Case Report

J Babol Univ Med Sci
Vol 19, Issu 2; Feb 2017. P:65-70

High Dose Oral Calcium Treatment in Patients with Vitamin D-dependent Rickets Type II

R. Vakili (MD)[1], S. Noroozi Asl (MD)[*1], M. Sezavar (MD)[2], H. Zaeri (MD)[3]

1.Department of Pediatrics Endocrinology, Faculty of Medicine, Mashhad university of Medical Sciences, Mashhad, I.R.Iran
2.Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, I.R.Iran
3.Neonatal and Children Health Research Center, Golestan University of Medical Sciences, Gorgan, I.R.Iran

J Babol Univ Med Sci; 19(2); Feb 2017; PP: 65-70
Received: Oct 6th 2016, Revised: Nov 26th 2016, Accepted: Jan 15th 2017.

ABSTRACT

BACKGROUND AND OBJECTIVE: Vitamin D-dependent rickets type II (VDDR2) is a rare genetic disorder caused by mutations in vitamin D receptor (VDR) and leads to resistance to biological effects of calcitriol. Based on the type of mutation, this disease is resistant to calcitriol even at high doses of calcitriol and successful treatment of these patients requires hypocalcemic modification through administration of high doses of calcium and bypassing the intestinal defect in VDR signaling. In addition to the need for frequent hospitalization and high costs, intravenous administration of calcium is associated with complications and problems such as arrhythmia and sepsis, venous catheter infection and hypercalciuria. This study aims to report the positive treatment effects of high doses of oral calcium in 4 patients with vitamin D-dependent rickets type II.

CASE REPORT: In this study, 4 patients with vitamin D-dependent rickets type II, diagnosed based on clinical and biochemical symptoms of rickets with alopecia, underwent therapy using high doses of oral calcium (300 mg/kg/day) in pediatric endocrinology and metabolism center of Imam Reza hospital. After a short period, increased growth rate in height, strength and elasticity of muscles was observed in addition to biochemical improvements without serious side effects and even one patient started walking independently within the first week of therapy for the first time. Patients were regularly followed up in terms of height and weight, growth rate and biochemical factors including calcium, phosphorus and alkaline phosphatase every 3 months for one year.

CONCLUSION: Regardless of the type of mutation in vitamin D receptor, it is suggested that a 3-6 months trial of high dose oral calcium be started in each patient with vitamin D-dependent rickets type II, particularly for patients whose disease was diagnosed at lower ages.

KEY WORDS: *Vitamin D-dependent rickets type II, High dose oral calcium, Vitamin D receptor, calcitriol.*

Please cite this article as follows:
Vakili R, Noroozi Asl S, Sezavar M, Zaeri H. High Dose Oral Calcium Treatment in Patients with Vitamin D-dependent Rickets Type II. J Babol Univ Med Sci. 2017;19(2):65-70.

• **Corresponding author: S. Noroozi Asl (MD)**
Address: Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, I.R.Iran
Tel: +98 51 38593045
E-mail: Norouziasls@mums.ac.ir

[DOR: 20.1001.1.15614107.1395.19.2.9.8]
[DOI: 10.22088/jbums.19.2.65]

Introduction

Despite all the preventive measures and the use of supplements, vitamin D deficiency is still one of the most important causes of rickets. If rickets occurs in infants who regularly received 400 IU of vitamin D daily or did not recover from rickets after appropriate treatment with vitamin D, there is the possibility of genetic rickets due to defect in the synthesis or the function of vitamin D. The vitamin D absorbed by body transforms into 1,25(OH)2D3 or calcitriol and preserves the normal level of blood calcium by bonding to vitamin D receptor (1–6).

The inactivating mutations in vitamin D receptor homozygously cause resistance to the biological effects of calcitriol and the incidence of vitamin D-dependent rickets type II or hereditary vitamin D-resistant rickets. Bone pain, muscle weakness, hypotonia and hypocalcemia-induced seizures are among the clinical manifestations of this disease. Death due to respiratory complications caused by abnormal chest movements is possible. Pain in the lower limbs leads to delay in movements and learning motor skills. Frequent fractures, hypoplasia and dental caries are quite common in these patients. Alopecia is a valuable diagnostic finding in this specific type of rickets that exists in 80% of patients and usually exists since birth or appears during the first months of life. Alopecia may be the first symptom of rickets and it is easier to diagnose this disease in the families who have another child with this problem (7).

The extent and severity of alopecia is varied in patients with similar mutation. The severity of alopecia is directly related to the degree of resistance of the receptor and patients with alopecia are resistant to treatment with supraphysiologic dose of all types of vitamin D. The existence of alopecia and the lack of response to calcitriol are important results for differentiating vitamin D-dependent rickets type II from other causes of rickets (8). The receptor's lack of response to calcitriol causes hypocalcemia, secondary hyperparathyroidism, hypophosphatemia and severe increase in alkaline phosphatase despite the very high level of calcitriol (300–1000 pg/µL). The level of hydroxyvitamin D is normal, unless the patient simultaneously suffers from vitamin D deficiency. The skeletal radiographic findings illustrate rachitic changes at the end of the long bones.

Spontaneous improvement in rickets has been reported at the ages of 7 to 15 years and around the time of puberty, probably due to decrease in the skeletal calcium needs and activation of the mechanisms of intestinal absorption of calcium, which are independent of vitamin D (8–10). Diagnosis of vitamin D-dependent rickets type II with high levels of calcitriol was reported in a patient with rickets, which is proved by identification of the inactivating mutations in vitamin D receptor. More than 100 cases of vitamin D-dependent rickets type II and more than 45 types of mutation in vitamin D receptor have been reported so far (8).

There is no appropriate guideline for the treatment of vitamin D-dependent rickets type II and a successful treatment depends on the severity of hormone resistance. Most patients, particularly those with alopecia do not respond to treatment with calcitriol (in fact, the level of endogenous calcitriol is greatly increased) and a successful treatment requires modification and elimination of hypocalcemia and secondary hyperparathyroidism, which is achieved by intravenous administration of high dose calcium. The intravenous route bypasses the defect in intestinal absorption of calcium due to receptor dysfunction. However, the existence of a central catheter is its prerequisite and it is consequently accompanied by complications such as infection and sepsis, subcutaneous necrosis and cardiac arrhythmia and problems related to catheter blockage.

It is also requires frequent hospitalizations and high costs (11). Moreover, when the intravenous therapy stops, symptoms of the disease will return over time (8). Considering the reports regarding successful treatment of these patients using high dose oral calcium (300 mg/kg/day) and the absence of intravenous therapy problems and similar therapeutic effects, oral calcium is accepted as the preferred therapy in these patients.

It is suggested that oral calcium be administered for patients undergoing intravenous therapy after modification of rachitic changes (12–14). This study aims to report the positive therapeutic effects of high dose oral calcium in 4 patients with vitamin D-dependent rickets type II. Therefore, 4 patients diagnosed with vitamin D-dependent rickets type II who underwent therapy with high dose oral calcium are presented in this study.

Case Report

4 patients with clinical symptoms of rickets and alopecia, in whom the biochemical and radiological results confirmed vitamin D-dependent rickets type II, who were hospitalized in pediatric endocrinology and

[DOR: 20.1001.1.15614107.1395.19.2.9.8]
[DOI: 10.22088/jbums.19.2.65]

metabolism center of Imam Reza hospital in Mashhad, underwent therapy with high dose oral calcium (300 mg/kg/day):

Havva, a 2 years and 9 months old girl from Golestan province (Turkmen Sahara), was the first child of the family with normal birth weight and height. She had normal hair at birth and the signs of alopecia appeared on the entire body during the first months. She was admitted to the hospital because of short stature, curvature of the lower limbs and broadening in the extremities without history of seizures when she was 1 year old.

According to laboratory results, the level of calcium and phosphorus was low, while the level of alkaline phosphatase and parathormone was high and radiologic evidence of rickets could be observed at the end of long bones, the patient was diagnosed with vitamin D-dependent rickets type II and the treatment started with low dose oral calcium with 10 cc calcium every 6 hours daily and 1 microgram calciteriol. Since December 2015, the treatment started with 3 gr oral calcium and 1 µg calciteriol.

A few months after the beginning of treatment, signs of increased height growth, increased muscular strength and elasticity, decreased bone pain, decreased number of falls and better control of walking could be observed. Moreover, the improved biochemical results could be observed as increased calcium and phosphorus and decreased alkaline phosphatase. The radiologic changes were not clear and the recovery process was not observed in alopecia (table 1).

Table 1. Laboratory findings of the first sick child, before and after the treatment

Variable \ Time	Before treatment	Beginning	3 months later
Age(months)	24 months	32 months	35 months
Weight (kg)	12	11.5	11
Height (cm)	82	84	87
Calcium(mg/dl)	8.5	9.5	9.8
Phosphate(mg/dl)	2.8	4.5	3.8
Alp (mg/dl)	2767	1992	1899

Meysam, a 3-year-old boy from Turkmen Sahara, was the first child of the family (parents were cousins) and had a distant kinship relationship with the first case in our study (Havva). He had a birth weight of 3300 g and height of 51 cm, born by vaginal delivery. His mother noticed alopecia in him within the first months. When he was 8 months old, despite receiving vitamin supplements due to wide fontanelle and inappropriate height growth, he was examined and the tests demonstrated low calcium and phosphorus and very high alkaline phosphatase and the hand radiograph demonstrated signs of rickets and he was treated with 600000 IU vitamin. However, there was no sign of improvements.

When he was 16 months, he was hospitalized because of hypocalcemia-induced seizures and was referred to Pediatric Endocrinology and Metabolism Service in Mashhad after receiving intravenous calcium. He had a weight of 9 kg and a height of 70 cm at the age of 18 months. Based on examinations, he had alopecia in the whole body, wide fontanelle, wide wrist and wide ankle and he walked with frequent falls and could not run or climb up the stairs. The level of calcium, phosphorus and phosphatase were 6.3 mg/dl, 2.6 mg/dl and 3100 mg/dl, respectively along with normal level of vitamin D. The treatment started with 1 microgram of calcitriol and 10 cc calcium every 6 hours daily and the treatment changed to 3 g oral calcium and 4 micrograms of calcitriol from December2015 (table 2).

Table 2. Laboratory findings of the second sick child, before and after the treatment

Variable \ Time	Before treatment	Beginning	3 months later
Age(months)	24 months	32 months	35 months
Weight(kg)	9.5	10	11
Height(cm)	76	79	81.5
Calcium(mg/dl)	6.3	8.5	8
Phosphate(mg/dl)	4.2	3.9	2.8
Alp(mg/dl)	3600	926	442

After starting treatment with oral calcium, in addition to biochemical improvements such as increased calcium and phosphorus and decreased alkaline phosphatase, the patient could walk and run independently and the number of falls decreased while the elasticity and strength of muscles clearly improved. The pain in lower limbs decreased and the height growth rate increased, but no obvious change could be observed in radiologic findings and the severity of alopecia. Mehdi, a 4-year-old boy from Bandar Torkaman, from non-related parents with alopecia totalis, short stature,

[DOR: 20.1001.1.15614107.1395.19.2.9.8]
[DOI: 10.22088/jbums.19.2.65]

curvature and deformity of the lower limbs and history of hypocalcemia-induced seizures was diagnosed with this problem at the age 2 years. He was treated with 6 micrograms of calcitriol and 10 cc calcium every 6 hours daily.

From October 2015, his treatment changed to 3 g oral calcium and 4 micrograms of calcitriol daily (table 3). Clinically, the patient was able to walk after the beginning of treatment. The activity and mobility of the patient increased, whereas the bone pain and falls decreased and the height growth rate increased. Hamidreza, a 4-year-old boy from Chenaran (table 4), was the first child of the family. When he was one year old, he was diagnosed with rickets due to inability to sit and having wide fontanelle and was treated with vitamin D. However, he was referred to the Endocrinology and Metabolism Service after 8 months, due to lack of clinical response. Considering alopecia totalis, short stature, skeletal and biochemical changes of rickets and lack of response to vitamin D treatment, the patients was diagnosed with vitamin D-dependent rickets type II and was treated with 30 micrograms of calcitriol and 5 cc oral calcium every 6 hours. However, the patient had history of frequent hospitalizations (every month) to receive intravenous calcium (an average of 5.6-6 mg/dl).

The patient could not walk up to age of 4 and complained about severe pain in the lower limbs. One week after treatment with 3 g oral calcium, the patient dramatically started walking for the first time and the height growth rate and muscular strength increased after a while and he was not hospitalized for receiving intravenous calcium any more.

In addition to clinical improvements, the biochemical changes could be observed in the form of increase in calcium and phosphorus and decrease in alkaline phosphatase. Relative clinical and biochemical improvements could be observed in all the reported patients and we probably need more time to observe radiological changes. None of the treated patients revealed symptoms of constipation and gastrointestinal disorders and U/A control, Cal/Crt ratio and renal ultrasonography showed no sign of hypercalciuria. The patients were followed for 3 months in terms of weight and height, growth rate and biochemical factors such as calcium, phosphorus and alkaline phosphatase.

Table 3. Laboratory findings of the third sick child, before and after the treatment

Time / Variable	Before treatment	Beginning	3 months later	6 months later
Age (months)	48	52	55	58
Weight (kg)	15.7	16	16	17
Height (cm)	90	91	92	95
Calcium (mg/dl)	8.2	8.5	9.3	9.6
Phosphate (mg/dl)	3.7	4.5	6.3	4.62
Alp (mg/dl)	1232	1560	1143	1003

Table 4. Laboratory findings of the forth sick child, before and after the treatment

Time / Variable			Beginning	6 months later	8 months later	9 months later
Age (months)	28	35	39	45	47	48
Weight (kg)	10	10.2	10.5	10.8	11	12
Height (cm)	74	81	88	89	90	94
Calcium (mg/dl)	6.8	6.2	6.5	7.83	7.19	7.79
Phosphate (mg/dl)	3.6	2.6	2.6	2.89	3.98	4.02
Alp (mg/dl)	8626	11194	9699	6075	4165	3560

Discussion

In this study, 4 patients with vitamin D-dependent rickets type II underwent treatment with 300 mg/kg/day oral calcium and after a short period, improvements could be observed in clinical symptoms including increased strength, elasticity and muscle power and gaining the ability to walk and run. One of the patients was able to walk for the first time after one week. Weight and height growth rate increased significantly, while the severity of alopecia did not change considerably. The patients did not complain about

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[DOI: 10.22088/jbums.19.2.65]

digestive issues and U/A control, Cal/Crt ratio and renal ultrasonography showed no sign of hypercalciuria and nephrocalcinosis. According to a study by Hochberg et al., gastrointestinal complications and abdominal discomfort was prevalent in patients during the first months of treatment with high dose oral calcium. However, this issue disappeared with gradual increase in the dosage and after this adaptation period, no complaint or side effect could be observed in patients (12).

Improvements in biochemical findings revealed as increased calcium and phosphorus and decreased alkaline phosphatase. However, we could not observe clear changes in radiologic symptoms and we probably need more time to see improvements in radiologic symptoms. Perhaps densitometry can be effective in this regard. Wong et al. started treatment with high dose oral calcium in an 8-year-old girl with vitamin D-dependent rickets type II and after observing clinical and radiologic improvements stated that high dose oral calcium is an appropriate therapy for these patients (13).

Sakati et al. treated a 6-year-old boy with vitamin D-dependent rickets type II and after observing considerable clinical and radiologic improvements by receiving 3 – 4 g oral calcium concluded that high dose oral calcium can be an appropriate substitute for calcitriol (14). In the study by Hochberg et al. among 10 patients with vitamin D-dependent rickets type II, 8 patients were first treated with intravenous calcium using intra-caval catheter.

After observing signs of radiologic improvements of rickets, treatment with 3.5–9 g/m2/day oral calcium started and 2 patients, aged 1.1 and 2.2 year, were treated with oral calcium immediately after diagnosis. One week after the treatment started, bone pains started to disappear and the height growth rate increased in both groups. Calcium, phosphorus and alkaline phosphatase returned to normal levels. However, improvements in radiologic symptoms of rickets appeared faster in the group receiving intravenous therapy. Patients who received intravenous calcium experienced various issues and complications. Cardiac arrhythmias, particularly bradycardia during the first week of treatment and cases of septicemia (with a frequency of once every 8 months) occurred in all patients and led to hospitalization, discontinuation of calcium therapy and intravenous antibiotic. The central venous catheter with the frequency of one in 14 months needed to be replaced under general anesthesia and hypercalciuria was observed in all patients after concentration of calcium reached normal level, yet no sign of nephrocalcinosis was observed in ultrasonography (12). In the study of Huahg et al. on a patient with vitamin D-dependent rickets type II, maintenance of the intravenous route was not possible due to recurrent infections and enteral high dose calcium using gastric tube proved to be effective in modification of metabolic disorders of the disease (15). Considering that hyperparathyroidism plays a significant role in the pathophysiology of rachitic changes, Srivastava T et al. used cinacalcet (which is used to reduce hyperparathyroidism in renal failure) with high dose oral calcium to treat patients with vitamin D-dependent rickets type II.

This led to modification of hyperparathyroid and other metabolic disorders of rickets (16). In a study by Azemi et al. on a patient with vitamin D-dependent rickets type II, after receiving intravenous calcium with daily infusion more than 18 hours for 3.5 months, high dose oral calcium constantly kept the serum levels of calcium above 8 mg/dl (17).

Due to similar therapeutic effects, lack of major side effects and easy administration of high dose oral calcium in patients with vitamin D-dependent rickets type II, a trial period of 3–6 months of high dose oral calcium is suggested to be started in each patient, particularly those who are diagnosed at lower ages, regardless of the type of mutation in vitamin D receptor. In addition, in patients who are resistant to oral therapy at first and undergo intravenous therapy, changing the treatment method to high dose oral calcium (3.5–9 g/kg/daily) after clinical improvements in rickets improves muscle strength and elasticity, increases height growth rate and decreases bone pains and fractures.

Acknowledgments

Hereby, we express our deepest sense of gratitude and indebtedness to all professors, students and personnel of pediatric Endocrinology and Metabolism center of Imam Reza hospital in Mashhad and Ms. Nooshin Abdollahpour for their cooperation.

[DOR: 20.1001.1.15614107.1395.19.2.9.8]
[DOI: 10.22088/jbums.19.2.65]

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[DOR: 20.1001.1.15614107.1395.19.2.9.8]
[DOI: 10.22088/jbums.19.2.65]