J Ped Nephrol
Journal of Pediatric Nephrology
Autumn 2023. Volume 11. Number 4

Review Article

Hypercalciuria in Children: A Review

Mohsen Akhavan Sepahi[1, 2*], **Mohammad Hossein Akhavan Sepahi**[3], **Ali Akhavan Sepahi**[4]

1. Department of Pediatric Nephrology, School of Medicine, Qom University of Medical Sciences, Qom, Iran.
2. Pediatric Clinical Research Development Unite, Hazrat-E Fatemeh Masoumeh Hospital, Qom University of Medical Sciences, Iran.
3. Federal State Budgetary Educational Institution of Higher Education, A.I. Yevdokimov Moscow State University of Medicine and Dentistry (MSUMD), Moscow, Russia.
4. Department of Dentistry, First Moscow State Medical University (Sechenov University), Moscow, Russia.

Use your device to scan and read the article online

Citation Akhavan Sepahi M, Akhavan Sepahi MH, Akhavan Sepahi A. Investigating New Update in Hypercalciuria in Children. Journal of Pediatric Nephrology. 2023; 11(4):175-180. http://dx.doi.org/10.22037/jpn.v11i4.45111

http://dx.doi.org/10.22037/jpn.v11i4.45111

Article info:
Received: 22 Feb 2023
Accepted: 21 Mar 2023
Publish: 01 Oct 2023

Corresponding Author:
Mohsen Akhavan Sepahi, MD.
Address: Department of Pediatric Nephrology, School of Medicine, Qom University of Medical Sciences, Qom, Iran.
E-mail: akhavansepahimm@gmail.com

ABSTRACT

Background and Aim: Severe loss of calcium in the urine is called hypercalciuria. This study aimed to review the etiology of hypercalciuria in children to provide information on the management and complications that can improve the prognosis of hematuria.

Methods: In this narrative review study, information was extracted from the related articles found in databases, such as Scopus, Google Scholar, Embase, Web of Science, PubMed, and the Directory of Open Access Journals.

Results: The main cause of nephrolithiasis in children is metabolic cause, and hypercalciuria is considered the most common cause. Hypercalciuria increases the risk of urinary stones and other problems.

Conclusion: Hypercalciuria is a very important cause of kidney stones. This study provides information for the initial evaluation and monitoring of children with hypercalciuria. There is no evidence-based method for its diagnostic evaluation. It is recommended that extensive public attention should be paid to the cause and management of hypercalciuria in children.

Keywords: Calcium, Nephrolithiasis, hypercalciuria

J Ped Nephrol
Journal of Pediatric Nephrology

Introduction

Continuing education activity

Calcium is an important factor in cell membrane transport, coagulation, hormone secretion, neuromuscular activation myocardial contraction, and many other physiological processes in the body. Severe loss of calcium in the urine is called hypercalciuria. The main identifiable cause of nephrolithiasis in children is metabolic causes, and hypercalciuria is considered the most common cause. This study describes the etiology, evaluation, presentation, and treatment of hypercalciuria and provides an up-to-date overview.

Study objectives

The objectives of this study include the following items:

- Study of calcium metabolism
- Definition of idiopathic hypercalciuria (IH)
- Prevalence, cause, and symptoms of hypercalciuria
- Diagnosis and evaluate patients with hypercalciuria
- Discuss the treatments for hypercalciuria

Introducing and review calcium metabolism

Elemental calcium (Ca) is a cation that is almost all bound in bones. In serum, about 50% of calcium is free ionized (Ca^{2+}), 40% is bound to protein, and 10% is complexed with bicarbonate, citrate, or phosphate [1, 2]. Calcium is obtained in the body through the intestines as well as the stores in the bones. Only the free and ionized part is responsible for the important biological effects of Ca. Extracellular calcium levels are normally maintained by a complex system of hormonal interactions.

Intestinal absorption, renal excretion and transport of Ca in bone and soft tissue are controlled by the coordinated action of different hormonal systems and keep the blood calcium level within a narrow physiological range [1-3]. These include 1,25-$(OH)_2$-vitamin D3, parathyroid hormone (PTH), and fibroblast growth factor-23 (FGF-23). FGF23 is a growth hormone factor produced in bone tissue that causes hypophosphatemia in association with PTH and vitamin D [1-3]. Serum-filtered calcium is reabsorbed by the proximal tubule (>60%), the thick ascending limb of Henle (25%), and the rest in the distal convoluted tubule and collecting ducts [1, 2]. Hypercalciuria means excessive excretion of calcium through urine, and it is caused by a genetic disorder in one of the ways of reabsorption of calcium in the kidney [1, 4]. The different methods used to diagnose hypercalciuria are not yet standardized and the prevalence of hypercalciuria varies in different countries [1-4]. The recommended normal range for the calcium/creatinine ratio varies by age, as infants and neonates typically have lower urinary creatinine excretion and higher urinary calcium levels [4-7]. Normal range urinary calcium excretion (UCaE) in adults is 100-300 mg/day or <4 mg/kg/24 hours with standard Ca intake. Hypercalciuria in children is defined as UCaE >4 mg/kg/24 h [4-6]:

Normal creatinine ratios (mg/dL:mg/dL) may be as high as 0.8 in infants aged <7 months, but a ratio >0.2 suggests hypercalciuria in older children. Hypercalciuria is the most common risk factor for nephrolithiasis and nephrocalcinosis in children [1, 7]. Most patients are classified as idiopathic hypercalciuria despite increasing knowledge of underlying causes [1, 7].

Definition of IH

Severe urinary calcium loss is hypercalciuria, but the definition of hypercalciuria is confusing [1, 6]. IH is defined as increased UCaE for no apparent reason, which can be an autosomal dominant disorder. IH is defined by the following items:

- Persistent hypercalciuria despite normal or restricted Ca intake;
- Absence of hypercalcemia or any other etiologies for hypercalciuria;
- Despite hypercalciuria, normal levels of PTH, P, serum levels of calcium and 1, 25-dihydroxyvitamin D [7].

IH is another name for fasting hypercalciuria because urinary calcium remains high despite fasting or a low-calcium diet [8].

Prevalence of hypercalciuria

The prevalence of IH depends on various factors, such as occupation, geographical areas, nutritional variables, climate, and genetic factors [4]. IH has been reported in 20% to 40% of children with kidney stones and 40% to 95% of children who form the first stone [7]. The prevalence of IH in the general population without kidney stones and children without first-degree relatives with stones is 2% to 10% [8, 9]. Hypercalciuria is more com-

mon in close relatives of affected patients. Up to 40% of the first and second-degree relatives of hypercalciuric recurrent stone formers will also have hypercalciuria [8-10].

Review of the etiology of hypercalciuria

A multifactorial cause is assumed with a complex interaction of environmental and genetic factors [1, 4]. The traditional view of hypercalciuria includes increased absorption or reabsorption of intestinal calcium, and renal calcium leakage, which is a genetic defect of the kidney. Resorptive is increased in renal reabsorption of Ca, such as in hyperparathyroidism and renal phosphate leakage [1, 7]. Hypercalciuria is usually associated with conditions that lead to the following items: Williams syndrome, inherited as an autosomal dominant disorder affecting 50% of first-degree relatives are affected; drug (loop diuretics, corticosteroid therapy); Cushing syndrome; tubular dysfunction (Bartter or Fanconi syndrome, distal renal tubular acidosis [RTA]); hypercalcemia (primary hyperparathyroidism, hyperthyroidism, Paget disease, myeloma, malignancy, immobility, accelerated osteoporosis, vitamin D intoxication, immobilization, sarcoidosis); dent disease [6, 7-11].

Hypercalciuria is the result of decreased tubular reabsorption of calcium, which is caused by increased excretion of more sodium in the urine, resulting in an increase in sodium in the blood. High salt intake is a contributing factor and rarely the only cause of significant hypercalciuria [7, 8]. Hypercalciuria is caused by a diet rich in animal protein due to the creation of a high acid load in the blood, followed by the inhibition of calcium reabsorption in the renal tubules and the release of calcium from the bones [7, 8].

Describing the symptoms of hypercalciuria

In the cases of calcium nephrolithiasis, nephrocalcinosis, hypercalcemia, hyperparathyroidism, urinary crystalluria, osteopenia, and osteoporosis, hypercalciuria is expected. However, there are no specific clinical findings in hypercalciuria [7, 8, 12]. Although the cause of hematuria and urinary symptoms of microscopic and local tissue damage is not known, it is caused by microcrystals and focal stones, which are difficult to detect and confirm [6, 10]. Hypercalciuria can cause fever, painful urination, recurrent abdominal or flank pain, dysuria, nocturnal enuresis, recurrent gross hematuria, impairment of renal function, chronic kidney disease, nephrocalcinosis, and reduction in bone mineral density and increased risk of osteoporosis [9, 13-18]. The most common cause of isolated hematuria in children is IH [6]. Some studies have reported the prevalence of IH to be 20% in children with recurrent urinary tract infections [9]. As an important recommendation, the presence of IH should be diagnosed in children with urinary tract infections with or without vesicoureteral reflux [9, 19]. A risk factor in 40%-95% of children with first-time kidney stones and 40%-50% of children with recurrent nephrolithiasis is IH. IH is present in 40-50% of children with recurrent kidney stones and 40-95% of children with nephrolithiasis [7, 10]. In patients with calcium stones, bone mineral density decreases and the risk of osteoporosis increases [7, 16].

Diagnosis and description of the evaluation of patients with hypercalciuria

The presence of hypercalciuria may be recorded in different ways, but there is still no standard diagnostic method for hypercalciuria [6]. Although it is difficult to measure UCa/Cr in 24-h urinalysis in children, it is necessary to diagnose hypercalciuria [1, 2]. Previous studies have been conducted on the correlation between UCa/Cr and 24-h Ca in healthy children [4, 6]. The replacement of 24-h UCaE with UCa/Cr is controversial. Reports have found inconclusive evidence, while others have found strong correlations [5-21]. A 24-h urinalysis is very sensitive and important in diagnosis because spot urine chemical analysis has shown poor sensitivity and specificity for the diagnosis of hypercalciuria [8, 20]. Spot urine samples underestimate the 24-h urinary calcium (–71 mg/24 h), and postprandial sampling overestimates it (+61 mg/24 h) [8]. Although the exact value is not known because this ratio varies with age and geographic location, the UCa/Cr cut-off value allows screening for hypercalciuria. The random ratio of UCa/Cr is useful for screening and diagnosis, as well as for documenting the benefits and effects of treatment [6].

Treatment in hypercalciuria

In children, treatment of hypercalciuria is primarily dietary, at least initially, such as avoiding excessive dietary Ca intake, avoiding vitamin D supplements, limiting animal protein diet, low salt (sodium) and increase fluid intake [5, 8, 11, 18, 22-26]. Because Ca is a vital requirement for growth and other body functions, restricting Ca in children's diets is not recommended [5]. However, no strong evidence supports a relationship between decreased calcium intake and decreased urinary Ca levels [5]. Low calcium intake is associated with an increased risk of stone formation, which is evident in many studies [7]. Hypercalciuria has been confirmed to be associated with decreased bone density in

J Ped Nephrol
Journal of Pediatric Nephrology

patients [5, 7, 8]. In one study, changing the diet from animal protein to plant protein reduced urinary Ca excretion by 50% [8]; if this was also ineffective, start other treatments. Thiazides can increase positive calcium balance and reduce UCaE by 40% [8, 27]. From the group of thiazides, hydrochlorothiazide, chlorthalidone and indapamide and are often used. Chlorthalidone and indapamide have longer half-lives, but hydrochlorothiazide has a short half-life and must be administered twice daily [8, 26]. Thiazides also tend to increase the incidence of melanoma, increase serum glucose and uric acid levels, and increase urinary excretion of potassium, magnesium, and citrate [16]. If thiazides fail, even after adjusting the dose and moderating sodium intake, then the patient could have start other treatments. It is often helpful to add potassium citrate to these patients during thiazide therapy [11, 16, 20]. Potassium citrate increases urinary citrate excretion prevents hypokalemia and increases renal calcium reabsorption, which can help inhibit the crystallization of Ca salts [8, 16, 26]. Urinary calcium excretion was reduced by approximately 30% in potassium citrate treatment [28]. If amiloride, a potassium-sparing diuretic, is added to thiazides, it increases calcium reabsorption. Due to the possibility of hyperkalemia, taking amiloride with potassium citrate is not recommended [11, 12]. It is not recommended to use triamterene in patients with kidney stones because it produces stones [29-31]. Orthophosphate increases serum phosphate levels, decreases vitamin D3 activation and gastrointestinal calcium absorption, thereby increasing renal calcium reabsorption. Orthophosphates can reduce urinary calcium excretion by up to 50% and may be given together with thiazides when necessary [8-32]. In IH, the role of cytokines in stimulating bone resorption has been established. Several nonsteroidal anti-inflammatory agents (e.g. indomethacin, diclofenac) have been investigated; however, more studies are needed [8, 33]. Omega-3 fatty acids can potentially reduce urinary Ca and oxalate excretion and increase urinary citrate, thus potentially reducing stone formation by altering prostaglandin metabolism [8, 34].

Conclusion

The diagnosis and management of hypercalciuria are difficult. According to the current findings, it is recommended to carry out more studies on early diagnosis and careful long-term management of this disorder. The random screening of UCa/Cr for hypercalciuria is not suitable, but it is suitable for diagnosing hypercalciuria in children. Evaluation of serum Ca, vitamin D3, PTH, and FGF-23 and urine Ca is necessary to investigate the causes. There are few published articles. Further large studies with multicenter design are recommended.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualisation, study design and revision of the manuscript and critical evaluation of the intellectual content: All authors; Review and editing: Mohsen Akhavan Sepahi.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to thank the Clinical Research of Development Unit, Hazrat-e Fatemeh Masoumeh Hospital, Qom University of Medical Science, Qom, Iran.

References

[1] Schlingmann KP, Konrad M. Inherited disorders of renal calcium handling. In: Emma F, Goldstein SL, Bagga A, Bates CM, Shroff R, editors. Pediatric nephrology. Cham: Springer; 2022. [DOI:10.1007/978-3-030-52719-8_110]

[2] Tinawi M. Disorders of calcium metabolism: Hypocalcemia and hypercalcemia. Cureus. 2021; 13(1):e12420. [DOI:10.7759/cureus.12420]

[3] Battafarano G, Chiellini G, Saponaro F. Editorial: Calcium metabolism: Hormonal crosstalk, pathophysiology and disease. Front Med (Lausanne). 2022; 9:899416. [DOI:10.3389/fmed.2022.899416] [PMID]

[4] Gül A, Özer S, Yılmaz R, Sönmezgöz E, Kasap T, Takçı Ş, et al. Prevalence of hypercalciuria and urinary calcium excretion in school-aged children in the province of Tokat. Turk Pediatri Ars. 2016; 51(4):193-7. [DOI:10.5152/TurkPediatriArs.2016.4162] [PMID]

[5] English KA, Lines KE, Thakker RV. Genetics of hereditary forms of primary hyperparathyroidism. Hormones (Athens). 2024; 23(1):3-14. [DOI: 10.1007/s42000-023-00508-9] [PMID]

[6] Akhavansepahi M, Tabarai Y. Screening of hypercalciuria among children with persistent asymptomatic hematuria. J Biostat Epidemiol. 2018; 3(3-4):106-10. [Link]

[7] Edvardsson VO, Sas DJ. Urinary stone disease and nephrocalcinosis. In: Emma F, Goldstein SL, Bagga A, Bates CM, Shroff R, editors. Pediatric nephrology. Cham: Springer; 2022. [DOI:10.1007/978-3-030-52719-8_53]

[8] Ryan LE, Ing SW. Idiopathic hypercalciuria: Can we prevent stones and protect bones? Cleve Clin J Med. 2018; 85(1):47-54. [DOI:10.3949/ccjm.85a.16090] [PMID]

[9] Esteghamati M, Ghasemi K, Nami M. Prevalence of idiopathic hypercalciuria in children with urinary system related symptoms attending a pediatric hospital in Bandar Abbas in 2014. Electron Physician. 2017; 9(9):5261-4. [DOI:10.19082/5261] [PMID]

[10] Spivacow FR, Del Valle EE, Rey PG. Metabolic risk factors in children with asymptomatic hematuria. Pediatr Nephrol. 2016; 31(7):1101-6. [DOI:10.1007/s00467-015-3282-4] [PMID]

[11] Elder J S. Urinary Lithiasis. In: Kleigman R.M, Blum NG, Geme ST, editors. Nelson Textbook of Pediatrics, 2-Volume Set. Philadelphia: Elsevier; 2020. [Link]

[12] García Nieto VM, Yanes MIL, Carreno PT, Suarez GP, Mesa TM. [The idiopathic hypercalciuria reviewed. Metabolic abnormality or disease (Spanish)]. Nefrologia. 2019; 39:592–602. [DOI: 10.1016/j.nefro.2019.02.011]

[13] Mortazavi F, Sheykhloo M .Role of hypercalciuria in recurrent urinary tract infection in children. J Ped Nephrology. 2014; 2(4):147-50. [DOI:10.22037/jpn.v2i4.7141]

[14] Akhavan-Sepahi M, Sharifian M, Mohkam M, Vafadar M, Hejazi S. Biochemical risk factors for stone formation in healthy school children. Acta Medica Iranica. 2012; 50(12):814-8. [Link]

[15] Pavlou M, Giapros V, Challa A, Chaliasos N, Siomou E. Does idiopathic hypercalciuria affect bone metabolism during childhood? A prospective case-control study. Pediatr Nephrol. 2018; 33(12):2321-8. [DOI:10.1007/s00467-018-4027-y] [PMID]

[16] Penido MGMG, Tavares MS. Should pediatric idiopathic hypercalciuria be treated with hypocalciuric agents? World J Nephrol. 2021; 10(4):47-58. [DOI:10.5527/wjn.v10.i4.47] [PMID]

[17] Letavernier E, Daudon M. Vitamin D, Hypercalciuria and kidney stones. Nutrients. 2018; 10(3):366. [DOI:10.3390/nu10030366] [PMID]

[18] Gurevich E, Levi S, Borovitz Y, Alfandary H, Ganon L, Dinour D, et al. Childhood hypercalciuric hypercalcemia with elevated vitamin D and suppressed parathyroid hormone: Long-term follow up. Front Pediatr. 2021; 9:752312. [DOI:10.3389/fped.2021.752312] [PMID]

[19] Balestracci A, Battaglia LM, Toledo I, Martin SM, Wainsztein RE. Idiopathic hypercalciuria in children with urinary tract infection. Arch Argent Pediatr. 2014; 112(5):428-33. [DOI:10.5546/aap.2014.eng.396]

[20] Figueres L, Hourmant M, Lemoine S. Understanding and managing hypercalciuria in adults with nephrolithiasis: Keys for nephrologists. Nephrol Dial Transplant. 2020; 35(4):573-5. [DOI:10.1093/ndt/gfz099] [PMID]

[21] Peris Vidal A, Ferrando Monleón S, Marín Serra J, Quiñones-Torrelo C, Hervás Andrés A, Fons Moreno J, et al. Urinary excretion of calcium, phosphate, magnesium, and uric acid in healthy infants and young children. Influence of feeding practices in early infancy. Pediatr Nephrol. 2024; 39(3):761-70. [DOI:10.1007/s00467-023-06145-z] [PMID]

[22] Nouvenne A, Meschi T, Guerra A, Allegri F, Prati B, Borghi L. Dietary treatment of nephrolithiasis. Clin Cases Miner Bone Metab. 2008; 5(2):135-41. [PMID]

[23] Ince BA, Anderson EJ, Neer RM. Lowering dietary protein to U.S. recommended dietary allowance levels reduces urinary calcium excretion and bone resorption in young women. J Clin Endocrinol Metab. 2004; 89(8):3801-7. [DOI:10.1210/jc.2003-032016] [PMID]

[24] Gutbrod J, Keys McKay CC, Coe L, Bergsland K, Coe F, Worcester E, et al. Clinical effectiveness of calcium oxalate stone treatments. Am J Nephrol. 2022; 53(10):761-6. [DOI:10.1159/000527940] [PMID]

[25] Olefir YV, Yavorskii AN, Butnaru DV, Shatalova OV, Gorbatenko VS, Gerasimenko AS. [Idiopathic hypercalciuria. Diagnosis and treatment (Russian)]. Urologiia. 2017; (6):112-9. [PMID]

[26] Coe FL, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. Nat Rev Nephrol. 2016; 12(9):519-33. [DOI:10.1038/nrneph.2016.101] [PMID]

[27] Cheng L, Zhang K, Zhang Z. Effectiveness of thiazides on serum and urinary calcium levels and bone mineral density in patients with osteoporosis: A systematic review and meta-analysis. Drug Des Devel Ther. 2018; 12:3929-35. [DOI:10.2147/DDDT.S179568] [PMID]

[28] Song Y, Hernandez N, Shoag J, Goldfarb DS, Eisner BH. Potassium citrate decreases urine calcium excretion in patients with hypocitraturic calcium oxalate nephrolithiasis. Urolithiasis. 2016; 44(2):145-8. [DOI:10.1007/s00240-015-0819-8] [PMID]

[29] Harmacek D, Blanchard A, Wuerzner G, Maillard M, Jeunemaitre X, Azizi M, et al. Acute decrease of urine calcium by amiloride in healthy volunteers under high-sodium diet. Nephrol Dial Transplant. 2022; 37(2):298-303. [DOI:10.1093/ndt/gfab159] [PMID]

[30] Johny KV, Lawrence JR, O'Halloran MW. Amiloride hydrochloride, a hypercalciuric diuretic. Australas Ann Med. 1969; 18(3):267-70. [DOI:10.1111/imj.1969.18.3.267] [PMID]

[31] Leslie SW, Sajjad H. Hypercalciuria. 2024. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. [PMID]

[32] Van Den Berg CJ, Kumar R, Wilson DM, Heath H 3rd, Smith LH. Orthophosphate therapy decreases urinary calcium excretion and serum 1,25-dihydroxyvitamin D concentrations in idiopathic hypercalciuria. J Clin Endocrinol Metab. 1980; 51(5):998-1001. [DOI:10.1210/jcem-51-5-998] [PMID]

[33] Filipponi P, Mannarelli C, Pacifici R, Grossi E, Moretti I, Tini S, et al. Evidence for a prostaglandin-mediated bone resorptive mechanism in subjects with fasting hypercalciuria. Calcif Tissue Int. 1988; 43(2):61-6. [DOI:10.1007/BF02555148] [PMID]

J Ped Nephrol
Journal of Pediatric Nephrology

[34] Rodgers AL, Siener R.The efficacy of polyunsaturated fatty acids as protectors against calcium oxalate renal stone formation: A review. Nutrients. 2020; 12(4):1069. [DOI:10.3390/nu12041069] [PMID]