

REVIEW PAPER

Nephrocalcinosis: the latest reports on risk factors – a review

Tomasz Dudzik , Łucja Dudzik, Igor Domański, Aleksandra Koziół, Paulina Wójcik, Natalia Kuderska

Faculty of Medicine, Medical University of Wrocław, Wrocław, Poland

ABSTRACT

This review synthesizes recent discoveries in the risk factors of nephrocalcinosis, with a particular focus on novel findings. Nephrocalcinosis, characterized by the deposition of calcium salts in the renal parenchyma, is linked to a variety of genetic, metabolic, dietetic, and environmental factors. The study emphasizes the critical role of advanced imaging techniques in diagnosis and the identification of new genetic mutations in genes such as *CLCN5*, *CASR*, and *SLC34A3* as significant factors contributing to the condition. The paper highlights the importance of recognizing these novel risk factors for better diagnosis, treatment, and prevention of nephrocalcinosis. It calls for further research to explore these new dimensions, particularly the genetic underpinnings and environmental exposures, to develop more effective management strategies and potentially prevent the onset of this complex renal condition.

KEY WORDS:

risk factors, nephrocalcinosis, latest report.

INTRODUCTION

Nephrocalcinosis (NC), an intricate pathological condition, is characterized by the accumulation of calcium salts within the renal parenchyma, a vital component of the kidneys. This condition emerges as a considerable clinical challenge, primarily due to its complex association with a spectrum of kidney dysfunctions and disorders, underscoring its significance in nephrology. The pathophysiological underpinnings of NC are multifaceted, encompassing an array of mechanisms including, but not limited to, aberrant calcium metabolism, disturbances in renal acid-base homeostasis, and the impact of certain genetic predispositions. When located within the renal pyramids, it is referred to as medullary nephrocalcinosis (MNC), which is more prevalent than its cortical counterpart. This higher incidence can be attributed

to the medulla being the site where crucial calcium re-absorption pathways and acid-base regulatory segments are situated [1]. Dietary habits, particularly high intake of sodium and animal protein, and low fluid consumption, have been implicated in the pathophysiology of NC. This condition can lead to chronic kidney disease (CKD), impaired kidney function, and, in severe cases, kidney failure (KF), highlighting the importance of understanding its etiology and risk factors.

The prevalence of NC varies widely, reflecting differences in diagnostic criteria, underlying causes, and population characteristics studied. It is difficult to determine an exact and rigid frequency of occurrence, as it varies depending on the type of factor causing NC. Diagnostically, the detection of NC hinges on imaging modalities, with ultrasound and computed tomography (CT) scans being pivotal in visualizing calcific deposits. The diagnostic

ADDRESS FOR CORRESPONDENCE:

Tomasz Dudzik, Faculty of Medicine, Medical University of Wrocław, 2-6 Karola Marcinkowskiego St., 50-368 Wrocław, Poland, e-mail: tomek4732@gmail.com

process is complemented by a thorough evaluation of clinical history, biochemical analyses, and, in certain cases, genetic testing, to elucidate the underlying etiological factors. Ultrasonography stands out as the most effective technique for the detection of NC, offering enhanced sensitivity. Frequently, the discovery of NC occurs unexpectedly during imaging procedures, emphasizing the necessity of subsequent analysis to pinpoint the root cause. Thus, the role of imaging in identifying this condition is fundamentally important for guiding its treatment strategy [2]. In the realm of medical imaging, the utilization of [^{18}F]-sodium fluoride autoradiography emerges as a novel technique for the visualization of microcalcifications. While not yet widely adopted in clinical practice, initial investigations into its efficacy and application present promising prospects. This innovative imaging modality holds the potential to enhance our understanding and detection of microcalcifications, paving the way for advancements in diagnostic accuracy and therapeutic strategies [3]. It is worth noting that NC can also be part of a bigger picture. This is clearly demonstrated in a paper discussing three different cases, where NC was the first symptom, and the true conditions of the patients were Sjögren's syndrome, primary hyperparathyroidism, and an aldosterone-secreting adenoma [4].

This review aims to synthesize the latest research findings on the genetic, metabolic, dietetic, and environmental factors contributing to NC, providing insights into pathogenesis, risk factors, and potential management strategies. While numerous studies could have been included in this work, our aim was to concentrate on the most significant achievements in recent years. Indeed, one might consider other risk factors such as vitamin D₃ or the appropriate levels of sodium and potassium. However, we did not find studies that introduced groundbreaking findings in these areas.

METHODOLOGY

We searched the databases PubMed, Scopus, Web of Science, and Google Scholar for studies published since 2017 up to February 2024. We used keywords and phrases alone and in many combinations together: “nephrocalcinosis”, “genetic factors”, “metabolic factors”, “dietetic factors”, “environmental factors”, “*CLCN5* gene mutations”, “*CASR* gene mutations”, “*SLC34A3* mutations”, “hypercalcemia”, “hyperoxaluria”, “hypocitraturia”, “acid-base imbalances”, “calcium intake”, “oxalate consumption”, “protein intake”, “fluid consumption”, “agricultural chemicals”, “lifestyle and pollution”, “urinal infections”, “prenatal.”

Our inclusion criteria were: peer-reviewed research articles, case studies, meta-analyses and review articles published in English.

Our exclusion criteria were: non-peer-reviewed articles, commentaries, and editorials.

We selected studies by a two-stage screening process involving initial title and abstract review followed by full-

text assessment to confirm eligibility based on the inclusion and exclusion criteria.

We extracted relevant data from the included studies as follows: author(s), publication year, study design, population characteristics, interventions (if any), outcomes related to NC, and key findings. A standardized data extraction form was used, and the process was conducted independently by two team members to ensure accuracy and consistency. The quality of included studies was assessed using appropriate tools, such as the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for randomized controlled trials. Studies were categorized as high, moderate, or low quality based on their scores, which was considered in the synthesis and interpretation of findings.

A narrative synthesis approach was adopted to integrate findings across the genetic, metabolic, dietetic, and environmental domains. Where possible, subgroup analyses were conducted based on specific risk factors or patient populations to identify particular vulnerabilities or protective factors associated with NC.

At the end, we added to the study a few investigations beyond those criteria. The rationale for their inclusion is to provide an explanation of the context of the studies we cited or to clarify the pathophysiology of the phenomenon, new discoveries, or to show prevalence.

The review has some limitations, including publication bias, heterogeneity among studies, and the predominance of observational studies over randomized controlled trials.

RESULTS

GENETIC FACTORS

Genetic mutations, specifically in genes such as *CLCN5*, *CASR*, and *SLC34A3*, have been identified as significant contributors to NC, underscoring the critical role of genetic predisposition in the disease's pathogenesis [5]. Genetic causes of NC, though uncommon, result in different outcomes depending on the patient's genetic makeup. Quick and accurate identification of these causes allows for the early application of treatments, potentially preventing or slowing the deterioration of kidney function. Additionally, pinpointing the genetic mutation aids in offering precise prognostic information and enables the testing of relatives [6]. Despite the fact that we are able to identify an increasing number of mutations that can lead to NC, genetic factors still account for 29.4% of the disease cases according to data from 2018, with 80% being recessive mutations and 20% dominant [7]. In a 2015 study, the frequency was determined to be 20.8% in the pediatric population. However, many mutations were not known at the time and could not be considered in these calculations [8].

CLCN5 GENE MUTATIONS

The *CLCN5* gene, encoding the CLC-5 chloride channel, has been long associated with Dent disease. Dent disease is a rare genetic kidney disorder characterized by features such as low molecular weight proteinuria, hypercalciuria, nephrolithiasis, and progressive KF, primarily affecting males due to its X-linked inheritance [9]. It is caused by mutations in either the *CLCN5* gene (Dent disease 1) or the *OCRL* gene (Dent disease 2), which lead to dysfunction in the kidney tubules [10]. Almost 60% of patients have causative mutations in the *CLCN5* gene (Dent 1), and 15% of affected individuals have mutations in the *OCRL* gene (Dent 2). The prevalence of NC in Dent disease is 42% for type 1 and 11% for type 2 [11].

A study conducted in 2023 reported two novel mutations in the *CLCN5* gene: one frameshift mutation (c.1241_1242dupAA) and one splicing mutation (c.805-2A>G). Also, this study identified one novel mutation in the *OCRL* gene [12].

CASR GENE MUTATIONS

The *CASR* gene encodes the calcium-sensing receptor (CaSR), a crucial G protein-coupled receptor involved in regulating calcium homeostasis by sensing changes in extracellular calcium levels, influencing processes such as parathyroid hormone secretion and kidney calcium handling. Inactivating mutations of this gene cause hypercalcemia, whereas activating mutations result in hypocalcemia and hypercalciuria. Approximately 10% of individuals with activating mutation are estimated to develop NC and nephrolithiasis [13].

In 2023 a study conducted by Zung *et al.* [14] identified a novel activating mutation in the *CASR* gene that causes NC in three generations in one family. Also, extensive clinical data gathered allowed researchers to propose specific upper limits for serum calcium levels based on age. Their recommendation takes into account the relationship between the amount of calcium in the blood and the excretion of calcium through the kidneys. Those findings highlight the importance of adjusting calcium level thresholds according to age to better understand and manage the balance between serum and kidney calcium levels.

SLC34A3 MUTATIONS

The *SLC34A3* gene is responsible for encoding the renal type IIc sodium-phosphate cotransporter, which is crucial for phosphate homeostasis and is primarily expressed in the kidneys. Mutations in this gene lead to conditions such as hereditary hypophosphatemic rickets with hypercalciuria, characterized by renal phosphate wasting, hypophosphatemia, and elevated serum levels of 1,25-dihydroxyvitamin D [15]. Individuals with both

compound heterozygous and homozygous mutations in the *SLC34A3* gene face a high risk of developing kidney stones and MNC. Notably, those with mutations in both alleles of *SLC34A3* exhibit a 46% prevalence of NC, in stark contrast to the 6% prevalence seen in healthy relatives with only the normal gene variant [16].

A study conducted in 2019 showed that the missense variant p.Ser192Leu in *SLC34A3* leads to reduced transport activity of inorganic phosphate. On the other hand, the authors concluded that the clinical consequences of p.Ser192Leu may be relatively mild [17].

CYP24A1

The enzyme CYP24A1, encoded by the *CYP24A1* gene, plays a crucial role in vitamin D metabolism, specifically in the inactivation of 1,25-dihydroxyvitamin D₃ through hydroxylation. Mutations in this gene can lead to a decrease in the enzyme's function, resulting in increased vitamin D levels, which causes hypercalcemia and hypercalciuria. These conditions are key factors in the development of NC, nephrolithiasis and potentially CKD. A study from Poland reported an incidentally found homozygous mutation (R396W) in the *CYP24A1* gene. The mutation manifested with increased calcium excretion in urine while maintaining normal serum calcium levels. The patient also showed a deficiency of vitamin D₃ as well as decreased parathyroid hormone levels. The researchers stated that the occurrence of this mutation in Poland is estimated at about 0.68% [18].

METABOLIC FACTORS

HYPERCALCEMIA

Hypercalcemia in NC can result from conditions that cause increased calcium reabsorption in the kidneys, often compounded by disturbances in other metabolic processes such as vitamin D dysregulation. For instance, mutations in the *CYP24A1* gene can impair the breakdown of active vitamin D metabolites, leading to excessive calcium absorption and subsequent hypercalcemia and NC [19].

On the other hand, there are studies showing less obvious conditions leading to hypercalcemia. A 2019 case study highlights an unusual instance demonstrating the connection between NC and extrapulmonary (genitourinary) tuberculosis, emphasizing that hypercalcemia is a recognized complication in granulomatous conditions. This example underscores the diagnostic and treatment challenges of NC when linked to infectious diseases such as tuberculosis [20]. A different case report outlines the uncommon occurrence of a patient with distal renal tubular acidosis (RTA) who exhibited hypercalcemia. This case provides insight into the intricate relationship between RTA and the regulation of calcium in the body,

highlighting the importance of comprehensive assessments for unexplained cases of hypercalcemia [21].

In newborns, the primary culprit is often the hypercalciuria found in premature infants, which stems from a variety of iatrogenic causes. It is crucial to always explore and examine the possibility of primary hyperoxaluria, a condition that can trigger early NC and often progresses to CKD [22, 23].

HYPEROXALURIA

Hyperoxaluria, a condition of elevated urinary oxalate levels, leads to the formation and deposition of calcium oxalate crystals in the kidney parenchyma, contributing to NC and potential chronic kidney damage. This excessive oxalate can originate from endogenous overproduction, dietary intake, or gut absorption issues, and results in crystal-induced kidney inflammation and tubular obstruction, which may progress to KF [24].

Research in this area has demonstrated that lumasiran, a therapeutic based on RNA interference (RNAi), is effective in lowering the excretion of oxalate in urine for patients with primary hyperoxaluria type 1 (PH1), marking a substantial progression in treating this disease. After six months of treatment, most patients receiving lumasiran achieved normal or almost normal levels, representing a significant breakthrough in the therapy of PH1 [25]. Jayachandran *et al.* [26] explored how populations of urinary extracellular vesicles (EVs) carrying specific biomarkers and proteins differ among PH1 patients with and without NC or kidney stones. The study suggested that specific populations of urinary EVs and proteins could serve as potential biomarkers to assess the pathogenic mechanisms between kidney stones versus NC among PH1 patients. Patients with kidney stones excreted fewer EVs, while the urinary concentration of specific calcification-related proteins were greater in PH1 patients with kidney stones compared to PH1 patients without NC or kidney stones or with NC [26].

HYPOCITRATURIA

Citrate inhibits stone formation by binding to urinary calcium, preventing the formation of calcium salts. Hypocitraturia, or low urinary citrate levels, removes this protective mechanism, facilitating NC. In 2023 a study found a modest association between hypocitraturia and osteoporosis or fracture, suggesting that other factors might contribute to the relationship between kidney stone disease and diminished bone health [27].

ACID-BASE IMBALANCES

Acid-base imbalances, particularly acidosis, can exacerbate NC by increasing urinary calcium excretion, a process driven by decreased reabsorption of calcium in the kid-

ney tubules and mobilization of calcium from bone [28]. Additionally, disturbances in acid-base balance can influence mineral metabolism and calcium-phosphate handling, which are key factors in the development and progression of NC, further implicating acidosis in this kidney pathology [29]. A study conducted in 2019 tested mice deficient in proton-activated ovarian cancer G-protein coupled receptor 1 (OGR1) under chronic metabolic acidosis conditions induced by ammonium chloride. They found that OGR1 plays a crucial role in sensing acidosis and inducing increased urinary calcium excretion, thus potentially contributing to the development of NC. The findings suggest that novel drugs targeting OGR1 activity may improve kidney calcium handling and help manage conditions like NC that are exacerbated by acid imbalance [39].

DIETARY FACTORS

CALCIUM INTAKE

Increased calcium intake can lead to NC by promoting the precipitation of calcium salts in the kidney parenchyma. This condition occurs due to supersaturation of calcium in the urine and its subsequent deposition in the kidneys, leading to potential kidney damage and impaired function. Moreover, high dietary calcium, especially when not balanced with other minerals such as phosphorus, magnifies the risk and severity of NC by increasing kidney calcium content and NC incidence, although very high levels of dietary calcium can sometimes paradoxically reduce NC due to complex interactions with phosphate and other factors. Contrary to intuitive assumptions, low dietary calcium has been also associated with an increased risk of stone formation and, potentially, NC due to compensatory hyperoxaluria. A study that investigated the impact of conventional therapy, including calcium supplementation, on patients with primary hypoparathyroidism, noting the occurrence of NC as a complication, is worth mentioning [31].

PROTEIN INTAKE

Dietary protein, particularly from animal sources, can influence calcium and oxalate excretion. A comprehensive review and meta-analysis examined the impact of diets low in protein on kidney function and nutritional status, with a particular focus on disorders such as NC. The findings suggested that diets with reduced protein content can lead to enhancements in conditions related to kidney disease, notably nephropathy. However, the analysis also highlighted potential risks associated with such dietary restrictions, notably the heightened risk of malnutrition. This underscores the need for careful dietary planning and monitoring to ensure that the health benefits of reduced protein intake do not come at the expense of overall nutritional well-being [32].

FLUID CONSUMPTION

Increased fluid intake is crucial for preventing NC, as it helps reduce urine concentration and lowers the supersaturation of stone-forming salts, thereby reducing the likelihood of calcium salt crystallization in the kidneys. Adequate hydration is particularly important in conditions that predispose individuals to higher solute excretion, which can promote NC by increasing the risk of calcium salt precipitation in kidney tissue. A study from 2013 emphasized the crucial role of hydration in treating nephrolithiasis, a condition often associated with NC. It suggests a preventive effect of increased fluid intake on the risk of developing a first kidney stone and on the recurrence of stones. Recommendations include increasing fluid intake to at least 2.5 l/day, and even to 3.5–4 l/day in severe forms of nephrolithiasis, balancing intake between day and night to avoid urinary supersaturation [33]. Furthermore, a cross-sectional study confirmed that higher total plain water and total fluid intake were associated with a lower risk of nephrolithiasis. Encouraging a daily water intake of > 2500 ml and maintaining a urine output of 2 l/day were linked with a lower prevalence of kidney stones [34].

ENVIRONMENTAL FACTORS

FETAL LIFE AND EARLY POSTNATAL PERIOD

In a multivariate analysis, key factors have been identified that significantly increase the likelihood of NC in neonates. These factors include the prematurity of the neonate, as indicated by gestational age, which underscores the critical role of kidney maturity at birth. Low birth weight further compounds this risk, highlighting the importance of fetal growth on renal outcomes. The occurrence of sepsis in neonates is a notable risk factor, pointing to the impact of infection on kidney health. Being small for gestational age, a sign of intrauterine growth restriction, and maternal pregnancy-induced hypertension were also identified as significant contributors. These insights collectively emphasize the complex interplay between prenatal and neonatal health in the development of NC, suggesting avenues for targeted interventions to reduce risk in this vulnerable demographic [35].

URINARY INFECTIONS

A study pinpointed a history of urinary tract infections (UTIs) as a notable risk factor for the development of NC and kidney stones in newborns. This finding emphasizes the significant relationship between UTIs and the onset of these kidney conditions within this vulnerable population. Moreover, the research implies that the majority of these NC/kidney stones cases tend to resolve on their own, without the need for surgical

procedures. This observation suggests that, while UTIs are a critical risk factor warranting attention, the natural course of NC/kidney stones in neonates often leads to spontaneous resolution, minimizing the necessity for invasive interventions [36].

AGRICULTURAL CHEMICALS

Pesticides and herbicides used in agriculture can enter the human body through food and water, potentially affecting kidney health. Specific chemicals have been shown to disrupt kidney function and increase the risk of kidney stones and NC. A study by Zhang *et al.* [37] found that the combination of glyphosate (a widely used herbicide) and hard water could induce kidney injury through excessive mitochondrial fission mediated by dynamin-related protein 1, suggesting a potential environmental factor contributing to kidney disease, including NC in specific conditions.

LIFESTYLE AND POLLUTION

Urbanization and associated lifestyle factors, including air pollution and reduced access to clean water, can also impact NC risk. Airborne pollutants have been implicated in systemic inflammation and oxidative stress, which may indirectly contribute to kidney stone formation and NC. A systematic review and meta-analysis by Wu *et al.* [38] found air pollution, specifically long-term exposure to particulate matter (PM_{2.5} or PM₁₀) and gaseous pollutants (CO, SO₂, NO₂), to be associated with increased risk of CKD and renal function decline. This suggests that environmental pollutants could potentially contribute to kidney conditions including NC, which often coexists with CKD.

CONCLUSIONS

We believe that further research into these factors is essential for a more comprehensive understanding of the full pathophysiology of this condition. Particularly, the genetic aspect seems to be a broad field for further analysis and research. Despite playing a minor role in the overall number of NC cases, it is through the identification of these mutations that we will be able to search for targets for new drugs.

We require thorough analysis and exploration of new methods of treatment, such as nephroceuticals, or preventing the onset of this condition. Nephroceuticals are emerging as a promising avenue for treating kidney conditions including NC, utilizing mechanisms such as antioxidant effects, inflammation reduction, nerve regeneration, and the prevention of cell death [39].

Recent research included in our review has revealed novel risk factors and mechanisms contributing to NC, including unexpected metabolic pathways such as

hyperoxaluria and the impact of dietary habits. Additionally, emerging evidence points to environmental influences, including exposure to agricultural chemicals and urban pollution, as new areas of concern. It is also important to highlight the skillful adjustment of blood ion concentrations in individuals with other risk factors. We believe that patients at risk of NC should be monitored, which is possible thanks to the knowledge of risk factors. Thanks to quick intervention, we can address the problem earlier, resulting in better treatment outcomes.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

REFERENCES

1. Zacchia M, Capolongo G, Rinaldi L, Capasso G. The importance of the thick ascending limb of Henle's loop in renal physiology and pathophysiology. *Int J Nephrol Renovasc Dis* 2018; 11: 81-92.
2. Aldana JC, Rodríguez LC, Bastidas N, Vásquez A. Radiological features of nephrocalcinosis, a common but forgotten entity. *Br J Radiol* 2023; 96. DOI: <https://doi.org/10.1259/bjr.20221096>.
3. Benjamins S, Antunes IF, Hillebrands JL, et al. [18F]-sodium fluoride autoradiography imaging of nephrocalcinosis in donor kidneys and explanted kidney allografts. *Sci Rep* 2021; 11: 1841. DOI: <https://doi.org/10.1038/s41598-021-81144-4>.
4. Atlani M, Rai N, Kohat A, et al. Nephrocalcinosis – a gateway to the diagnosis. *Indian J Nephrol* 2021; 31: 562. DOI: https://doi.org/10.4103/ijn.IJN_397_19.
5. Colares Neto GP, Ide Yamauchi F, Hueb Baroni R, et al. Nephrocalcinosis and nephrolithiasis in X-linked hypophosphatemic rickets: diagnostic imaging and risk factors. *J Endocr Soc* 2019; 3: 1053-1061.
6. Dickson FJ, Sayer JA. Nephrocalcinosis: a review of monogenic causes and insights they provide into this heterogeneous condition. *Int J Mol Sci* 2020; 21: 369. DOI: <https://doi.org/10.3390/ijms21010369>.
7. Daga A, Majmundar AJ, Braun DA, et al. Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. *Kidney Int* 2018; 93: 204-213.
8. Halbritter J, Baum M, Hynes AM, et al. Fourteen monogenic genes account for 15% of nephrolithiasis/nephrocalcinosis. *J Am Soc Nephrol* 2015; 26: 543-551.
9. Devuyst O, Thakker RV. Dent's disease. *Orphanet J Rare Dis* 2010; 5: 28. DOI: <https://doi.org/10.1186/1750-1172-5-28>.
10. Sakakibara N, Nagano C, Ishiko S, et al. Comparison of clinical and genetic characteristics between Dent disease 1 and Dent disease 2. *Pediatric Nephrol* 2020; 35: 2319-2326.
11. Blanchard A, Curis E, Guyon-Roger T, et al. Observations of a large Dent disease cohort. *Kidney Int* 2016; 90: 430-439.
12. Mollataheri A, Mojabafan M, Hosseini R, et al. A Study on the CLCN5 gene in Iranian patients: a report of novel and recurrent mutations. *Nephron* 2023; 147: 470-477.
13. Vahe C, Benomar K, Espiard S, et al. Diseases associated with calcium-sensing receptor. *Orphanet J Rare Dis* 2017; 12: 19. DOI: <https://doi.org/10.1186/s13023-017-0570-z>.
14. Zung A, Barash G, Banne E, Levine MA. Novel calcium-sensing receptor (CASR) mutation in a family with autosomal dominant hypocalcemia type 1 (ADH1): genetic study over three generations and clinical characteristics. *Horm Res Paediatr* 2023; 96: 473-482.
15. Lorenz-Depiereux B, Benet-Pages A, Eckstein G, et al. Hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in the sodium-phosphate cotransporter gene SLC34A3. *Am J Hum Genet* 2006; 78: 193-201.
16. Dasgupta D, Wee MJ, Reyes M, et al. Mutations in SLC34A3/NPT2c are associated with kidney stones and nephrocalcinosis. *J Am Soc Nephrol* 2014; 25: 2366-2375.
17. Schönauer R, Petzold F, Lucinescu W, et al. Evaluating pathogenicity of SLC34A3-Ser192Leu, a frequent European missense variant in disorders of renal phosphate wasting. *Urolithiasis* 2019; 47: 511-519.
18. Nowicki JK, Maćkowska A, Rychwalska M, et al. Accidentally detected nephrocalcinosis in a boy with a homozygous R396W mutation in the CYP24A1 gene – 7-year follow-up. *Pediatr Pol* 2023; 98: 351-361.
19. Rozhinskaya LYa, Pushkareva AS, Mamedova EO, et al. Parathyroid hormone-independent hypercalcemia and hypercalciuria of a patient with nephrolithiasis and nephrocalcinosis and impaired vitamin D metabolism due to a defect in the CYP24A1 gene. *Osteoporosis and Bone Diseases* 2021; 24: 26-33.
20. Malakar S, Negi B, Singh G, Sharma T. Nephrocalcinosis in a patient with extrapulmonary tuberculosis – a rare entity. *J Family Med Prim Care* 2019; 8: 296. DOI: https://doi.org/10.4103/jfmpc.jfmpc_385_18.
21. Saneifard H, Parviz S, Mohkam M, Jamee M. Hypercalcemia in distal renal tubular acidosis: A case report. *J Clin Transl Endocrinol Case Rep* 2020; 18: 100069. DOI: <https://doi.org/10.1016/j.jecr.2020.100069>.
22. Monet-Didailier C, Chateil J-F, Allard L, et al. Néphrocalcinose de l'enfant. *Nephrol Ther* 2021; 17: 58-66. DOI: <https://doi.org/10.1016/j.nephro.2020.12.001>.
23. Yadav M, Bagga A. Nephrocalcinosis: biochemical evaluation and genetic analysis. *Indian Pediatr* 2020; 57: 397-398.
24. Hoppe B, von Unruh GE, Blank G, et al. Absorptive hyperoxaluria leads to an increased risk for urolithiasis or nephrocalcinosis in cystic fibrosis. *Am J Kidney Dis* 2005; 46: 440-445.
25. Garrelfs SE, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med* 2021; 384: 1216-1226.
26. Jayachandran M, Yuzhakov SV, Kumar S, et al. Specific populations of urinary extracellular vesicles and proteins differentiate type 1 primary hyperoxaluria patients without and with nephrocalcinosis or kidney stones. *Orphanet J Rare Dis* 2020; 15: 319. DOI: <https://doi.org/10.1186/s13023-020-01607-1>.
27. Ganesan C, Thomas I, Montez-Rath ME, et al. Hypocitraturia and risk of bone disease in patients with kidney stone disease. *JBM Plus* 2023; 7. DOI: <https://doi.org/10.1002/jbm4.10786>.
28. Alexander RT, Cordat E, Chambrey R, et al. Acidosis and urinary calcium excretion: insights from genetic disorders. *J Am Soc Nephrol* 2016; 27: 3511-3520.
29. Evenepoel P, Daenen K, Bammens B, et al. Microscopic nephrocalcinosis in chronic kidney disease patients. *Nephrol Dial Transplant* 2015; 30: 843-848.
30. Imenez Silva PH, Wagner CA. Physiological relevance of proton-activated GPCRs. *Pflugers Arch* 2022; 474: 487-504.
31. Saha S, Kandasamy D, Sharma R, et al. Nephrocalcinosis, renal dysfunction, and calculi in patients with primary hypoparathyroidism

- on long-term conventional therapy. *J Clin Endocrinol Metab* 2020; 105: e1215-e1224. DOI: <https://doi.org/10.1210/clinem/dgz319>.
32. Yue H, Zhou P, Xu Z, et al. Effect of low-protein diet on kidney function and nutrition in nephropathy: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr* 2020; 39: 2675-2685.
33. Courbebaisse M, Travers S, Boudierlique E, et al. Hydration for adult patients with nephrolithiasis: specificities and current recommendations. *Nutrients* 2023; 15: 4885. DOI: <https://doi.org/10.3390/nu15234885>.
34. Wang JS, Chiang HY, Chen HL, et al. Association of water intake and hydration status with risk of kidney stone formation based on NHANES 2009-2012 cycles. *Public Health Nutr* 2022; 25: 2403-2414.
35. Han SE, Cha T, Kim J, et al. Risk factors for nephrocalcinosis in very low birth weight infants. *Perinatology* 2019; 30: 14. DOI: <https://doi.org/10.14734/PN.2019.30.1.14>.
36. Huynh M, Clark R, Li J, et al. A case control analysis investigating risk factors and outcomes for nephrocalcinosis and renal calculi in neonates. *J Pediatr Urol* 2017; 13: 356.e1-356.e5. DOI: <https://doi.org/10.1016/j.jpuro.2017.06.018>.
37. Zhang L, Ding F, Wang R, et al. Involvement of mitochondrial fission in renal tubular pyroptosis in mice exposed to high and environmental levels of glyphosate combined with hard water. *Environ Pollut* 2021; 283: 117082. DOI: <https://doi.org/10.1016/j.envpol.2021.117082>.
38. Wu MY, Lo WC, Chao CT, et al. Association between air pollutants and development of chronic kidney disease: a systematic review and meta-analysis. *Sci Total Environ* 2020; 706: 135522. DOI: <https://doi.org/10.1016/j.scitotenv.2019.135522>.
39. Zahmatkesh M. Nephroceuticals as a new hope for the treatment of kidney diseases. *J Renal Endocrinol* 2023; 9: e25112. DOI: <https://doi.org/10.34172/jre.2023.25112>.