and causes delayed tooth eruption for teeth impaction, gingival fibromatosis, multiple calcifications in pulp and gingiva, hyperplastic dental follicles and bilateral nephrocalcinosis [85–87].

### Diagnosis and Treatment of DDEs

It is appropriate to make a differential diagnosis in CKD patients between intrinsic enamel discolorations (such as DDEs) and extrinsic enamel discolorations. In fact, the latter are very frequent in CKD patients with anemia because pharmacological iron supplementation can, in some formulations, deposit brownish-black spots on the enamel surface [88,89].

In a recent study, intrinsic discoloration (22%) and extrinsic discoloration (40%) were observed in hemodialyzed children with a statistically significant difference compared to the control group (healthy subjects) [84]. From an operational point of view, extrinsic stains can be removed through the utilization of abrasive pastes during professional oral hygiene follow-up, while intrinsic stains cannot be removed except through conservative interventions. Moreover, DDEs can determine an increase in the risk of dental caries [90,91], dental erosions, tooth sensitivity and altered occlusal functions [92], and can compromise dental esthetics, especially in those clinical cases in which the anterior dental elements are involved [61,62]. Enamel opacities can cause esthetic dissatisfaction and can impact social judgments [93].

The aim of the DDEs treatment is to resolve the symptoms and to provide esthetic and functional restoration. The DDEs conservative interventions are divided in invasive treatments (traditional restorative treatments, crowns/veneers), that determine excessive tooth cutting and minimal invasive treatments, which include remineralizing agents, microabrasion–remineralization (Mab-Re) and resin infiltration (RI) techniques [94]. The efficacy of these new treatments for hypomineralised and hypoplastic lesions was analyzed in recent clinical studies [95,96].

The Mab-Re combines microabrasion and remineralizing products. The remineralizing agents release ions that obliterate the microtags generated by the microabrasion. Instead, in the RI technique, the photopolymerizable resin with lower viscosity fills the intracrystalline spaces in hypoplastic enamel lesions [97], forming an enamel hybrid layer [98]. The infiltration of the resin increases the refractive index of the hypomineralized enamel, reaching values similar to the healthy enamel. In this way, the DDEs are effectively masked after treatment with resin infiltration [98], because the infiltrated enamel looks like the healthy adjacent enamel.

According to a randomized clinical trial, the RI technique shows improvements (like lightness and color changes) already after a single session, whereas the Mab-Re technique requires multiple sittings to achieve desirable results [97].

Currently, the RI technique is a valid alternative to traditional techniques and can also lead to a significant improvement in dentinal hypersensitivity and in the mechanical characteristics of the treated enamel [98,99]. The limitation of this technique is the lack of predictability in the esthetic results compared to the deep enamel opacities, which make the defect not completely permeable to the resin. Further studies are needed to perform a preoperative assessment of the DDEs depth, which is crucial for the choice of treatment when planning [99].

### *4.2. Dental Caries*

In the literature, some studies have evaluated a possible association between CKD and dental caries, but the results are discordant. In fact, some authors state that there is a higher prevalence of dental caries in CKD patients [100–102], while others argue that CKD subjects have a lower percentage of caries than non-CKD subjects (Figure 3) [61–63,83].

Two systematic reviews show that CKD patients present with a lower decayed–missing–filled-teeth index (DMFT) than non-CKD patients [64,103].

These conflicting results, regarding dental caries and CKD, could be determined by study samples, by different CKD stages of enrolled patients and/or by the presence of kidney-transplanted patients [64], whereas they should be analyzed in separated groups in order to reduce this bias. For example, Sezer et al. analyzed the dental caries in children (aged 4/17) with different stages of CKD in kidney-transplanted children and in healthy children. Their results showed that, according to the International Caries Detection and Assessment System (ICDAS-II) categories, the percentage of children with severe caries

was higher in healthy children (53.8%), while it decreased in kidney-transplanted children (44.4%) in stage 1–3 (25.9%) and in stage 4–5 children (11.4%) [62]. Moreover, in a study by Tadakamadla et al., it was highlighted that patients in more advanced stages of the disease presented with poorer oral health [104].

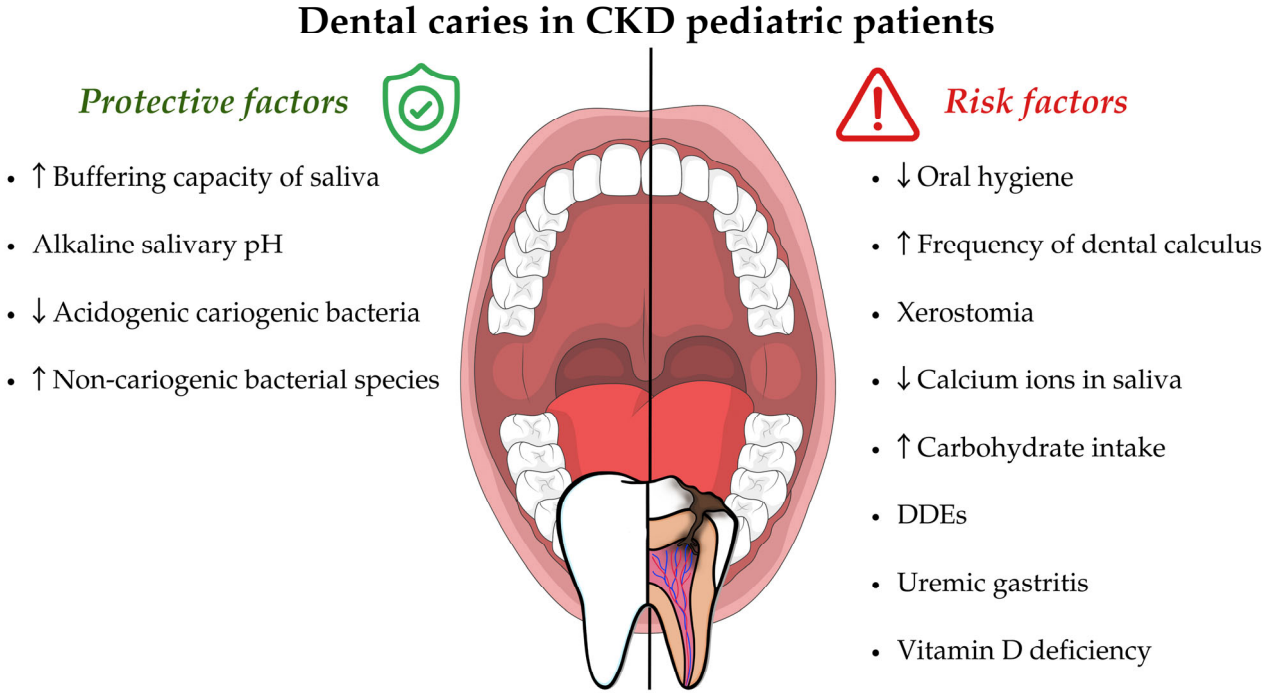


**Figure 3.** Risk and protective factors of dental caries in CKD pediatric patients. Abbreviations: CKD, chronic kidney disease; DDEs, development defects of enamel.

The contrasting results, reported in the literature regarding caries pathology and CKD, could also be related to different risks and protective factors of dental caries that can vary according to the study sample examined. In particular, the risk factors of dental caries in CKD patients that could justify the high prevalence are poor oral hygiene, dental calculus accumulation, xerostomia, high carbohydrate intake, DDEs, uremic gastritis and vitamin D deficiency. The risk factors are detailed below:

- Oral hygiene. Oral hygiene in CKD pediatric patients is poor compared to the control group of healthy subjects [61,66,84]. Some authors underline how there are differences in oral hygiene between CKD patients in the different stages of the disease. Indeed, the highest mean of the simplified oral hygiene index (OHI-S) score was observed in stage 4–5 children (2.10 ± 1.08), followed by kidney-transplanted children (1.46 ± 1.19), by stage 1–3 (1.27 ± 0.61) and by healthy children (0.45 ± 0.44), respectively [62]. Poor oral hygiene is directly related to the increased risk of dental caries formation.
- Dental calculus. Dental calculus in CKD patients is more frequent than in healthy subjects [62] and can also occur in 57.5% of CKD pediatric patients [67], especially in dialysis patients [105]. Dental calculus accumulation can cause difficulties in home oral hygiene, represent a retentive factor for dental plaque, and thus, can increase the risk of dental caries and periodontal disease. Dental calculus formation is determined by the precipitation of salivary calcium–phosphorus and calcium oxalate due to the high salivary pH and the changes in mineral balance with high levels of salivary urea and phosphate [105].

  It is crucial to emphasize that CKD patients should be included and monitored in a preventive oral hygiene program. Frequent dental check-ups and non-surgical peri-

odontal therapy sessions are important not only for adult CKD patients but also for pediatric ones. Indeed, the pediatric CKD patients may also exhibit alterations related to the periodontal attachment apparatus, such as gingival inflammation, gingival overgrowth, gingival recessions and, rarely, periodontal attachment loss [106]. Although these diseases are beyond the aim of this review, they must be diagnosed and treated early in order to ensure oral health. The oral prophylaxis intervention is related to the baseline degree of inflammation, assessed by periodontal indices (like gingival index, papilla bleeding index and periodontal screening index) and includes professional mechanical plaque removal, the local application of chlorhexidine gel, mouth rinses, oral hygiene instructions/motivation and periodic follow-ups [107].
Moreover, the oral prophylaxis intervention for CKD children/adolescents with an accelerated rate of dental calculus formation should include the professional mechanical calculus removal (scaling). The scaling must be performed at least every three months [108].

- Xerostomia. In CKD patients, xerostomia (decreased salivary flow) can be caused by a restricted fluid intake and by a side effect of drug therapy [109]. Several studies also state that salivary flow tends to decrease in CKD and in hemodialysis patients [49,110]. The decreased salivary flow could cause important alterations of its function [111]. In fact, saliva exerts various protective functions against caries development through the dilution and the clearing of the oral cavity, the buffering capacity, the antimicrobial and immune activity and the ion exchange capacity on tooth surfaces (re-mineralization) [112].
- Composition of saliva. The composition of saliva is altered due to the fewer calcium ions in it [59,113]. Furthermore, lower salivary calcium levels could also alter the re-mineralization mechanism (as described above).
- Diet. A diet characterized by a controlled protein intake and a high caloric intake derived from carbohydrate, that is recommended for CKD conservative patients, could be another risk factor for caries disease [50,114], whereas in hemodialysis patients the nutritional-dietetic treatment is characterized by a high protein intake (1.1–1.2 g/kg of ideal body weight/day) and a normal-high caloric intake (30–35 kcal/kg of ideal body weight/day) [115,116].
  In this regard, a study conducted on CKD patients undergoing hemodialysis highlighted how a higher sugar intake, more frequent in CKD patients than healthy controls, was associated with an altered oral microbiota (characterized by an increase in the supragingival plaque samples of *Streptococcus mutans*, *Lactobacillus salivarius*, *Lactobacillus fermentum*, *Lactobacillus vaginalis*, *Scardovia wiggsiae F0424* and *Actinomyces naeslundii*) and a higher DMFT [101].
- DDEs. The DDEs are risk factors for the development of carious lesions [91]. Enamel defects with their rough and irregular surfaces can promote the accumulation of plaque and the determination of a cariogenic bacterial ecological niche [117]. Furthermore, teeth with DDEs have a lower enamel hardness and are subject to wear, especially when the thin enamel layer is subjected to masticatory loads [48]. Moreover, they are shown to have a lower resistance to acid insult when compared to healthy enamel [81]. On the contrary, CKD patients show a lower percentage of dental caries despite having a high prevalence of DDEs compared to healthy subjects [62]. This observation could be explained by analyzing the protective factors of dental caries in CKD subjects.
- Uremic gastritis. CKD patients, especially in more advanced stages, are often characterized by a condition known as uremic gastritis, that among the possible consequences, may induce gastroesophageal reflux and vomiting. These manifestations can lead to enamel erosion, with a consequent increased risk of dental caries [118].

- Vitamin D Deficiency. Several cross-sectional studies state that vitamin D deficiency is associated with an increased incidence of dental caries in the primary dentition [117,119] and in permanent dentition [120,121]. Moreover, the recent systematic reviews point out a relationship between low serum vitamin D levels and dental caries in children and adolescents in primary dentition [122] and in permanent dentition [123]. In a study by Seminario and Velan [113], several mechanisms are proposed to explain this relationship: (1) the alteration of enamel mineralization with consequent presence of DDEs, which constitute a risk factor for dental caries (as described above); (2) the reduced activation of antimicrobial (AMPs) peptides, such as cathelicidins and defensins, which have antimicrobial properties against several bacteria and participate in the innate immune response [74,124–126]; (3) decreased saliva flow and the alteration of its composition by reducing the amount of calcium ions.

As previously mentioned, numerous studies underline how CKD could also represent a protective factor for caries development. These factors in CKD patients are as follows: increased salivary buffering capacity, alkaline salivary pH, and the modification of salivary microbiota.

- Buffer system and salivary pH. In CKD patients, an increased buffering capacity of saliva and an alkaline salivary pH are observed, probably due to the higher concentration of ammonia obtained from the urea hydrolyzation in the mouth through bacterial ureases [84,127]. In fact, the qualitative composition of saliva in CKD patients tends to change compared to healthy subjects; namely, it is characterized by a higher concentration of urea, creatinine, sodium, potassium, chloride and phosphorus [128]. Menezes et al. also report that the salivary levels of urea and the IgA anti-Streptococcus mutans are higher in CKD patients (especially in chronic maintained hemodialysis patients) than in the healthy group and it may be a protective factor against dental caries [83]. According to the study by Al-Nowaiser et al., conducted on CKD children (aged 4–13.6), the mean salivary urea level was significantly higher (11.6 mmol/L) compared to the healthy controls (3.6 mmol/L); a significant difference was also highlighted between the buffering capacity (pH 6.4) compared to the healthy controls (pH 5.6) [66]. Moreover, in a case–control study conducted on hemodialysis pediatric patients (aged 4–17), it was observed that 89.5% of them showed a high salivary buffer capacity [129].

  The alkaline salivary pH determines the acids neutralization and protects the tooth from demineralization [130]. In fact, the tooth surfaces are continuously subjected to acid attack from organic acids formed by the bacterial fermentation of refined carbohydrates [112] or by an excessive consumption of acidic beverages and foods [131].
- Oral microbiota. The alkaline salivary pH creates an unfavorable environment for acidogenic cariogenic bacteria and ecological shift, modifying the salivary microbiota to non-cariogenic bacterial species [48]. In a study conducted on hemodialysis patients (aged 4–17), the salivary levels of *Streptococcus mutans* and Lactobacilli were significantly lower than in the control group of healthy subjects [129]. The same evidence was highlighted by a further study conducted on hemodialyzed children [84]. On the contrary, in kidney-transplanted patients, a decrease in oral pH is observed, which could modify the oral microbiota and promote the onset of caries pathology, especially in those subjects who have poor eating habits (rich in free sugars) [48]. Furthermore, kidney-transplanted patients may take immunosuppressive drugs (such as cyclosporine A) and antihypertensive calcium-blocking agents, which can determine gingival overgrowth (Drug-Induced Gingival Overgrowth—DIGO) and complicate daily tooth brushing maneuvers for the removal of dental plaque [132]. In a recent

study, it was found that 16.7% of pediatric subjects undergoing kidney transplant had DIGO, especially grade 1 [67].

## 5. Natural Bioactive Compounds as Innovative Tools in the Prevention and Adjuvant Treatment of Remineralization and Dental Caries in CKD Pediatric Patients

In CKD pediatric patients, DDEs and dental caries can be treated with traditional therapies adapted to children; however, for their prevention, an important role can be played by natural bioactive compounds (NBCs) derived from plant-based foods [133]. These innovative treatments, although they do not replace standard treatments, can represent a valid adjuvant therapy in the prevention of dental caries especially.

NBCs are described as organic compounds of various origins (mainly from plant-based foods) and with different chemical structures, which exert important actions at the level of biological tissues. They can be classified via their chemical structure and their biological activity through the following molecules: phenols, carotenoids, alkaloids, phytosterols, nitrogen compounds and organosulfur compounds [134,135]. These molecules exert numerous beneficial effects for human health and several clinical studies have highlighted how they could play a pivotal role in the treatment of the DDEs and in dental caries prevention.

Some literature studies pointed out how tannins and phenolic compounds, contained in numerous herbaceous plants, would seem to stimulate, through a wide variety of mechanisms of action (such as the suppression of ATP synthesis or energy metabolism), the re-mineralization of dental enamel, both in adults and in children [136–138]. Another study demonstrated that the use of a toothpaste based on theobromine, a purine alkaloid present in cocoa beans, has an important re-mineralizing effect on tooth enamel, comparable to that of a fluoride-based toothpaste [139]. Therefore, the use of plant-based oral hygiene products could be a valid strategy for the treatment of DDEs in CKD children.

The main NBCs studied for the dental caries prevention are polyphenols. This class of compounds can act through two main mechanisms. The first exerts an important antimicrobial action at the oral cavity level, thus reducing the risk of accumulation of cariogenic bacteria, while the second one can improve the balance of dental de-/remineralization [140,141].

Propolis is a resinous substance naturally produced by bees, rich in a series of organic and inorganic compounds, such as flavonoids, phenols, terpenes, fatty acids, alcohols, alkaloids, sugars, amino acids and numerous vitamins and minerals. Several in vitro and in vivo studies have highlighted the possible action of propolis in dentistry as an agent for biofilm control and dental caries prevention. In particular, propolis would seem to be able to inhibit the adhesion, growth and cellular metabolism of cariogenic bacteria (like *E. faecalis*, *S. aureus*, *P. gingivalis* and Streptococcus species) and inhibit the activity of glucosyltransferase enzymes, responsible for biofilm formation [142].

Cocoa beans (*Theobroma cacao* L.) are a rich source of numerous NBCs, including methylxanthines (such as theobromine, caffeine and theophylline) and flavonoids with notable antioxidant, anti-inflammatory and antimicrobial properties [143]. Numerous studies have shown that cocoa beans are able to counteract the principal oral pathogens, like cariogenic bacteria. In fact, cocoa beans would seem to inhibit the adherence and growth of *S. mutans*, as well as the activity of the enzyme glycosyltransferase, responsible for cariogenic bacteria adhesion to the enamel surface. Furthermore, cocoa flavonoids appear to contribute to the integrity of dental tissue by inhibiting the expression and the activity of matrix metalloproteinases (MMPs). These enzymes can be activated by cariogenic bacteria and they are able to stimulate the collagen degradation. The inactivation of MMPs by cocoa prevents the degradation of the dentinal organic matrix [144].

Furthermore, several in vivo studies showed how NBCs from plant-based foods can be used for innovative food-formulations intended for children, such as lollipops or chewing gum. These innovative products seem to be effective in preventing the caries in high-risk children [145].

Chen et al. studied the anti-cariogenic activity of a daily consumption of two lollipops containing licorice extracts in high-risk children, aged 3 to 6 years. After three weeks of administration, the authors observed that treatment characterized by the consumption of the licorice lollipops significantly reduced the levels of *S. mutans* in children's saliva without affecting salivary biodiversity, compared to the control group [146].

Similarly, Mahd et al. studied the effects of a pomegranate mouthwash on dental plaque formation in 8–10 years-old children. In fact, in the literature, it has been demonstrated that pomegranate extract has, both in vitro and in vivo, powerful antimicrobial proprieties and can exert beneficial effects on oral health [147]. The authors highlighted an important antibacterial effect on *S. mutans* and *L. acidophilus*, the main cariogenic pathogens, with a 38% reduction in plaque formation in treated children compared to the control group [148].

However, even if the literature data seem promising, the mechanisms of the anti-caries effects of CNBs are not yet completely clear. Therefore, further in vitro and in vivo studies are needed to demonstrate, once and for all, the anti-caries adjuvant effects of plant-based foods.

## 6. Conclusions

In recent years, research has focused on the oral manifestations of CKD, both in adult and pediatric patients. In fact, a large amount of evidence shows that there is a bidirectional correlation between oral health and CKD, where the alteration of calcium–phosphorus balance plays a pivotal role, which induces both the progression of CKD itself and the consequent oral pathological manifestations, especially in children. The main oral pathological manifestations of hard dental tissues related to CKD are summarized as follows:

- Developmental defects of enamel related to an altered amelogenesis, both primary and permanent teeth.
- Rachitic teeth with anomalies of enamel mineralization, dentin hypomineralization and various degrees of interglobular dentine.
- Dental caries related to poor oral hygiene, dental calculus accumulation, xerostomia, the alteration of the remineralization mechanism, vitamin D deficiency and DDEs; on the other hand, the CKD could determine the presence of protective factors for dental caries.

In this context, the multidisciplinary approach is fundamental for the management of these patients. In fact, the collaboration between pediatrics, nephrologists, nutritionists and pediatric dentists is essential to intercept and/or manage any early oral manifestation related to CKD in children and adolescents. All specialists should work together to improve the health status and quality of life of their patients. For example, a regular dental check-up, an oral hygiene education and a dietary counseling, in association with regular nephrological check-ups, can significantly reduce the incidence of the oral manifestations in CKD pediatric patients.

Preventive measures should be adopted as dental follow-up controls both dental hard tissues and intraoral soft tissues in all CKD stages. Nutritional education instructions (also suggesting the consumption of foods characterized by high NBCs content), in combination with at-home oral hygiene, should be carried out specifically by all CKD pediatric patients

and their parents, because oral health is essential not only for masticatory, esthetic, phonetic and swallowing functions, but it is also closely related to systemic health status [149].

In this field, it should be necessary to investigate the impact of CKD on hard dental tissues in pediatric patients in-depth, both analyzing the previous literature in a metanalysis and conducting an innovative clinical trial on a larger simple size; these data should also be integrated with those obtained on soft periodontal tissues.

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