© Pediatr Med Rodz 2019, 15 (2), p. 152–156
DOI: 10.15557/PiMR.2019.0026

Agnieszka Koniarek-Maniecka, Małgorzata Olszowiec-Chlebna, Daniela Podlecka, Joanna Jerzyńska, Iwona Stelmach

Received: 24.10.2018
Accepted: 28.11.2018
Published: 31.07.2019

The effect of treatment with calcitriol and cholecalciferol on calcium and phosphate metabolism in patients with cystic fibrosis

Wpływ leczenia kalcytriolem i cholekalcyferolem na gospodarkę wapniowo-fosforanową u pacjentów chorych na mukowiscydozę

Department of Paediatrics and Allergy, Korczak Paediatric Centre, Copernicus Memorial Hospital in Lodz, Medical University of Lodz, Łódź, Poland
Correspondence: Professor Iwona Stelmach, MD, PhD, Department of Paediatrics and Allergy, Korczak Paediatric Centre, Copernicus Memorial Hospital in Lodz, Medical University of Lodz, Piłsudskiego 71, 90-329 Łódź, Poland, tel.: +48 42 207 47 26, fax: +48 42 677 63 58, e-mail: alergol@kopernik.lodz.pl

Abstract

Cystic fibrosis patients are characterised by disorders of fat-soluble vitamin absorption and bone metabolism. The aim of this study was to compare the effect of 3-month supplementation with calcitriol and cholecalciferol on calcium–phosphate balance in patients with cystic fibrosis. The study included 23 cystic fibrosis patients aged from 6 to 19 years. It was a cross-over, placebo-controlled trial. There were 3 visits during which blood and urine were collected for analysis. The patients were treated with cholecalciferol (1,000 IU/day) or calcitriol (0.5 μg 1,25OHD) and placebo, and then received medications according to the cross-over regimen. The second visit took place after 3 months. The concentration of calcium, phosphate, parathyroid hormone and 25OHD were determined in blood serum; calcium/creatinine index was determined in urine. It was shown that after 3-month supplementation with calcitriol, the phosphate concentration decreased significantly, from 1.48 mmol/L (±*SD* 0.27 mmol/L) to 1.35 mmol/L (±*SD* 0.20 mmol/L) ($p = 0.021$). The calcium concentration increased significantly after 3 months of calcitriol treatment, from 3.50 mg/dL (±*SD* 2.60 mg/dL) to 4.35 mg/dL (±*SD* 3.35 mg/dL) ($p = 0.001$). The level of parathyroid hormone decreased significantly after 3 months of treatment with calcitriol, from 36.54 pg/mL (±*SD* 17.61 pg/mL) to 29.36 pg/mL (±*SD* 13.08 pg/mL) ($p = 0.019$). In the cholecalciferol supplementation group, there were no changes in phosphate, calcium or parathyroid hormone concentrations. Supplementation with either cholecalciferol or calcitriol did not affect serum 25OHD levels. In patients with cystic fibrosis, calcitriol supplementation at a dose of 0.5 μg is safe and has a more beneficial effect on the calcium–phosphate metabolism and bone metabolism than that of cholecalciferol at a daily dose of 1,000 IU.

Keywords: vitamin D, children, cystic fibrosis

Streszczenie

U chorych na mukowiscydozę obserwuje się zaburzenia wchłaniania witamin rozpuszczalnych w tłuszczach, a także zaburzenia metabolizmu kości. Celem niniejszej pracy było porównanie wpływu 3-miesięcznej suplementacji kalcytriolem i cholekalcyferolem na gospodarkę wapniowo-fosforanową u pacjentów z mukowiscydozą. Badanie objęło 23 pacjentów w wieku 6–19 lat cierpiących na tę chorobę. Było to badanie *cross-over*, kontrolowane placebo. Odbyły się 3 wizyty, podczas których pobrano krew oraz mocz do analizy. Pacjenci byli leczeni cholekalcyferolem (1000 IU/dobę) lub kalcytriolem (0,5 μg 1,25OHD) oraz placebo, a następnie otrzymali leki zgodnie ze schematem *cross-over*. Druga wizyta odbyła się po 3 miesiącach. W surowicy krwi oznaczono stężenia: wapnia i fosforanów, parathormonu oraz 25OHD; w moczu określono wskaźnik wapniowo-kreatyninowy. Wykazano, że w wyniku 3-miesięcznej suplementacji kalcytriolem stężenie fosforanów znacząco się zmniejszyło, tj. z 1,48 mmol/l (±*SD* 0,27 mmol/l) do 1,35 mmol/l (±*SD* 0,20 mmol/l) ($p = 0,021$). Stężenie wapnia wzrosło istotnie statystycznie po 3 miesiącach leczenia kalcytriolem, tj. z 3,50 mg/dl (±*SD* 2,60 mg/dl) do 4,35 mg/dl (±*SD* 3,35 mg/dl) ($p = 0,001$). Poziom parathormonu statystycznie znacząco zmniejszył się po 3 miesiącach leczenia kalcytriolem, tj. z 36,54 pg/ml (±*SD* 17,61 pg/ml) do 29,36 pg/ml (±*SD* 13,08 pg/ml) ($p = 0,019$). W grupie suplementacji cholekalcyferolem nie obserwowano zmian stężenia fosforanów, wapnia i parathormonu. Suplementacja cholekalcyferolem i kalcytriolem nie wpłynęła na surowicze stężenie 25OHD. U chorych na mukowiscydozę suplementacja kalcytriolem w dawce 0,5 μg jest bezpieczna i ma korzystniejszy wpływ na gospodarkę wapniowo-fosforanową i metabolizm kostny niż cholekalcyferolem w dobowej dawce 1000 IU.

Słowa kluczowe: witamina D, dzieci, mukowiscydoza

INTRODUCTION

Cystic fibrosis (CF) is a relatively common genetic disorder in the population of white people[1–3]. The clinical picture is usually dominated by typical respiratory signs and symptoms. However, most patients are diagnosed with exocrine pancreatic dysfunction and present with gastrointestinal signs and symptoms[1–3]. Despite optimal treatment, CF leads to malnutrition in certain patients. This is mainly a consequence of insufficient food intake (relative to requirement), but also of worse usage of delivered nutrients due to impaired pancreatic function and inadequate secretion of pancreatic enzymes. This factor does affect survival in CF patients[1,3].

In CF patients, attention should be paid to increased energy requirement, which is caused by enhanced basic metabolism and greater effort at respiration and cough, the struggle of the organism with frequent infections (particularly those with fever) and loss of nutrients excreted with faeces. Steatorrhea is the most common sign associated with impaired fat digestion or fat malabsorption in the gastrointestinal tract. Apart from appropriate nutrition, it is necessary to supplement pancreatic enzymes to replace the function of the insufficient pancreas and ensure better food digestion, and to additionally administer fat-soluble vitamins.

Despite pancreatic enzyme supplementation, fat malabsorption is still observed, including malabsorption of fat-soluble vitamins (A, D, E, K)[1,4,5]. The currently recommended vitamin D supplementation in CF patients aged from 1 year to 10 years is 800 IU daily (upper limit 2,000 IU daily), and in children over 10 years of age: 4,000 IU daily[2]. CF patients are more and more often diagnosed with bone metabolism disorders in the form of osteopenia and osteoporosis. Apart from a low vitamin D level, risk factors for these disorders may include corticotherapy, low physical activity and low body weight[1,2].

The basic role of vitamin D is to preserve mineral homeostasis by increasing bowel absorption and renal tubular reabsorption of calcium and phosphate. In bones, however, it is needed for proper mineralisation, remodelling and growth. It maintains appropriate calcium and phosphate serum levels. Moreover, it stimulates collagen production by osteoblasts[1–3]. Whether delivered with food or synthesised in the skin, vitamin D undergoes double hydroxylation: in the liver to 25-hydroxyvitamin D and in the kidneys to the active form of vitamin D, i.e. 1,25-hydroxyvitamin D, called calcitriol. Although 1,25OH-hydroxyvitamin D is the active form of vitamin D, its serum level should not be routinely assessed. This is because the serum levels may vary depending on a disease entity and because its half-life is merely 6–8 hours[1,4]. The main circulating vitamin D metabolite is 25OH vitamin D whose serum level is the indicator of the amount of vitamin D in the body. The half-life of this form of vitamin D is approximately 3 weeks. Its optimal level is the one at which calcium absorption from the gastrointestinal tract is not decreased and the parathyroid hormone (PTH) concentration is not increased[2,3]. When suspecting hypersensitivity to or overdose of vitamin D, it is indicated to assess the calcium/creatinine index, which expresses the amount of calcium in urine in relation to excreted creatinine.

The aim of this study was to compare the effect of 3-month supplementation with calcitriol and cholecalciferol on calcium–phosphate balance in patients with CF.

MATERIAL AND METHODS

The study was carried out from September 2015 to April 2016. Twenty-three patients with CF, both boys and girls, aged 6–19 years (mean age 16.5 years) were enrolled. They were all patients of the Cystic Fibrosis Clinic of Korczak Paediatric Centre in Lodz, Poland. Children who received oral steroids within 6 months before the analysis were excluded.

This was a cross-over, placebo-controlled trial. It envisaged 3 visits. At the first visit, the participants were informed about the aim of the analyses. Also, 10 mL of blood and a urine sample were collected for laboratory tests. The patients were randomised to the following groups:

- cholecalciferol: oral 25OHD (1,000 IU daily) and placebo instead of calcitriol;
- calcitriol: oral 0.5 μg of 1,25OHD and placebo instead of cholecalciferol; the calcitriol dose was based on the available literature[6].

At the second visit, conducted 3 months later, blood and urine samples were again collected for laboratory analyses; all patients received medications in accordance with the cross-over regimen. At the third visit, 3 months after the second, blood and urine were collected again for the assessment of calcium–phosphate metabolism. Blood and urine were sampled at the same time of the day.

The following parameters were assayed from blood serum: 1) calcium and phosphate levels with standard methods offered by a laboratory; 2) PTH concentrations with chemiluminescence using an Elecsys kit with the measuring range of 1.20–5,000 pg/mL, within-run precision of 4.0% and between-run precision of 4.3% for PTH of 62.2 pg/mL; 3) vitamin D metabolite concentration, i.e. 25-hydroxycholecalciferol (25OHD) level, with radioimmunoenzymatic assay (RIA) using a 25-OH-vitD-RIA-CT kit with the test analytic sensitivity of 0.6 ng/mL, within-run precision of 5.2% and between-run precision of 3.3% for 25OHD 0 ± 1.2 ng/mL. As for urine, calcium excretion in relation to creatinine was calculated (calcium/creatinine index).

Consent to participate was obtained in writing from parents or legal guardians and from children over 16 years of age. The study was approved by the University Ethics Committee (No. RNN/21/14/KE).

 DOI: 10.15557/PiMR.2019.0026

Statistical analysis

The evaluated features were described using means (a measure of location) and measures of dispersion, i.e. standard deviation and confidence interval of 95% as well as minimal and maximal values of the variable. The analysis involved mixed-effects regression models with elastic standard errors. Moreover, repeated measurements conducted separately in two tests (arms) and differences between these two arms were also taken into account. Results at the level of $p < 0.05$ were deemed statistically significant. All statistical calculations were conducted in Stata/Special Edition, version 14.2 (StataCorp LP, College Station, Texas, USA).

RESULTS

It was shown that 3-month supplementation with 0.5 µg of calcitriol contributed to an evident decrease in the phosphate concentration: from 1.48 mmol/L [± standard deviation (*SD*) 0.27 mmol/L] to 1.35 mmol/L (±*SD* 0.20 mmol/L) ($p = 0.021$) (Fig. 1). In the cholecalciferol supplementation group, there were no changes in phosphate levels.

After 3-month treatment with 0.5 µg of calcitriol, the calcium concentration increased significantly, from 3.50 mg/dL (±*SD* 2.60 mg/dL) to 4.35 mg/dL (±*SD* 3.35 mg/dL) ($p = 0.001$) (Fig. 2). There were no changes in serum calcium levels in the cholecalciferol supplementation group.

PTH levels significantly decreased after 3 months of treatment with 0.5 µg of calcitriol, from 36.54 pg/mL (±*SD* 17.61 pg/mL) to 29.36 pg/mL (±*SD* 13.08 pg/mL) ($p = 0.019$) (Fig. 3). In the cholecalciferol supplementation group, there were no changes in PTH concentrations.

There were no significant changes in 25OHD levels after supplementation with either cholecalciferol or calcitriol.

DISCUSSION

CF is a disease with vitamin D malabsorption and metabolic disorders. The gastrointestinal tract with normal structure and function, in particular the small bowel, liver and pancreas, is necessary to metabolise this vitamin. The gastrointestinal tract is a site of vitamin D absorption after its oral administration. The vitamin is metabolised in the liver, which is also where vitamin D binding proteins (DBPs), i.e. proteins needed for vitamin D transport, are produced. The intestinal-hepatic circulation, which changes with the patient's age, used medications or comorbidities, has a particular impact on vitamin D turnover[7]. According to recent reports on vitamin D supplementation in CF patients, it is difficult to increase serum 25OHD levels[8–10]. In these cases, it is necessary to administer higher vitamin D doses[11–14]. Hepatic problems in the course of CF are

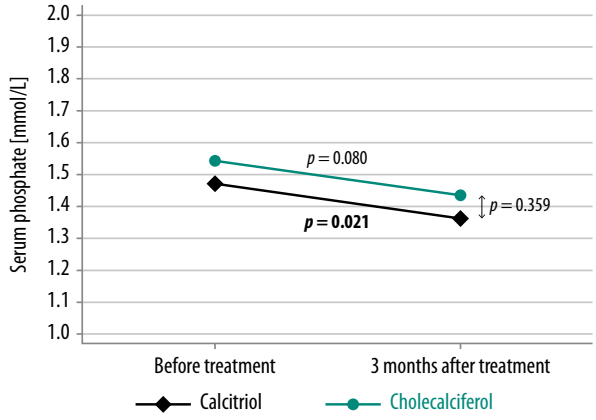

Fig. 1. Serum phosphate levels before treatment and after calcitriol and cholecalciferol supplementation

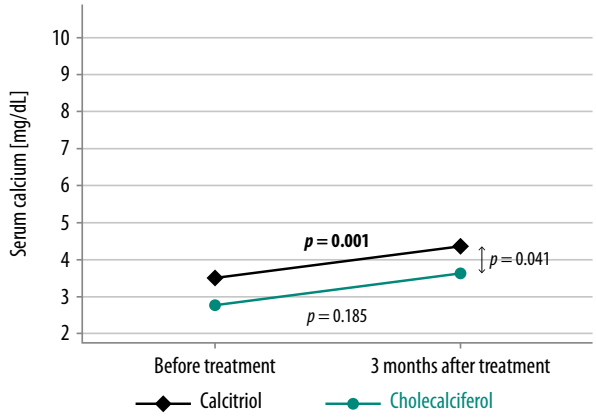

Fig. 2. Serum calcium levels before treatment and after calcitriol and cholecalciferol supplementation

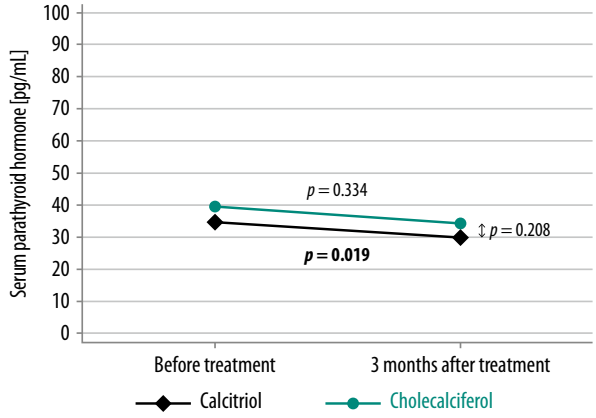

Fig. 3. Serum PTH levels before treatment and after calcitriol and cholecalciferol supplementation

DOI: 10.15557/PiMR.2019.0026

relatively early complications of this disease. Hepatic and hepatobiliary pathology is found in approximately 30% of patients[1,2]. Primary changes appear in the bile ducts. Lower production of bile of increased viscosity leads to impaired intrahepatic bile duct patency with inflammation that initiates the process of liver fibrosis[1,2].

This study revealed that supplementation with 0.5 μg of calcitriol contributed to an evident decrease in the phosphate concentration after 3 months, while no reduction was observed in the group treated with cholecalciferol at a daily dose of 1,000 IU. The calcium level increased in a statistically significant way after 3-month calcitriol supplementation, but there were no relevant increases in serum calcium levels in the group treated with cholecalciferol. PTH levels decreased significantly after 3-month calcitriol supplementation, whereas no changes were observed in the cholecalciferol supplementation group. There were no significant changes in 25OHD levels after supplementation with either cholecalciferol or calcitriol.

Rovner et al. have demonstrated that impaired hydroxylation of vitamin D at position 25 is a significant cause of abnormal vitamin D action in patients with chronic liver pathology other than bile malabsorption[3,4]. This can explain why calcitriol was effective in the CF patients in our study. Similar results have been presented by Brown et al.[8] who observed beneficial effects of 0.5 μg daily of calciferol on the phosphate–calcium metabolism as early as after 14 days of supplementation and noted no effects on serum 25OHD levels; the same was demonstrated in the present trial. In two cross-sectional studies[9,10] which investigated daily cholecalciferol supplementation at a daily dose of 400–1,600 IU, there was no improvement in terms of phosphate–calcium metabolism or an increase in serum 25OHD levels. Khazai et al.[11], on the other hand, observed a significant increase in serum 25OHD concentrations after administering 50,000 units of cholecalciferol weekly.

Short follow-up was a limitation of the presented study. However, an improvement in phosphate–calcium metabolism was observed even after this short calcitriol supplementation, and there was no calciuria as a poor prognostic factor of nephrolithiasis. Another limitation was a broad age range of the patients, which made it more difficult to standardise a mean daily dose in relation to vitamin D supplementation recommendations in CF[2].

To conclude, in patients with CF, calcitriol supplementation at a dose of 0.5 μg is safe and has a more beneficial effect on the calcium–phosphate metabolism and bone metabolism than that of cholecalciferol at a daily dose of 1,000 IU. Further long-term studies are needed to compare efficacy and safety of higher cholecalciferol doses with calcitriol supplementation in CF patients.

CONCLUSIONS

1. In patients with CF, calcitriol supplementation at a dose of 0.5 μg is safe and has a more beneficial effect on the calcium–phosphate metabolism and bone metabolism than that of cholecalciferol at a daily dose of 1,000 IU. The improvement of calcium–phosphate metabolism was independent of the serum 25OHD level.
2. There were no significant changes in 25OHD levels after supplementation with either cholecalciferol or calcitriol.
3. In the cholecalciferol supplementation group, there were no changes in phosphate, calcium and PTH concentrations.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations that could adversely affect the content of the publication and claim the right to publish it.

Funding/Support and role of the sponsor

The study was financed by the Medical University of Lodz; grant No 503/2-056-01/503-21-001.

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DOI: 10.15557/PiMR.2019.0026