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Assessment of Serum Level of Vitamin D in Infants with Nephrolithiasis

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Original Paper

Introduction. Detection of nephrolithiasis is readily possible in infants with the advent of new imaging technology. Vitamin D is routinely given to newborn infants shortly after birth during infancy. Vitamin D is known to increase urinary calcium excretion which may be responsible for the increased incidence of nephrolithiasis during infancy. To test this hypothesis we studied the serum level of vitamin D and renal handling of calcium in infants with nephrolithiasis .

Methods. In this prospective case-controlled study, we measured serum levels of vitamin D and calcium accompanied by urinary calcium level in infants between 1 to 12 months with nephrolithiasis who fed with breast milk and vitamin D supplement and compared these parameters with healthy infants without nephrolithiasis after matching for sex and postnatal age as the control group. All infants with nephrolithiasis were evaluated for metabolic disorders and other risk factors and positive cases were excluded from the study.

Results. Fifty infants between 1 to 12 months with mean postnatal age 6.96 ± 2.29 months with nephrolithiasis and 50 control infants with mean postnatal age 6.94 ± 2.55 months were enrolled in the study. Mean serum level of vitamin D in the case and control groups was 41.49 ± 11.69 and 35.67 ± 6.76 ng/mL, respectively. Mean serum level of calcium in case group was 9.63 ± 0.32 vs. 8.59 ± 1.21 mg/dL in the control group. Mean urinary calcium- creatinine ratio (Ca/Cr) in the study and control groups was 0.15 ± 0.16 and 0.08 ± 0.02, respectively, Differences were statistically significant in all three variables ($P < .05$).

Conclusion. Routine consumption of vitamin D increases urinary level of calcium and in presence of other predisposing factors could accelerate the genesis of nephrolithiasis in infants.

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INTRODUCTION

Nephrolithiasis is one of the best known diseases that can be seen in children as in adults.

Ibn- Sina, one of the ancient Iranian scientists, in his medical book (canon) has written about clinical signs and treatment of renal stones.[1]

Incidence of urinary stone varies in different countries (about 5 to 15%) and is seen in all age groups. In children under age of 16, about 7% of nephrolithiasis have been reported and the rate of stone diagnosis is increasing by using new imaging methods.[2-4]

Multifactorial elements such as climate, diet, genetic and socioeconomic have impact on the

incidence of nephrolithiasis in children. Urinary tract infection (UTI), urologic anomalies and metabolic disorders such as hypercalciuria, hyperoxaluria, hyperuricosuria, cystinuria, hypocitruria, and hypomagnesuria are important predisposing factors in formation of nephrolithiasis. The most common component of nephrolithiasis is calcium and the most important cause is hypercalciuria.[5-12] Hypercalciuria may be absorptive, renal, or resorptive. Increased calcium absorption from the gut can be primary or under the influence of excessive vitamin D intake. Renal hypercalciuria is a disorder of renal calcium reabsorption in the tubules. Renal calcium leakage causes mild hypocalcemia, which stimulates the production of parathyroid hormone by increasing intestinal calcium absorption and increasing calcium reabsorption from the bones. Resorptive hypercalciuria is rare and is seen in patients with primary hyperparathyroidism.[13-14]

Vitamin D facilitates the absorption of calcium and phosphorus in intestine and inhibits the secretion of parathyroid hormone and stimulates osteoblasts to form bones. 11% of the human need for vitamin D is supplied by consumption of foods containing vitamin D (egg, fish, milk, etc.) and another 90% is provided by exposure to sunlight and conversion of 7-dehydrocholesterol to cholecalciferol and after going through many stages in the liver and kidneys, active, 1,25- dihydroxy vitamin D3 is produced ultimately.[15-18]

Today, due to the well-known role of vitamin D in bones health and other physiological effects, routine vitamin D administration is recommended for all infants shortly after birth.[2]

As the role of vitamin D in increasing intestinal absorption of calcium is known, the question is whether routine use of vitamin D can increase urinary calcium excretion and incidence of kidney stones in infancy.

Therefore, we decided to measure the serum levels of vitamin D and calcium and urinary level of calcium in infants under the age of one year who routinely use vitamin D and have nephrolithiasis and compare with healthy control group.

MATERIALS AND METHODS

The present study was performed as a prospective case-control trial which was carried out in the pediatric nephrology clinic of Besat Hospital in Sanandaj, Iran, 2017 to 2018 after approval ethics committee of Kurdistan University of Medical Sciences (IR.MUK.REC.1396/314) approved the project.

To determine the sample size the following formula was used:

$N = (z1\text{-}a / 2 + z1\text{-}B)\ 2\ (\delta 12 + \delta 22) / (\mu 2\text{-}\mu 1)\ 2$

According to previous studies and considering 95% confidence and 90% test power, sample size of 35 was obtained in each group at least, and 50 cases who were selected by simple random sampling were studied in each group for greater confidence,.

The statistical population of the present study included all infants between 1 to 12 months of age who were breastfed and supplemented with vitamin D. The amount of vitamin D consumed was about 400 units per day and started on the 14th day of life. They had been referred to the pediatric nephrology clinic of Besat hospital of Sanandaj, Iran due to restlessness or discoloration of the urine with the possibility of urinary stones.

Infants with nephrolithiasis were selected as the patient group and healthy infants were selected as the control group. The diagnosis of stone was based on ultrasound finding that was performed by an experienced radiologist.

The following tests were performed to investigate the cause of stones in infants with stones: blood gas (VBG), serum levels of sodium, potassium, urea, creatinine, calcium, vitamin D,urinalysis, urine culture and in the random urine samples the amount of oxalate, citrate, uric acid, calcium, creatinine, and cystine were measured. In the presence of underlying diseases such as metabolic disorder, endocrine, urologic and nephrology problems, urinary tract infection and formula feeding, all of these infants were excluded from the study.

Data collected in pre-designed forms including: sex, age, size and number of stones, serum level of vitamin D, serum level of calcium, urinary calcium and creatinine levels after the necessary coordination and informed consent was obtained from each parents of the selected infants. It should be noted that the Ca/Cr ratio was used to measure urinary calcium level to eliminate the effect of urine concentration and osmolality on urinary calcium level.

We used SPSS statistical software version 21 for data analyzing and descriptive statistical methods to determine the frequency, mean and standard

deviation. To compare the nominal variables between two groups chi-square test was used and to compare the mean parameters, independent t-test was used. The significance level was $P < .05$.

RESULTS

Descriptive results of this study showed that infants with urinary stones were 44% girls and 56% boys with an average age of 6.96 ± 2.29 months and in the control group,they were 60% girls and 40% boys with an average age of 6.94 ± 2.55 months, this difference was not statistically significant ($P > .05$) (Table 1).

The size of the stones was as following:less than 3 mm in 34 patients (68%),between 3 to 5 mm in 13 patients (26%) and more than 5 mm in only 3 patients (6%). 43 patients (86%) had less than 3 stones and only 7 patients (14%) had more than 3 stones.

Mean serum level of vitamin D in the case and control groups was 41.49 ± 11.69 and 35.67 ± 6.76 ng/mL, respectively, and mean serum level of calcium in the case and control groups was 9.63 ± 0.32 and 8.59 ± 1.21 mg/dL, respectively. Urinary Ca/Cr ratio in the case and control groups was 0.15 ± 0.16 and 0.08 ± 0.02, respectively.

Results of the independent t-test showed significant differences ($P \leq .05$) between the mean serum levels of vitamin D and calcium, and the mean urinary calcium/cr ratio in infants with urinary stones compared with the control group. In fact, the average serum level of vitamin D, the mean serum calcium level and the mean urinary calcium level in infants with urinary stones significantly were higher than the control group (Table 2).

Table 1. Frequency Distribution of Infants Based on Gender

Group	Sex	Frequency	Percent	
Case	Girl	22	44	$X^2 = 2.546$ P > .05
	Boy	28	56	
Control	Girl	30	60	
	Boy	20	40	

Table 2. Independent t-test results to compare serum levels of vitamin D, serum calcium and urinary calcium levels in two groups.

Variable	Group	Mean ± SD	*P*
Vit D, ng/mL	Case	41.49 ± 11.69	< .05
	Control	35.67 ± 6.76	
Ca, mg/dL	Case	9.63 ± 0.32	< .05
	Control	8.59 ± 1.21	
Ca/Cr Ratio	Case	0.15 ± 0.16	< .05
	Control	0.08 ± 0.02	

DISCUSSION

In addition to playing an important role in the health of the musculoskeletal system, vitamin D has important positive effects on the immune and cardiovascular systems and other organs.[19-23] Usually the amount of vitamin D in breast milk does not meet the needs of the infant, according to the American Breastfeeding Committee, 400 units of vitamin D is given orally daily to infants.[24]

Based on the findings of this study, which was performed on 50 infants with nephrolithiasis, it was shown that although the mean serum level of vitamin D and the serum level of calcium and Urine Ca/Cr ratio are in normal levels in these infants, but clearly are higher than infants without nephrolithiasis ($P \leq .05$). This finding suggests that routine intake of vitamin D during infancy can make infant prone to nephrolithiasis.

Because the body receives Vitamin D from various sources, more than physiological needs intake of vitamin D supplements in infants can lead to increase serum level of calcium and urinary calcium and in the presence of other risk factors such as climate, genetic, urinary tract infections, phototherapy, use of warmer and dehydration, the formation of urinary crystals and nephrolithiasis can be accelerated.[6,14,25-27]

A study in Shiraz by Fallahzadeh *et al*. on infants with urinary stones found that serum level of vitamin D was higher than healthy infants that could play an important role in the occurrence of urinary stones and it was recommended to deal with this, serum levels of vitamin D should be measured in these children.[28]

Another study by Abbaszadeh in Tehran at 2014 found that there was a direct link between serum levels of calcium and vitamin D, and that cases with bilateral kidney stones had higher serum levels of vitamin D.[29] In a meta-analysis performed by Henglong Hu, it was suggested that urolithiasis is associated with higher serum level of vitamin D.[11]

In a review article published by Letavernier, the effect of vitamin D on hypercalciuria and urinary stone formation was evaluated and concluded that taking vitamin D even during infancy increases the risk of urinary stone formation by increasing urinary calcium excretion.[30] The results of these studies are

consistent with the results of our research and all indicate an increased risk of nephrolithiasis with increased serum levels of vitamin D.

CONCLUSION

According to this study, it can be said that routine consumption of vitamin D during infancy increases urinary level of calcium and in the presence of other risk factors can lead to urinary stones in infants and young children.

Therefore, it is recommended that consumption of vitamin D supplements should be monitored during infancy by measuring serum levels of vitamin D.

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