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Kidney Stones in Transfusion-Dependent Thalassemia: Prevalence and Risk Factors

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Abstract

Purpose: As patients with transfusion-dependent thalassemia (TDT) are living longer, novel morbidities are being recognized. The purpose of this review is to summarize the current knowledge regarding the prevalence and risk factors of nephrolithiasis in patients with TDT. *Methods*: A non-systematic, narrative review of the current literature published up to August 2021 was conducted. *Results*: Nephrolithiasis has been reported in 18% - 59% of patients with TDT, which is at least twice the prevalence in the general US population. The risk factors for nephrolithiasis can be classified into behavioral (dietary and lifestyle), environmental, metabolic, disease-specific, and genetic factors. While clarifying the true prevalence of nephrolithiasis in different age groups and diagnostic categories of TDT requires further research, prevention, and management of nephrolithiasis is a growing clinical concern. Physicians should be aware of the potential increased risk of stone disease in splenectomized and diabetic patients as well as those treated with certain chelation regimens. *Conclusions*: The etiology of nephrolithiasis and potential TDT-specific risk factors that may put patients at greater risk are highlighted. There is insufficient evidence at this time to recommend universal screening for nephrolithiasis using ultrasound. Evidence-based recommendations on monitoring, prevention, and management of nephrolithiasis in TDT are provided.

Keywords

Thalassemia, Nephrolithiasis, Kidney Stone, Etiology, Risk Factors

1. Background

Nephrolithiasis (kidney stone disease) is a disorder of mineral metabolism characterized by episodes of acute renal colic that often recurs accompanied by pain, nausea, and vomiting [1]. For those who suffer a stone, quality of life is reduced during the time surrounding the occurrence. At least 50% of all patients will experience recurrence of stone formation in their lifetime. Kidney stones are also associated with end-stage renal disease [2], decreased bone density, and increased fracture risk [3] [4] [5]. The prevalence of kidney stones in thalassemia patients has been estimated to be double that of the general population [1] [3] [6], but the true prevalence is unknown since large, population-based studies have yet to be conducted. As the life expectancy of patients with thalassemia increases, age-related conditions such as nephrolithiasis are becoming more common [7] [8]. A better understanding of the risk factors that predispose to nephrolithiasis in thalassemia will help develop primary and secondary prevention strategies.

1.1. Beta Thalassemia

Beta thalassemias are a group of inherited hematological disorders characterized by reduced synthesis of beta globin chains of the hemoglobin molecule. Beta thalassemia major is characterized by severely decreased production of beta-globin chains resulting in increased hemolysis, ineffective erythropoiesis, and severe anemia. These patients require chronic blood transfusions starting in infancy for survival. Beta thalassemia intermedia is characterized by a milder reduction in beta-globin production resulting in a less severe phenotype. Patients may need transfusion support later in life to suppress complications of ineffective erythropoiesis and worsening anemia. A key feature of transfusion-dependent thalassemia (TDT) is the development of iron overload from repeated red cell transfusions, which is a significant cause of morbidity and mortality secondary to liver cirrhosis, cardiac failure, and endocrinopathies such as hypogonadism, diabetes, osteoporosis, and hypothyroidism. Survival of patients with TDT has significantly increased in the last several decades due to advances in monitoring and treatment of iron load [9]. As patients are living into their sixties and beyond, chronic conditions such as nephrolithiasis, are emerging as a new challenge to their health and the quality of life [7] [8]. In the past decade, reviews have focused on risk factors related to renal dysfunction and proposed biomarkers for renal disease [10] [11] [12] [13] [14], yet there remains a paucity of evidence-based information for clinicians in monitoring nephrolithiasis, an increasing problem for patients with TDT.

1.2. Epidemiology of Nephrolithiasis

Currently, the prevalence of kidney stones in the general population is 9%, which represents a 70% increase since the 1990s [15]. Historically, kidney stones were most common among middle-aged white men, but the incidence of stones

has increased substantially among women, children, and African-Americans [16]. Though the cause of these shifts is unclear, hypotheses include increased use of diagnostic imaging, and increasing incidence of dietary, metabolic, and environmental impacts including global warming [17] (**Table 1**). There is also a growing awareness that nephrolithiasis can be associated with other chronic diseases, as exemplified by thalassemia, where prevalence estimates are as high as 18% to 59% [3] [18].

1.3. Types of Kidney Stones

Kidney stones are a consequence of pathophysiological biomineralization at the interface of the renal papilla or collecting duct with the urine, or seeded within the urine itself. Stone formation may be triggered by changes in saturation, solubility, hydrodynamics, or the balance between stone promoting and inhibiting constituents [19]. Most stones are calcium-based, and for this review, we will focus on risk factors for the most common, calcium oxalate stones. There is at least one report that patients with thalassemia may have a different profile of stone components, that is, both struvite and calcium oxalate type stones are equally observed [18], but this has not been well studied.

Table 1. Risk factors for nephrolithiasis in the general population.

Factor Category	Risk Factor
Dietary and Lifestyle Factors	High animal protein intake High fructose intake High sodium chloride intake Low fluid intake Low dietary calcium intake High dose vitamin C supplementation (>1000 mg/day) Low physical activity High dietary oxalate
Environmental Factors	Living in warm climates with daily temperatures > 30˚C Occupations with a high ambient temperature
Biochemical Factors	Hypercalciuria Hyperuricosuria Hyperoxaluria Hypocitraturia
Disease Associated Factors	Diabetes Obesity Metabolic syndrome Osteopenia/osteoporosis Neurogenic bladder Sarcoidosis Primary hyperparathyroidism Intestinal malabsorption

Adapted from information found in: Scales CD *et al.* 2016 [1].

2. Risk Factors for Nephrolithiasis in Patients with Thalassemia

In the general population, approximately 50% of the risk of nephrolithiasis is heritable [20]. The remainder of the risk is determined by modifiable (behavioral, environmental) and non-modifiable (metabolic, disease-associated) exposures. Few reports are available on the risk factors for kidney stones in thalassemia. Here we discuss the relevance of established risk factors in the general population to patients with thalassemia, highlighting the disease-specific features and metabolic abnormalities (Table 2).

2.1. Disease-Associated Factors

Several pathological conditions have been associated with an increased risk of developing kidney stones, including diabetes, hypertension, hyperlipidemia, and chronic kidney disease [21] [22]. Nephrolithiasis, therefore, may be just one manifestation of a more complex syndrome. In thalassemia, disease-specific factors are some of the most unique aspects of additional risk factors for nephrolithiasis, including splenectomy, increased erythropoiesis, iron overload and chelation therapy.

1) *Splenectomy and Excess Erythroblasts*. Splenectomy has been identified as a major risk factor for stone formation in thalassemia [6]. In one study, 91% of patients with kidney stones were splenectomized [6]. Higher circulating erythroblasts due to decreased clearance post-splenectomy may lead to increased urinary uric acid. Hyperuricemia and hyperuricosuria in patients with thalassemia may also be due to the increased cell turnover and higher number of erythroblasts as a result of the increased ineffective erythropoiesis [23]. Up to 40% of

Table 2. Proposed risk factors for nephrolithiasis in patients with thalassemia.

Factor Category	Risk Factors
Dietary and Lifestyle Factors	Low dietary calcium intake Calcium supplementation High dose vitamin C supplementation High fat mass per body mass index Low physical activity
Environmental Factors	Living in warm climates with daily temperatures > 30˚C.
Biochemical Factors	Hypercalciuria Hyperuricosuria Hyperoxaluria Hypocitraturia
Disease Associated Factors	Splenectomy Ineffective erythropoiesis Iron overload Iron chelation Diabetes Hypoparathyroidism

TDT patients have increased uric acid excretion. Patients with thalassemia intermedia have a high prevalence of hyperuricemia needing treatment as well as nephrolithiasis [6]. Further research is needed to evaluate the role of hyperuricemia and hyperuricosuria in the pathogenesis of nephrolithiasis in thalassemia.

2) *Iron Overload and Chelation Therapy*. Control of systemic iron burden is the most important determinant of morbidity and overall survival in thalassemia. However, Wong and colleagues found serum ferritin to be significantly lower in thalassemia patients with nephrolithiasis, suggesting a complex relationship with chelation therapy [3]. Urinary iron is elevated in thalassemia compared to the general population, although it is mostly present as iron-chelator complexes and varies widely, based on the type of chelator [24]. In the general population, the iron content in calcium-based kidney stones is highly variable (0.005 - 5.6 mg/g) [25], but comparable studies have not been published for iron-overload conditions such as thalassemia. Like calcium, iron excreted in the urine can bind to oxalate and phosphate anions, which might interfere with calcium mineralization and slow the rate of stone formation. However, iron binding to citrate and other important endogenous inhibitors of calcium oxalate nucleation, aggregation, and crystal growth can indirectly promote stone formation [26]. Interestingly, lower urinary iron excretion was correlated with poor shockwave lithotripsy success rates for calcium oxalate stones [27]. The balance of these chemical interactions of iron on lithogenic potential has not been defined for patients with or without iron overload.

Currently, the three options for iron chelation are deferoxamine, deferasirox and deferiprone. Each chelator has its own profile of efficacy, toxicity and acceptability, and some patients are prescribed a combination of two drugs to overcome these limitations. Of the three chelators, deferasirox has the greatest effect on renal function, causing a reversible mild elevation of creatinine and proximal tubular dysfunction; patients most affected appear to be those with low total body iron burden [10] [28] [29]. A few studies have suggested that deferasirox might increase the incidence of nephrolithiasis [8] [30]. However, baseline abnormalities in renal function are present in thalassemia irrespective of the chelation regimen [14]. Mean urinary calcium excretion is 3-fold higher compared with non-thalassemia controls in younger patients (4 - 23 years), with hypercalciuria observed in 36% [31]. Urine calcium excretion is significantly associated with proteinuria, but not with ferritin, serum creatinine, Cystatin C, beta2-microglobulin or creatinine clearance. Urine calcium excretion is greater with deferasirox compared with deferoxamine and is correlated with the dose of deferasirox. The effect of deferasirox on the incidence of nephrolithiasis was suggested by one retrospective study [30], but not by another [32]. Thus, baseline hypercalciuria is present in many patients with TDT from an early age, which may be exacerbated by deferasirox. The mechanism by which deferasirox increases tubular damage may be related to mitochondrial swelling from the excessive removal of iron from cells [28]. Prospective studies to evaluate the risk of nephrolithiasis using different chelators are lacking.

3) *Zinc*. Both insufficient and excess dietary zinc have been associated with a higher risk of nephrolithiasis in the general population [33] [34]. Urinary zinc loss is nearly 4 times higher in patients with thalassemia compared with controls [35], which is further increased in the presence of diabetes [36] and the use of iron chelators [37]. Zinc deficiency is observed in 18% of patients using deferiprone for chelation [37], and up to 30% of non-diabetic TDT patients [38]. However, the impact of zinc deficiency on the risk of nephrolithiasis in thalassemia has not been evaluated.

4) *Diabetes*. In the general population, diabetes is an independent risk factor for the development of kidney stones, increasing the risk by 29% - 60% [39]. The mechanism may be related to the effect of insulin resistance on ammoniagenesis and the resultant changes in urine composition, a lower urine pH, and hypercalciuria. Diabetes is a common complication of pancreatic iron overload in TDT occurring in approximately 20% [40] of adult patients, and thus could contribute to the risk of nephrolithiasis in this population.

2.2. Dietary and Lifestyle Factors

In the general population, vegetarians have reduced stone incidence due in part to low animal protein intake and higher intakes of citrate and phytate, which act as inhibitors of stone formation in the urine by competing for the binding of calcium and other minerals [19]. Elevated consumption of animal protein increases stone risk, presumably by increasing calciuria and uricosuria, reducing citrate excretion, and increasing oxaluria [41]. Elevated consumption of fructose increases urinary excretion of calcium, oxalate, and uric acid, and has therefore been associated with an increased risk of incident kidney stones among adults [42]. High dietary sodium chloride intake also increases stone risk by increasing calciuria and reducing urinary citrate excretion [43]. Diets containing average amounts of calcium, moderate protein, and low sodium content reduce the risk of kidney stone recurrence [44]. Although dietary risk factors have not been specifically studied in thalassemia, diets tend to contain less meat (purine-rich foods), sodium (processed food), and foods with high iron and zinc content (meats and seafood) due to nutrition and disease management recommendations [45].

Fluid intake has an inverse relationship with stone formation in the general population likely by increasing the dilution of minerals and other components in the urine [46]. Tea beverage consumption is encouraged in thalassemia since the bioactive components in tea including epicatechins decrease absorption of dietary non-heme iron [45] [47]. While tea consumption was associated with 10% fewer stones in the general population, in part due to higher urine output, its association with stone risk has not been specifically studied in thalassemia [43].

1) *Calcium*. In the general population, increasing dietary calcium progressively from one to five servings daily has been associated with a decreased risk of incident nephrolithiasis [43]. This seemingly paradoxical effect has been attributed

to dietary calcium-binding oxalate in the gut, which reduces intestinal oxalate absorption and urinary excretion. There is, however, a difference between dietary and supplemental calcium, with supplemental calcium increasing the risk of stone formation [48]. Many thalassemia patients avoid dairy foods, the optimal dietary source of calcium, due to either self-reported lactose intolerance, personal choice, or cultural beliefs [45]. The prevalence of hypolactasia can reach nearly 100% in East-Asian populations [49]. Given the majority of patients with thalassemia in North America are Asian, dairy avoidance leading to low dietary calcium intake is a concern. Calcium supplementation is used to fill the gap between inadequate dietary intake and the requirement for osteoporosis prevention. In one small case-control study evaluating renal calculi in patients with thalassemia on iron chelation with deferasirox or deferoxamine, vitamin D and calcium supplementation did not appear to increase the risk for stone formation [32].

2) *Vitamin D*. Vitamin D deficiency is common in patients with thalassemia due to limited sun exposure and avoidance of dairy foods that are usually fortified with vitamin D. High-dose, infrequent supplementation of vitamin D (50,000 IU every 3 weeks) has become an effective tool to improve vitamin D status. It is uncertain if daily or intermittent supplementation with vitamin D increases the risk of kidney stones. In a 2016 meta-analysis, vitamin D supplementation was not associated with a higher risk of nephrolithiasis [50]. However, an increased incidence of hypercalciuria in thalassemia patients with serum 25OH vitamin D concentration > 30 ng/mL has been observed [14], but the impact on stone formation or recurrence was not studied. Since patients have baseline hypercalciuria, it is possible that vitamin D deficiency normalized the urinary calcium levels, which is reversed by supplementation. Clearly, further evaluation of the role of vitamin D supplementation in the development of nephrolithiasis in thalassemia is warranted.

3) *Vitamin C*. The use of high-dose vitamin C (≥1000 mg/d) has been associated with nephrolithiasis in healthy men, likely resulting from the metabolism of excess vitamin C to oxalate [51]. Therefore, patients at risk for renal stones are warned against taking high-dose vitamin C. In thalassemia, iron overload and the concomitant increase in non-transferrin bound iron leads to an exhaustion of circulating antioxidants, most notably vitamin C [52]. The majority of patients with TDT have low serum ascorbate levels, which further decrease with increasing iron overload [52]. At very high liver iron concentrations (>25 mg Fe/g liver tissue), nearly 100% of patients have serum ascorbate levels characteristic of vitamin C deficiency. Moderate doses of vitamin C are recommended to improve the efficacy of iron chelation. However, given the relationship between high-dose ascorbate supplementation and oxalate metabolism, it is prudent to avoid large doses of vitamin C [51].

4) *Obesity.* Obesity is an important risk factor for nephrolithiasis among adults in the general population. The association of obesity with incidence and prevalence of nephrolithiasis is stronger in women than in men, possibly because women have greater adiposity than men at a given body mass index [53].

While patients with thalassemia typically have a body mass index (BMI) within the normal range, their fat content may be unusually high for body weight [54] [55]. This is due to a combination of lower lean mass for height and low bone mass. Since body fat is a predictor of stone formation, the disproportionate body fat in thalassemia may be a risk factor for kidney stones. Patients with a history of nephrolithiasis have been observed to have a higher BMI than those without kidney stones [3] [18].

5) *Physical activity.* Physical activity protects against stone formation in the general population, especially among postmenopausal women [56]. Typically, levels of daily physical activity are lower in thalassemia and patients are more sedentary due to, fatigue, pain and other factors [41]. While feasible, the association of obesity, metabolic syndrome, or limited physical activity with nephrolithiasis in thalassemia has not been evaluated.

2.3. Environmental Risk Factors

Chronic exposure to the extremes in temperature due to season, climate and occupational conditions increases stone risk. The risk of kidney stone formation increases up to 68% within 2 days of high (>28˚C) daily temperatures [57]. Occupations that promote exposure to high temperatures are associated with higher stone risk [58]. The increase due to high ambient temperatures is probably mediated by low urine volume and increased concentration of lithogenic minerals (e.g. calcium, oxalate), leading to stone growth in susceptible patients. An inverse dose-response relationship between fluid intake and risk of stones has been observed with the greatest reduction (RR 0.52) occurring with daily intake > 2.5 L [43]. A urine output volume of 2.5 L is thus recommended for decreasing kidney stone recurrence [59]. The majority of patients with thalassemia reside in climates where the average annual temperature is above 26˚C, although the environmental risk factors for kidney stones have not been specifically evaluated in thalassemia.

2.4. Metabolic Risk Factors

Metabolic risk factors for stone formation are hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria, low urine volume, and alkaline urine pH. Hypercalciuria is most commonly due to increased intestinal calcium absorption, increased bone resorption, or increased postprandial renal fractional excretion of calcium. It is exacerbated by high salt and protein diets. Hypocitraturia is usually related to metabolic acidosis, as in chronic kidney disease, chronic diarrheal states, or a high protein diet. Hyperuricosuria, typically due to dietary purine excess or genetic predisposition, is a risk factor for calcium oxalate stones [60]. Hyperoxaluria may be due to a genetic mutation (primary hyperoxalurias), intestinal fat malabsorption, high dose vitamin C supplements, high dietary oxalate, or low dietary calcium.

1) *Hypercalciuria.* Although symptomatic kidney stones have only been re-

ported in 18% of thalassemia patients [3], the prevalence of hypercalciuria is much higher. In a study of 216 thalassemia patients (51% female, average age 23 yrs), nearly 30% had hypercalciuria as defined by 24-hour urinary calcium to creatinine ratio (UCa: UCr) ≥ 0.21 mg/mg [14]. Hypercalciuria was more common (32.2%) in the 180 subjects who were regularly transfused, compared to those not regularly transfused (11.1%). Most patients were on deferoxamine (89%) for iron chelation, while a small number were receiving deferasirox (10%), or deferiprone (1%). A 25-OH vitamin D level > 30 ng/ml was associated with a higher prevalence of hypercalciuria compared levels < 11 ng/ml (OR 4.1, CI 1.3 - 13.1) [14]. The possible association of iron chelators with stone risk is important to explore. In a prospective study of 30 young thalassemia patients, 24-hour urine collections were checked at baseline and 6 months after starting deferasirox (20 mg/kg/d) [61]. Only 2 patients had hypercalciuria (urine calcium > 4 mg/kg/d) at baseline, while 8 had hypercalciuria after deferasirox ($p = 0.037$). In a more recent study of 152 subjects with transfusion-dependent hemoglobinopathies (86% thalassemia, 58% female, and average age of 34 yrs), hypercalciuria was reported in 92% of the patients on deferasirox and 83% of the patients on deferoxamine [62]. In this study, hypercalciuria was defined as UCa:UCr ≥ 0.4 mol/mol (equivalent to UCa:UCr of 0.14 mg/mg), a lower threshold that may help explain the higher prevalence. Severe hypercalciuria (UCa:UCr > 1.5 mol/mol), however, was restricted to those receiving deferasirox. These two studies raise the possibility of the association of deferasirox with urinary calcium excretion. The true prevalence of hypercalciuria in thalassemia remains unknown since 24-hour urine collections are rarely performed. In addition, the definition of hypercalciuria in published studies is variable, which makes comparisons difficult. In thalassemia, the etiology of hypercalciuria is likely to be multifactorial, including renal dysfunction, hypoparathyroidism, iron chelation, diabetes, and high bone turnover. However, it is plausible that hypercalciuria is more common in patients on regular transfusions and exacerbated by deferasirox [62].

a) *Renal Dysfunction*. Patients with thalassemia are at risk for renal and tubular dysfunction due to anemia, hypoxia, iron overload, and the use of iron chelators [10] [14] [63]. Deferasirox has the most effect due to its role in producing a reversible increase in serum creatinine and proximal tubular dysfunction manifesting as renal tubular acidosis or Fanconi syndrome [61]. The pathogenesis of renal damage with deferasirox is not fully understood, but there is a direct toxic effect on the proximal renal tubule, which is responsible for most calcium reabsorption. Phosphate wasting in Fanconi syndrome causes hypercalciuria by stimulating 1,25-OH vitamin D production and promotes nephrolithiasis and nephrocalcinosis [64]. Whether hypercalciuria due to deferasirox is primarily associated with phosphate depletion has not been investigated.

b) *Hypoparathyroidism.* Iron overload in thalassemia is associated with several endocrinopathies, including hypoparathyroidism. In a study of 243 patients, subclinical hypoparathyroidism was present in 13.5% [65], although the preva-

lence of overt hypoparathyroidism is much lower at 1.4% [66]. Low parathyroid hormone (PTH) reduces renal calcium re-absorption. Patients with hypoparathyroidism and hypocalcemia often require calcium supplementation and calcitriol, and since calcium reabsorption is decreased, they can develop hypercalciuria with an increased risk of kidney stones. In these patients, hypercalciuria can be alleviated by targeting lower serum calcium in the range of 8.0 - 8.5 mg/dL.

c) *High Bone Turnover.* A link between hypercalciuria, kidney stones, osteoporosis and increased risk of fractures has been observed in several studies [3] [4] [5]. Patients had idiopathic hypercalciuria, which is accompanied by either elevated or suppressed PTH, is associated with increased bone turnover. Thiazide diuretics enhance renal tubular calcium re-absorption, and decrease urine calcium, PTH and bone turnover, which is associated with improved bone mineral density [67] [68].

Low bone mineral density with an increased risk of fracture is one of the most prevalent comorbidities in thalassemia. Approximately 50% of patients have low bone mineral density and 30% have had fractures [66]. The etiology for low bone mineral density in thalassemia is multifactorial, due to chronic anemia and bone marrow expansion, vitamin D deficiency, iron overload, iron chelators, hypogonadism and other endocrinopathies, nutritional deficiencies, decreased physical activity, and high bone turnover.

Bisphosphonates are anti-resorptive agents that are routinely employed to treat osteoporosis. In patients without thalassemia, alendronate reduces bone turnover and hypercalciuria [69]. The use of bisphosphonates in thalassemia leads to improvement in bone mineral density and a decrease in bone turnover markers [70]. However, these studies were not powered to determine fractures risk reduction, and the change in urinary calcium excretion was not reported [70]. The mechanism of hypercalciuria and low bone mineral density in thalassemia is multifactorial, but thiazide diuretics and bisphosphonates may have therapeutic potential by correction of hypercalciuria.

2.5. Genetic Causes

In twin studies, approximately 50% of the risk of nephrolithiasis among males was shown to be heritable [20]. While some genetic causes of kidney stones manifest from single-gene mutations (e.g. primary hyperoxaluria, cystinuria, and type 1 renal tubular acidosis), the large majority of heritable stone disease is polygenic [71]. The contribution of single gene polymorphisms to idiopathic calcium stone disease, including polymorphisms of the calcium receptor, vitamin D receptor, and osteopontin has been actively investigated [72] [73]. The role of these polymorphisms in stone formation in thalassemia patients is unknown.

3. Recommendations

Based on our evaluation of the specific risk factors for nephrolithiasis, we provide general recommendations on monitoring, prevention and management in patients with thalassemia (**Table 3**). In this evolving area, there is insufficient

Table 3. Proposed monitoring, prevention and management of nephrolithiasis in patients with thalassemia.

Monitoring for Risk Factors	
Variable to Measure	*Frequency*
Serum Ca, phosphorus, 25OHD, PTH, zinc, vitamin C, uric acid	Annual Monitoring
24-hour urine: Ca and creatinine	Annual Monitoring
DXA Assessment	Annual Monitoring starting at 10 years

Prevention of Nephrolithiasis	
Factor Category	*Guidance*
Hydration	Encourage adequate hydration. If prior history of nephrolithiasis, encourage fluid intake > 2.5 L/day
Sodium intake	Encourage less than 2300 mg sodium/day
Fruit and vegetable intake	Encourage 5 to 7 servings a day
Body weight	Encourage BMI between: 18.5 - 22.9 kg/m^2 (Asian) or: 18.5 - 24.9 kg/m^2 (all other races)
Non-contact weight bearing physical activity	Encourage minimum of 150 min/week of moderate intensity activity (adults); 60 min/day (children and adolescents)
Calcium intake	1000 mg/day (adults < 50 years) with focus on dietary sources. Limit supplemental calcium to 500 mg Ca (elemental) per day
25OH Vitamin D	Maintain between: 30 - 50 ng/mL (75 - 125 nmol/L)
Manage Diabetes	Maintain serum fructosamine < 270 umol/L
Transfusion therapy	Optimize therapy to reduce ineffective erythropoiesis
Vitamin C supplements	Avoid supplements > 1000 mg/day
Hypogonadism	Focus on prevention and management of hypogonadism
Chelator therapy	Monitor adverse effects of chelators on zinc, phosphate and calcium excretion

Management of Nephrolithiasis	
Factor Category	*Guidance*
Comprehensive care	Encourage clinical care management from team of specialists: urologist, nephrologist, endocrinologist, and dietitian
Treat hypercalciuria	Low salt diet, protein restriction (adults only) and consider a thiazide diuretic. In adults with hypercalciuria and osteoporosis, bisphosphonate therapy may be considered
Treat hyperuricosuria	Dietary purine restriction, increased fluid intake and urine alkalinization, improve transfusion regimen if evidence of increased ineffective erythropoiesis, and consider allopurinol
Treat hypocitraturia	potassium citrate

Continued

Hydration	Maintain urine output greater than 2 - 2.5 L/day
Chelation therapy	Reducing chelation dose or switching chelation therapy is unclear. May not be possible for many patients to change chelation due to concerns over iron overload and tolerance

Ca: calcium; PTH: parathyroid hormone; 25OHD: 25 hydroxy vitamin D; BMI: body mass index.

evidence in the thalassemia population for many of the recommendations. Hence, it is appropriate to adapt guidelines for the general population to known or proposed mechanisms of kidney stone formation in thalassemia.

4. Conclusions

The prevalence of nephrolithiasis is increased in adults with thalassemia as a result of multiple risk factors related to the underlying disease process, the co-morbidities of thalassemia as well as environmental, nutritional and biochemical risk factors. The elements of primary prevention of nephrolithiasis should be incorporated into routine health maintenance for thalassemia. The pathogenesis of hypercalciuria, which is frequent in thalassemia and may be associated with chelation, requires further elucidation. Until such time, it is reasonable to focus on the prevention of osteopenia, encouraging patients to meet daily calcium requirements through dietary sources, avoiding mega-dose nutritional supplements, staying physically active, and managing their weight.

Despite the increased risk of nephrolithiasis in the thalassemia population, there is insufficient evidence at this time to recommend universal screening of adults with thalassemia for nephrolithiasis using ultrasound. However, physicians should be aware of the potential increased risk of stone disease and consider 24 hr urine analysis for calcium, sodium, creatinine, pH, oxalate and citrate. Patients with symptomatic or asymptomatic nephrolithiasis should be placed under the care of an experienced medical team as several risk factors may not be modifiable.

Various questions about the prevalence, pathogenesis and management of nephrolithiasis in thalassemia remain unanswered. Prospective studies are necessary for this population, especially since patients are now living well into old age. An improved understanding of the risk factors for nephrolithiasis will help in primary and secondary prevention, which are important to maintain the quality of life of the aging patient with thalassemia.

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Declaration

This manuscript has not been published previously, is not in consideration of publication elsewhere.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Scales, C.D., Tasian, G.E., Schwaderer, A.L., Goldfarb, D.S., Star, R.A. and Kirkali, Z. (2016) Urinary Stone Disease: Advancing Knowledge, Patient Care, and Population Health. *Clinical Journal of the American Society of Nephrology*: *CJASN*, **11**, 1305-1312. https://doi.org/10.2215/CJN.13251215

[2] Alexander, R.T., Hemmelgarn, B.R., Wiebe, N., Bello, A., Morgan, C., Samuel, S., Klarenbach, S.W., Curhan, G.C. and Tonelli, M. (2012) Kidney Stones and Kidney Function Loss: A Cohort Study. *The BMJ*, **345**, e5287. https://doi.org/10.1136/bmj.e5287

[3] Wong, P., Fuller, P.J., Gillespie, M.T., Kartsogiannis, V., Strauss, B.J., Bowden, D. and Milat, F. (2013) Thalassemia Bone Disease: The Association between Nephrolithiasis, Bone Mineral Density and Fractures. *Osteoporosis International*: *A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, **24**, 1965-1971. https://doi.org/10.1007/s00198-012-2260-y

[4] Melton, L.J., Crowson, C.S., Khosla, S., Wilson, D.M. and O'Fallon, W.M. (1998) Fracture Risk among Patients with Urolithiasis: A Population-Based Cohort Study. *Kidney International*, **53**, 459-464. https://doi.org/10.1046/j.1523-1755.1998.00779.x

[5] Lauderdale, D.S., Thisted, R.A., Wen, M. and Favus, M.J. (2001) Bone Mineral Density and Fracture among Prevalent Kidney Stone Cases in the Third National Health and Nutrition Examination Survey. *Journal of Bone and Mineral Research*, **16**, 1893-1898. https://doi.org/10.1359/jbmr.2001.16.10.1893

[6] Ricchi, P., Ammirabile, M., Costantini, S., Di Matola, T., Spasiano, A., Genna, M.L., Cinque, P. and Prossomariti, L. (2012) Splenectomy Is a Risk Factor for Developing Hyperuricemia and Nephrolithiasis in Patients with Thalassemia Intermedia: A Retrospective Study. *Blood Cells, Molecules & Diseases*, **49**, 133-135. https://doi.org/10.1016/j.bcmd.2012.05.012

[7] Motta, I., Mancarella, M., Marcon, A., Vicenzi, M. and Cappellini, M.D. (2020) Management of Age-Associated Medical Complications in Patients with β-Thalassemia. *Expert Review of Hematology*, **13**, 85-94. https://doi.org/10.1080/17474086.2020.1686354

[8] Demosthenous, C., Vlachaki, E., Apostolou, C., Eleftheriou, P., Kotsiafti, A., Vetsiou, E., Mandala, E., Perifanis, V. and Sarafidis, P. (2019) Beta-Thalassemia: Renal Complications and Mechanisms: A Narrative Review. *Hematology* (*Amsterdam, Netherlands*), **24**, 426-438. https://doi.org/10.1080/16078454.2019.1599096

[9] Modell, B., Khan, M., Darlison, M., Westwood, M.A., Ingram, D. and Pennell, D.J. (2008) Improved Survival of Thalassaemia Major in the UK and Relation to T2* Cardiovascular Magnetic Resonance. *Journal of Cardiovascular Magnetic Resonance*: *Official Journal of the Society for Cardiovascular Magnetic Resonance*, **10**, Article No. 42. https://doi.org/10.1186/1532-429X-10-42

[10] Ponticelli, C., Musallam, K.M., Cianciulli, P. and Cappellini, M.D. (2010) Renal Complications in Transfusion-Dependent Beta Thalassaemia. *Blood Reviews*, **24**, 239-244. https://doi.org/10.1016/j.blre.2010.08.004

[11] Musallam, K.M. and Taher, A.T. (2012) Mechanisms of Renal Disease in β-Thalassemia. *Journal of the American Society of Nephrology*: *JASN*, **23**, 1299-1302. https://doi.org/10.1681/ASN.2011111070

[12] Bakr, A., Al-Tonbary, Y., Osman, G. and El-Ashry, R. (2014) Renal Complications of Beta-Thalassemia Major in Children. *American Journal of Blood Research*, **4**, 1-6.

[13] Tang, C.-H., Furnback, W., Wang, B.C.M., Tang, J., Tang, D., Lu, M.-Y., Huang, V. W.-H. and Musallam, K.M. (2021) Relationship between Transfusion Burden, Healthcare Resource Utilization, and Complications in Patients with Beta-Thalassemia in Taiwan: A Real-World Analysis. *Transfusion*, **61**, 2906-2917. https://doi.org/10.1111/trf.16636

[14] Quinn, C.T., Johnson, V.L., Kim, H.-Y., Trachtenberg, F., Vogiatzi, M.G., Kwiatkowski, J.L., Neufeld, E.J., Fung, E., Oliveri, N., Kirby, M. and Giardina, P.J. (2011) Renal Dysfunction in Patients with Thalassaemia. *British Journal of Haematology*, **153**, 111-117. https://doi.org/10.1111/j.1365-2141.2010.08477.x

[15] Scales, C.D., Smith, A.C., Hanley, J.M. and Saigal, C.S. (2012) Prevalence of Kidney Stones in the United States. *European Urology*, **62**, 160-165. https://doi.org/10.1016/j.eururo.2012.03.052

[16] Tasian, G.E., Ross, M.E., Song, L., Sas, D.J., Keren, R., Denburg, M.R., Chu, D.I., Copelovitch, L., Saigal, C.S. and Furth, S.L. (2016) Annual Incidence of Nephrolithiasis among Children and Adults in South Carolina from 1997 to 2012. *Clinical Journal of the American Society of Nephrology*: *CJASN*, **11**, 488-496. https://doi.org/10.2215/CJN.07610715

[17] Clayton, D.B. and Pope, J.C. (2011) The Increasing Pediatric Stone Disease Problem. *Therapeutic Advances in Urology*, **3**, 3-12. https://doi.org/10.1177/1756287211400491

[18] Wong, P., Milat, F., Fuller, P.J., Kerr, P.G., Doery, J.C.G., Oh, D.H., Jackson, D., Gillespie, M.T., Bowden, D.K., Pasricha, S.-R. and Lau, K.K. (2017) Urolithiasis Is Prevalent and Associated with Reduced Bone Mineral Density in β-Thalassaemia Major. *Internal Medicine Journal*, **47**, 1064-1067. https://doi.org/10.1111/imj.13533

[19] Ratkalkar, V.N. and Kleinman, J.G. (2011) Mechanisms of Stone Formation. *Clinical Reviews in Bone and Mineral Metabolism*, **9**, 187-197. https://doi.org/10.1007/s12018-011-9104-8

[20] Goldfarb, D.S., Fischer, M.E., Keich, Y. and Goldberg, J. (2005) A Twin Study of Genetic and Dietary Influences on Nephrolithiasis: A Report from the Vietnam Era Twin (VET) Registry. *Kidney International*, **67**, 1053-1061. https://doi.org/10.1111/j.1523-1755.2005.00170.x

[21] Rule, A.D., Bergstralh, E.J., Melton, L.J., Li, X., Weaver, A.L. and Lieske, J.C. (2009) Kidney Stones and the Risk for Chronic Kidney Disease. *Clinical Journal of the American Society of Nephrology*: *CJASN*, **4**, 804-811. https://doi.org/10.2215/CJN.05811108

[22] Taylor, E.N., Stampfer, M.J. and Curhan, G.C. (2005) Diabetes Mellitus and the Risk of Nephrolithiasis. *Kidney International*, **68**, 1230-1235. https://doi.org/10.1111/j.1523-1755.2005.00516.x

[23] Ali, D., Mehran, K. and Moghaddam, A.G. (2008) Comparative Evaluation of Renal Findings in Beta-Thalassemia Major and Intermedia. *Saudi Journal of Kidney Dis-*

eases and Transplantation: *An Official Publication of the Saudi Center for Organ Transplantation*, *Saudi Arabia*, **19**, 206-209.

[24] Christoforidis, A., Zevgaridou, E., Tsatra, I., Perifanis, V., Vlachaki, E., Papassotiriou, I., Apostolakou, F. and Athanassiou-Metaxa, M. (2007) Urinary Iron Excretion in Young Thalassemic Patients Receiving Combined Chelation Treatment with Deferoxamine and Deferiprone. *Journal of Pediatric Hematology/Oncology*, **29**, 598-601. https://doi.org/10.1097/MPH.0b013e318142b51e

[25] Ramaswamy, K., Killilea, D.W., Kapahi, P., Kahn, A.J., Chi, T. and Stoller, M.L. (2015) The Elementome of Calcium-Based Urinary Stones and Its Role in Urolithiasis. *Nature Reviews. Urology*, **12**, 543-557. https://doi.org/10.1038/nrurol.2015.208

[26] Muñoz, J.A. and Valiente, M. (2005) Effects of Trace Metals on the Inhibition of Calcium Oxalate Crystallization. *Urological Research*, **33**, 267-272. https://doi.org/10.1007/s00240-005-0468-4

[27] Küpeli, S., Arikan, N., Durak, I., Sarica, K., Akpoyraz, M. and Karalezli, G. (1993) Efficiency of Extracorporeal Shockwave Lithotripsy on Calcium-Oxalate Stones: Role of Copper, Iron, Magnesium and Zinc Concentrations on Disintegration of the Stones. *European Urology*, **23**, 409-412. https://doi.org/10.1159/000474640

[28] Scoglio, M., Cappellini, M.D., D'Angelo, E., Bianchetti, M.G., Lava, S.A.G., Agostoni, C. and Milani, G.P. (2021) Kidney Tubular Damage Secondary to Deferasirox: Systematic Literature Review. *Children* (*Basel*, *Switzerland*), ***8***, 1104. https://doi.org/10.3390/children8121104

[29] Díaz-García, J.D., Gallegos-Villalobos, A., Gonzalez-Espinoza, L., Sanchez-Niño, M.D., Villarrubia, J. and Ortiz, A. (2014) Deferasirox Nephrotoxicity—The Knows and Unknowns. *Nature Reviews. Nephrology*, **10**, 574-586. https://doi.org/10.1038/nrneph.2014.121

[30] Efthimia, V., Neokleous, N., Agapidou, A., Economou, M., Vetsiou, E., Teli, A. and Perifanis, V. (2013) Nephrolithiasis in Beta Thalassemia Major Patients Treated with Deferasirox: An Advent or an Adverse Event? A Single Greek Center Experience. *Annals of Hematology*, **92**, 263-265. https://doi.org/10.1007/s00277-012-1558-3

[31] Economou, M., Printza, N., Teli, A., Tzimouli, V., Tsatra, I., Papachristou, F. and Athanassiou-Metaxa, M. (2010) Renal Dysfunction in Patients with Beta-Thalassemia Major Receiving Iron Chelation Therapy either with Deferoxamine and Deferiprone or with Deferasirox. *Acta Haematologica*, **123**, 148-152. https://doi.org/10.1159/000287238

[32] Ricchi, P., Ammirabile, M., Costantini, S., Spasiano, A., Di Matola, T., Cinque, P., Casale, M., Filosa, A. and Prossomariti, L. (2014) Nephrolithiasis in Patients Exposed to Deferasirox and Desferioxamine: Probably an Age-Linked Event with Different Effects on Some Renal Parameters. *Annals of Hematology*, **93**, 525-527. https://doi.org/10.1007/s00277-013-1833-y

[33] Tasian, G.E., Ross, M.E., Song, L., Grundmeier, R.W., Massey, J., Denburg, M.R., Copelovitch, L., Warner, S., Chi, T., Killilea, D.W., Stoller, M.L. and Furth, S.L. (2017) Dietary Zinc and Incident Calcium Kidney Stones in Adolescence. *The Journal of Urology*, **197**, 1342-1348. https://doi.org/10.1016/j.juro.2016.11.096

[34] Tang, J., McFann, K. and Chonchol, M. (2012) Dietary Zinc Intake and Kidney Stone Formation: Evaluation of NHANES III. *American Journal of Nephrology*, **36**, 549-553. https://doi.org/10.1159/000345550

[35] Erdoğan, E., Canatan, D., Ormeci, A.R., Vural, H. and Aylak, F. (2013) The Effects

of Chelators on Zinc Levels in Patients with Thalassemia Major. *Journal of Trace Elements in Medicine and Biology: Organ of the Society for Minerals and Trace Elements* (*GMS*), **27**, 109-111. https://doi.org/10.1016/j.jtemb.2012.10.002

[36] Fung, E.B., Gildengorin, G., Talwar, S., Hagar, L. and Lal, A. (2015) Zinc Status Affects Glucose Homeostasis and Insulin Secretion in Patients with Thalassemia. *Nutrients*, **7**, 4296-4307. https://doi.org/10.3390/nu7064296

[37] Al-Refaie, F.N., Hershko, C., Hoffbrand, A.V., Kosaryan, M., Olivieri, N.F., Tondury, P. and Wonke, B. (1995) Results of Long-Term Deferiprone (L1) Therapy: A Report by the International Study Group on Oral Iron Chelators. *British Journal of Haematology*, **91**, 224-229. https://doi.org/10.1111/j.1365-2141.1995.tb05274.x

[38] Fung, E.B., Ahmad, T., Killilea, D.W., Hussain, R. and Lal, A. (2020) Zinc Supplementation Improves Markers of Glucose Homeostasis in Thalassaemia. *British Journal of Haematology*, **190**, e162-e166. https://doi.org/10.1111/bjh.16771

[39] Prochaska, M.L., Taylor, E.N. and Curhan, G.C. (2016) Insights into Nephrolithiasis from the Nurses' Health Studies. *American Journal of Public Health*, **106**, 1638-1643. https://doi.org/10.2105/AJPH.2016.303319

[40] Fung, E.B., Pinal, J. and Leason, M. (2015) Reduced Physical Activity Patterns in Patients with Thalassemia Compared to Healthy Controls. *Journal of Hematology and Oncology Research*, **2**, 7-21. https://openaccesspub.org/jhor/article/206

[41] Taylor, E.N., Stampfer, M.J. and Curhan, G.C. (2004) Dietary Factors and the Risk of Incident Kidney Stones in Men: New Insights after 14 Years of Follow-Up. *Journal of the American Society of Nephrology: JASN*, **15**, 3225-3232. https://doi.org/10.1097/01.ASN.0000146012.44570.20

[42] Taylor, E.N. and Curhan, G.C. (2008) Fructose Consumption and the Risk of Kidney Stones. *Kidney International*, **73**, 207-212. https://doi.org/10.1038/sj.ki.5002588

[43] Curhan, G.C., Willett, W.C., Rimm, E.B. and Stampfer, M.J. (1993) A Prospective Study of Dietary Calcium and Other Nutrients and the Risk of Symptomatic Kidney Stones. *The New England Journal of Medicine*, **328**, 833-838. https://doi.org/10.1056/NEJM199303253281203

[44] Borghi, L., Schianchi, T., Meschi, T., Guerra, A., Allegri, F., Maggiore, U. and Novarini, A. (2002) Comparison of Two Diets for the Prevention of Recurrent Stones in Idiopathic Hypercalciuria. *The New England Journal of Medicine*, **346**, 77-84. https://doi.org/10.1056/NEJMoa010369

[45] Fung, E.B., Xu, Y., Trachtenberg, F., Odame, I., Kwiatkowski, J.L., Neufeld, E.J., Thompson, A.A., Boudreaux, J., Quinn, C.T., Vichinsky, E.P. and Thalassemia Clinical Research Network (2012) Inadequate Dietary Intake in Patients with Thalassemia. *Journal of the Academy of Nutrition and Dietetics*, **112**, 980-990. https://doi.org/10.1016/j.jand.2012.01.017

[46] Curhan, G.C., Willett, W.C., Rimm, E.B., Spiegelman, D. and Stampfer, M.J. (1996) Prospective Study of Beverage Use and the Risk of Kidney Stones. *American Journal of Epidemiology*, **143**, 240-247. https://doi.org/10.1093/oxfordjournals.aje.a008734

[47] de Alarcon, P.A., Donovan, M.E., Forbes, G.B., Landaw, S.A. and Stockman, J.A. (1979) Iron Absorption in the Thalassemia Syndromes and Its Inhibition by Tea. *The New England Journal of Medicine*, **300**, 5-8. https://doi.org/10.1056/NEJM197901043000102

[48] Curhan, G.C., Willett, W.C., Speizer, F.E., Spiegelman, D. and Stampfer, M.J. (1997) Comparison of Dietary Calcium with Supplemental Calcium and Other Nutrients as Factors Affecting the Risk for Kidney Stones in Women. *Annals of Internal Medicine*, **126**, 497-504. https://doi.org/10.7326/0003-4819-126-7-199704010-00001

[49] Sahi, T. (1994) Genetics and Epidemiology of Adult-Type Hypolactasia. *Scandinavian Journal of Gastroenterology. Supplement*, **202**, 7-20. https://doi.org/10.3109/00365529409091740

[50] Malihi, Z., Wu, Z., Stewart, A.W., Lawes, C.M. and Scragg, R. (2016) Hypercalcemia, Hypercalciuria, and Kidney Stones in Long-Term Studies of Vitamin D Supplementation: A Systematic Review and Meta-Analysis. *The American Journal of Clinical Nutrition*, **104**, 1039-1051. https://doi.org/10.3945/ajcn.116.134981

[51] Ferraro, P.M., Curhan, G.C., Gambaro, G. and Taylor, E.N. (2016) Total, Dietary, and Supplemental Vitamin C Intake and Risk of Incident Kidney Stones. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*, **67**, 400-407. https://doi.org/10.1053/j.ajkd.2015.09.005

[52] Elalfy, M.S., Saber, M.M., Adly, A.A.M., Ismail, E.A., Tarif, M., Ibrahim, F. and Elalfy, O.M. (2016) Role of Vitamin C as an Adjuvant Therapy to Different Iron Chelators in Young *β*-Thalassemia Major Patients: Efficacy and Safety in Relation to Tissue Iron Overload. *European Journal of Haematology*, **96**, 318-326. https://doi.org/10.1111/ejh.12594

[53] Curhan, G.C., Willett, W.C., Rimm, E.B., Speizer, F.E. and Stampfer, M.J. (1998) Body Size and Risk of Kidney Stones. *Journal of the American Society of Nephrology: JASN*, **9**, 1645-1652. https://doi.org/10.1681/ASN.V991645

[54] Fung, E.B., Xu, Y., Kwiatkowski, J.L., Vogiatzi, M.G., Neufeld, E., Olivieri, N., Vichinsky, E.P., Giardina, P.J. and Thalassemia Clinical Research Network (2010) Relationship between Chronic Transfusion Therapy and Body Composition in Subjects with Thalassemia. *The Journal of Pediatrics*, **157**, 641-647, 647.e1-2. https://doi.org/10.1016/j.jpeds.2010.04.064

[55] Wong, P., Fuller, P.J., Gillespie, M.T., Kartsogiannis, V., Milat, F., Bowden, D.K. and Strauss, B.J. (2014) The Effect of Gonadal Status on Body Composition and Bone Mineral Density in Transfusion-Dependent Thalassemia. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, **25**, 597-604. https://doi.org/10.1007/s00198-013-2454-y

[56] Sorensen, M.D., Chi, T., Shara, N.M., Wang, H., Hsi, R.S., Orchard, T., Kahn, A.J., Jackson, R.D., Miller, J., Reiner, A.P. and Stoller, M.L. (2014) Activity, Energy Intake, Obesity, and the Risk of Incident Kidney Stones in Postmenopausal Women: A Report from the Women's Health Initiative. *Journal of the American Society of Nephrology: JASN*, **25**, 362-369. https://doi.org/10.1681/ASN.2013050548

[57] Tasian, G.E., Pulido, J.E., Gasparrini, A., Saigal, C.S., Horton, B.P., Landis, J.R., Madison, R., Keren, R. and Urologic Diseases in America Project (2014) Daily Mean Temperature and Clinical Kidney Stone Presentation in Five U.S. Metropolitan Areas: A Time-Series Analysis. *Environmental Health Perspectives*, **122**, 1081-1087. https://doi.org/10.1289/ehp.1307703

[58] Borghi, L., Meschi, T., Amato, F., Novarini, A., Romanelli, A. and Cigala, F. (1993) Hot Occupation and Nephrolithiasis. *The Journal of Urology*, **150**, 1757-1760. https://doi.org/10.1016/S0022-5347(17)35887-1

[59] Pearle, M.S., Goldfarb, D.S., Assimos, D.G., Curhan, G., Denu-Ciocca, C.J., Matlaga, B.R., Monga, M., Penniston, K.L., Preminger, G.M., Turk, T.M.T., White, J.R. and American Urological Association (2014) Medical Management of Kidney Stones: AUA Guideline. *The Journal of Urology*, **192**, 316-324. https://doi.org/10.1016/j.juro.2014.05.006

[60] Ettinger, B., Tang, A., Citron, J.T., Livermore, B. and Williams, T. (1986) Randomized Trial of Allopurinol in the Prevention of Calcium Oxalate Calculi. *The New*

England Journal of Medicine, **315**, 1386-1389.
https://doi.org/10.1056/NEJM198611273152204

[61] Naderi, M., Sadeghi-Bojd, S., Valeshabad, A.K., Jahantigh, A., Alizadeh, S., Dorgalaleh, A., Tabibian, S. and Bamedi, T. (2013) A Prospective Study of Tubular Dysfunction in Pediatric Patients with Beta Thalassemia Major Receiving Deferasirox. *Pediatric Hematology and Oncology*, **30**, 748-754.
https://doi.org/10.3109/08880018.2013.823470

[62] Wong, P., Polkinghorne, K., Kerr, P.G., Doery, J.C.G., Gillespie, M.T., Larmour, I., Fuller, P.J., Bowden, D.K. and Milat, F. (2016) Deferasirox at Therapeutic Doses Is Associated with Dose-Dependent Hypercalciuria. *Bone*, **85**, 55-58.
https://doi.org/10.1016/j.bone.2016.01.011

[63] Mahmoud, A.A., Elian, D.M., Abd El Hady, N.M., Abdallah, H.M., Abdelsattar, S., Khalil, F.O. and Abd El Naby, S.A. (2021) Assessment of Subclinical Renal Glomerular and Tubular Dysfunction in Children with Beta Thalassemia Major. *Children* (*Basel*, *Switzerland*), **8**, 100. https://doi.org/10.3390/children8020100

[64] Cochat, P., Pichault, V., Bacchetta, J., Dubourg, L., Sabot, J.-F., Saban, C., Daudon, M. and Liutkus, A. (2010) Nephrolithiasis Related to Inborn Metabolic Diseases. *Pediatric Nephrology* (*Berlin*, *Germany*), **25**, 415-424.
https://doi.org/10.1007/s00467-008-1085-6

[65] Angelopoulos, N.G., Goula, A., Rombopoulos, G., Kaltzidou, V., Katounda, E., Kaltsas, D. and Tolis, G. (2006) Hypoparathyroidism in Transfusion-Dependent Patients with Beta-Thalassemia. *Journal of Bone and Mineral Metabolism*, **24**, 138-145. https://doi.org/10.1007/s00774-005-0660-1

[66] Vogiatzi, M.G., Macklin, E.A., Fung, E.B., Cheung, A.M., Vichinsky, E., Olivieri, N., Kirby, M., Kwiatkowski, J.L., Cunningham, M., Holm, I.A., Lane, J., Schneider, R., Fleisher, M., Grady, R.W., Peterson, C.C., Giardina, P.J. and Thalassemia Clinical Research Network (2009) Bone Disease in Thalassemia: A Frequent and Still Unresolved Problem. *Journal of Bone and Mineral Research*: *The Official Journal of the American Society for Bone and Mineral Research*, **24**, 543-557.
https://doi.org/10.1359/jbmr.080505

[67] Reid, I.R., Ames, R.W., Orr-Walker, B.J., Clearwater, J.M., Horne, A.M., Evans, M.C., Murray, M.A., McNeil, A.R. and Gamble, G.D. (2000) Hydrochlorothiazide Reduces Loss of Cortical Bone in Normal Postmenopausal Women: A Randomized Controlled Trial. *The American Journal of Medicine*, **109**, 362-370.
https://doi.org/10.1016/S0002-9343(00)00510-6

[68] LaCroix, A.Z., Ott, S.M., Ichikawa, L., Scholes, D. and Barlow, W.E. (2000) Low-Dose Hydrochlorothiazide and Preservation of Bone Mineral Density in Older Adults. A Randomized, Double-Blind, Placebo-Controlled Trial. *Annals of Internal Medicine*, **133**, 516-526. https://doi.org/10.7326/0003-4819-133-7-200010030-00010

[69] Giusti, A., Barone, A., Pioli, G., Girasole, G., Siccardi, V., Palummeri, E. and Bianchi, G. (2009) Alendronate and Indapamide Alone or in Combination in the Management of Hypercalciuria Associated with Osteoporosis: A Randomized Controlled Trial of Two Drugs and Three Treatments. *Nephrology*, *Dialysis*, *Transplantation*: *Official Publication of the European Dialysis and Transplant Association—European Renal Association*, **24**, 1472-1477. https://doi.org/10.1093/ndt/gfn690

[70] Dede, A.D., Trovas, G., Chronopoulos, E., Triantafyllopoulos, I.K., Dontas, I., Papaioannou, N. and Tournis, S. (2016) Thalassemia-Associated Osteoporosis: A Systematic Review on Treatment and Brief Overview of the Disease. *Osteoporosis International*: *A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the*

USA, **27**, 3409-3425. https://doi.org/10.1007/s00198-016-3719-z

[71] Edvardsson, V.O., Palsson, R., Indridason, O.S., Thorvaldsson, S. and Stefansson, K. (2009) Familiality of Kidney Stone Disease in Iceland. *Scandinavian Journal of Urology and Nephrology*, **43**, 420-424. https://doi.org/10.3109/00365590903151479

[72] Ferreira, L.G., Pereira, A.C. and Heilberg, I.P. (2010) Vitamin D Receptor and Calcium-Sensing Receptor Gene Polymorphisms in Hypercalciuric Stone-Forming Patients. *Nephron. Clinical Practice*, **114**, c135-c144. https://doi.org/10.1159/000254386

[73] Thorleifsson, G., Holm, H., Edvardsson, V., Walters, G.B., Styrkarsdottir, U., Gudbjartsson, D.F., Sulem, P., Halldorsson, B.V., de Vegt, F., d'Ancona, F.C.H., den Heijer, M., Franzson, L., Christiansen, C., Alexandersen, P., Rafnar, T., Kristjansson, K., Sigurdsson, G., Kiemeney, L.A., Bodvarsson, M., Stefansson, K., *et al.* (2009) Sequence Variants in the CLDN14 Gene Associate with Kidney Stones and Bone Mineral Density. *Nature Genetics*, **41**, 926-930. https://doi.org/10.1038/ng.404