

Thiazide Diuretics Arrest the Progression of Nephrocalcinosis in Children With X-Linked Hypophosphatemia

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ABSTRACT. *Objective.* X-linked hypophosphatemia (XLH) is characterized clinically by rickets, hypophosphatemia, and hyperphosphaturia. Conventional treatment of XLH with oral phosphate and vitamin D is associated with increased urinary calcium excretion and nephrocalcinosis. Thiazide diuretics decrease urinary calcium excretion. The objective of this study was to determine the effect of thiazide diuretics on the clinical and radiologic course of nephrocalcinosis in children with XLH.

Methods. The effect of hydrochlorothiazide (HCTZ) on clinical and radiologic progression of nephrocalcinosis was evaluated in 11 children with XLH. All patients had been treated previously with vitamin D and oral phosphate and had radiologic evidence of nephrocalcinosis. The average age of the patients at the start of HCTZ was 6.6 ± 1.0 years. The effect of oral HCTZ at 0.8 ± 0.1 mg/kg body weight per day given for 3.3 ± 0.6 years on the progression of nephrocalcinosis and urinary calcium excretion was evaluated.

Results. There was no change in serum phosphorous, calcium, potassium, and chloride after HCTZ therapy. HCTZ therapy increased serum bicarbonate and decreased urinary calcium excretion. The grade of nephrocalcinosis increased from 0.4 ± 0.2 to 1.5 ± 0.3 in the 2.3 ± 0.3 years before initiation of HCTZ therapy, whereas the degree of nephrocalcinosis was stable after 3.3 ± 0.6 years of HCTZ therapy (1.5 ± 0.3 vs 3.0 ± 0.3).

Conclusion. HCTZ decreased urinary calcium excretion but did not result in the resolution of nephrocalcinosis. However, when compared with the control period, HCTZ prevented the progression of nephrocalcinosis in children with XLH. *Pediatrics* 2001;108(1). URL: <http://www.pediatrics.org/cgi/content/full/108/1/e6>; X-linked hypophosphatemia, rickets, nephrocalcinosis, thiazide diuretics.

ABBREVIATIONS. XLH, X-linked hypophosphatemia; HCTZ, hydrochlorothiazide; TmP/GFR, tubular maximum reabsorption of phosphate per deciliter of glomerular filtration; SEM, standard error of the mean.

X-linked hypophosphatemia (XLH) is the most common inherited cause of rickets. It is characterized by hypophosphatemia caused by impaired proximal tubular reabsorption of phospho-

rous and an inappropriately normal serum level of $1,25(\text{OH})_2$ vitamin D. The resulting hypophosphatemia leads to defective bone mineralization.¹ Current therapy includes administration of $1,25(\text{OH})_2$ vitamin D (calcitriol) and phosphate to replete urinary phosphate losses without stimulating parathyroid hormone release.² Such therapy often leads to hypercalcuria and nephrocalcinosis.^{3,4} Nephrocalcinosis can lead to renal tubular acidosis and possibly renal insufficiency.⁴⁻⁶

Hypercalcuria also has been shown to be associated with nephrocalcinosis in distal renal tubular acidosis, hyperparathyroidism, prolonged immobilization, Bartter's syndrome, hypophosphatasia, certain tumors, high-dose vitamin D therapy, and idiopathic and drug-induced hypercalcuria.⁷⁻¹³ Hydrochlorothiazide (HCTZ) decreases urinary calcium excretion. The effect of HCTZ on nephrocalcinosis in children with XLH is not known. The aim of the present study was to assess whether HCTZ therapy affects nephrocalcinosis in children with XLH. Our data suggest that although HCTZ did not enhance the resolution of nephrocalcinosis, HCTZ halts the progression of nephrocalcinosis.

METHODS

We evaluated the effect of HCTZ therapy in 11 children with XLH. All patients had a positive family history of rickets consistent with an X-linked mode of inheritance. The diagnosis of XLH was established by the clinical and biochemical criteria that we have described previously.¹⁴ The average age of the patients at the time of initiation of HCTZ was 6.6 ± 1.0 years. At the time of enrollment in the study, all patients were maintained on calcitriol (Rocaltrol; Hoffmann-La Roche, Nutley, NJ) at 58 ± 1 ng/kg body weight per day and oral phosphate therapy at 27 ± 4 mg/kg body weight per day. Conventional therapy with calcitriol and oral phosphate was adjusted to maintain normal parathyroid hormone concentration, clinical remission of rickets, and a urinary calcium excretion <1 mmol/kg body weight per day.

Clinical data from the period immediately preceding the initiation of HCTZ therapy was analyzed. Each patient was started on HCTZ, 0.8 ± 0.1 mg/kg body weight per day, in an open-label study for 3.3 ± 0.6 years. The dose of HCTZ was adjusted to maintain a urinary calcium-to-creatinine ratio of <0.2 . Therapy with HCTZ was well tolerated; however, 7 patients developed hypokalemia and required a high-potassium diet. No side effects were reported or observed in any of the patients treated.

Patients were evaluated every 3 months in the metabolic bone disease clinic at the Texas Scottish Rite Hospital for Children in Dallas. Evaluation included 1) complete physical examination; 2) blood analysis for electrolytes, calcium, and alkaline phosphatase; 3) fasting morning serum PO_4 and spot urine for creatinine, phosphorous, and calcium; 4) timed urine for creatinine, phosphorous, and calcium; and 5) renal ultrasound to evaluate the grade of nephrocalcinosis as previously described.¹⁵ The values reported were last measured at the end of

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the observation period. Renal ultrasound studies were performed with the use of multihertz vector or curved transducers and a Sequoia model ultrasound machine (Acuson, Mountain View, CA). The radiologist evaluated the grade of nephrocalcinosis in a blinded manner. The degree of echogenicity of the renal pyramids was graded on a scale of 0 to 4 as reported previously.¹⁵ Zero was considered normal; 1, consistent with a faint rim around the medullary pyramids; 2, a more intense echogenic rim with echoes faintly filling the entire medullary pyramid; 3, consistent with uniformly intense echoes throughout the medullary renal pyramid; and 4, discrete nephrolithiasis.

Data were evaluated with the use of a Student's *t* test and repeated measures analysis of variance. SigmaStat software (SPSS Inc, Chicago, IL) was used for all statistical computations. Data were summarized as the mean \pm standard error of the mean (SEM). *P* < .05 was required for statistical significance.

RESULTS

The clinical and biochemical data of patients with XLH before and after 3.3 ± 0.6 years of HCTZ therapy were compared (Table 1). HCTZ did not alter serum sodium or calcium. Conversely, serum bicarbonate increased after HCTZ therapy from 21.1 ± 0.3 to 25.5 ± 0.6 mmol/L (*P* < .05), and fasting serum phosphate decreased from 1.09 ± 0.06 to 0.78 ± 0.05 mmol/L during the treatment period (*P* < .05).

Tubular maximum reabsorption of phosphate per deciliter of glomerular filtration (TmP/GFR), estimated as described previously,¹⁶ was 1.45 ± 0.24 mg/dL GFR in the control period and was 1.77 ± 0.20 mg/dL GFR after HCTZ therapy (*P* = .35). However, the urinary calcium divided by urinary creatinine ratio decreased from 0.30 ± 0.07 to 0.10 ± 0.03 (*P* < .05) after 3.3 ± 0.6 years of HCTZ therapy.

The grade of nephrocalcinosis was compared in each patient during a control period and after treatment with HCTZ (Fig 1). Nephrocalcinosis was evaluated at the beginning of the control period and just before the initiation of HCTZ therapy (2.3 ± 0.3 years later) and after 3.3 ± 0.6 years of HCTZ therapy. There was a significant increase in the degree of nephrocalcinosis during the 2.3 ± 0.3 years before the initiation of HCTZ therapy (*P* < .05). During the control period, the degree of nephrocalcinosis increased from 0.5 ± 0.2 to 1.5 ± 0.3 (*P* < .05). The degree of nephrocalcinosis was 1.0 ± 0.3 after 3.3 ± 0.6 years of HCTZ therapy (*P* = .22). Thus, there was no progression of nephrocalcinosis after initiation of HCTZ therapy.

DISCUSSION

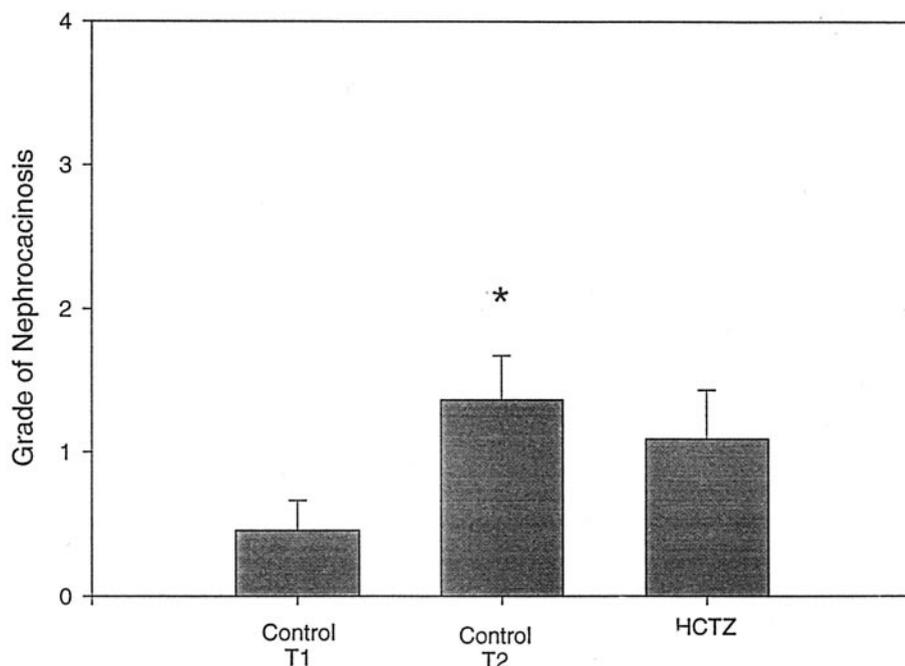
The pathogenesis of nephrocalcinosis in children with XLH is probably multifactorial. The nature and location of nephrocalcinosis in children with XLH was evaluated recently. Nephrocalcinosis is caused by the intratubular deposition of calcium phosphate.¹⁰ Supersaturation of urine with calcium results in intratubular crystal formation at the tip of the renal papilla.⁷ Increased urinary calcium excretion is a common complication of vitamin D and oral phosphate therapy, and it is associated with nephrocalcinosis.^{3,4} HCTZ decreases urinary calcium excretion both by direct tubular effect and by volume depletion, leading to increased distal tubular sodium and calcium resorption.¹⁷ Thiazide diuretics also were shown effectively to reverse hypercalcuria associated with vitamin D therapy.¹⁸ HCTZ therapy has been shown to protect against the development of nephrolithiasis in patients with idiopathic hypercalcuria.^{11,19}

The effect of HCTZ therapy on the severity of nephrocalcinosis in patients with XLH has not been studied previously. Knoll and Alon¹¹ showed that chlorothiazide therapy does not lead to the resolution of established nephrocalcinosis in furosemide-treated young rats. This is similar to the results of our current study, in which we showed that HCTZ therapy does not lead to the resolution of nephrocalcinosis in children with XLH. Of interest is that nephrocalcinosis was progressive during the control period preceding HCTZ therapy but was stable at the end of the treatment period. Whether the arrest of the progression of nephrocalcinosis is secondary to HCTZ or attributable to the natural course of these lesions cannot be ascertained with certainty. However, nephrocalcinosis in XLH is progressive. Studies that examined nephrocalcinosis in XLH used the same scale as in this study. Renal calcification was found to be severe, with 37% of patients having grade 3 in 1 report,³ and others have found 33% of patients with grade 4 nephrocalcinosis.^{20,21} By contrast, our cohort had only a moderate degree of renal calcification. Forty-five percent of our patients had grade 2 and 9% had grade 3 nephrocalcinosis. None of our patients had grade 4 nephrocalcinosis at the time of initiation of HCTZ therapy. Therefore, nephrocalcinosis potentially could have progressed to higher grades in our current cohort. Accordingly,

TABLE 1. Biochemical Data (Mean \pm SEM) From Patients With XLH Before and After 3.3 Years of HCTZ Therapy

Parameter	Before HCTZ (<i>n</i> = 11)	After 3.3 \pm 0.6 Years of HCTZ Therapy (<i>n</i> = 11)	<i>P</i> Value
Serum potassium (mEq/L)	4.0 \pm 0.1	4.0 \pm 0.1	.24
Serum chloride (mmol/L)	105 \pm 1	103 \pm 1	.06
Serum CO ₂ (mmol/L)	21.1 \pm 0.3	25.5 \pm 0.6	<.05
Fasting phosphorous (mmol/L)	1.09 \pm 0.06	0.78 \pm 0.05	<.05
Serum calcium (mmol/L)	2.43 \pm 0.05	2.37 \pm 0.05	.47
Urinary Ca/Cr	0.30 \pm 0.07	0.10 \pm 0.03	<.05
TmP/GFR (mg/dL GFR)	1.45 \pm 0.24	1.77 \pm 0.20	.325

Fig 1. Progression of nephrocalcinosis in 11 children with XLH before and after HCTZ therapy. Nephrocalcinosis was evaluated at the beginning of the control period (T₁) and just before the initiation of HCTZ therapy (T₂) (2.3 ± 0.3 years later) and after 3.3 ± 0.6 years of HCTZ therapy. There was a significant increase in the degree of nephrocalcinosis during the 2.3 ± 0.3 years between T₁ and T₂ (*, P < .05).



our data suggest that HCTZ therapy arrested the sonographic progression of nephrocalcinosis in children with XLH.

In children with XLH, the development of nephrocalcinosis has been related to the dose of oral phosphate received.³ High-phosphate diets also can induce nephrocalcinosis in rats.²² Hyperphosphaturia is a hallmark of XLH.¹ In our study, HCTZ therapy decreased urinary calcium excretion without affecting phosphate excretion measured by TmP/GFR (Table 1). Alon and Chan²³ studied the effect of HCTZ and amiloride in children with XLH. They also showed that urinary calcium, but not phosphate, excretion decreased in response to HCTZ and amiloride therapy.

We reported previously that nephrocalcinosis in children with XLH is associated with metabolic acidosis.⁴ Despite the lack of resolution of nephrocalcinosis, HCTZ therapy increased serum bicarbonate. We speculate that the improvement in serum bicarbonate is attributable to chronic volume contraction secondary to diuretic effect. Furthermore, serum phosphorous decreased in response to HCTZ therapy without a concomitant increase in TmP/GFR. The cause for decreased serum phosphorous is uncertain.

CONCLUSION

This study evaluated the effectiveness of HCTZ therapy in patients with XLH. HCTZ decreased urinary calcium excretion and arrested the progression of nephrocalcinosis in patients with XLH.

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