An Open Label, Randomized Controlled Study of Oral Calcitriol for the Treatment of Proteinuria in Patients with Diabetic Kidney Disease

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Background: *The progression of diabetic kidney disease (DKD) is highly correlated with proteinuria. Previous studies have suggested that vitamin D treatment may reduce proteinuria and has the potential to delay the progression of renal disease.*
Objective: *To evaluate efficacy of oral calcitriol to decrease proteinuria in type 2 diabetic mellitus (T2DM) patients with DKD.*
Material and Method: *In this 16-week, open label, prospective, randomized controlled study, 91 patients with T2DM with estimated glomerular filtration rate (eGFR) greater than 15 ml/min/1.73 m^2 and urine protein to creatinine ratio (UPCR) greater than 1 g/g were enrolled. They were randomly assigned to receive either oral calcitriol 0.5 mcg twice weekly (n = 46) or without oral calcitriol (n = 45). The primary outcome was determined by the change of UPCR from baseline after 16 weeks of treatment of both groups.*
Results: *At randomization, the mean UPCR was 3.7 $\pm$ 2.2 g/g in the calcitriol group and 3.4 $\pm$ 2.1 g/g in the control group. The mean UPCR at 16-week follow-up was 2.9 $\pm$ 1.7 g/g in the calcitriol group and 3.5 $\pm$ 2.3 g/g in the control group. Percent changes in UPCR from baseline to the last evaluation in the calcitriol and control groups were -18.7% and + 9.9% ($p < 0.01$) respectively. Patients with 30% or more decrement in proteinuria occurred 43.5% of the time in the calcitriol group and 11.1% in the control group ($p < 0.01$). The eGFR and blood pressure did not differ significantly between the two groups. No serious adverse side effects were noted in either group.*
Conclusion: *Calcitriol treatment can reduce proteinuria in patients with DKD without serious adverse events.*

Keywords: *Diabetic kidney disease, Proteinuria, Calcitriol*

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Diabetic kidney disease (DKD) is the most common renal complication that often leads to end-stage renal disease (ESRD) and high mortality[1]. Despite recently developed treatments, DKD remains the leading cause of ESRD and accounts for almost 30-40% of all cases of ESRD in industrialized countries and Thailand[2]. Proteinuria is not only a marker of kidney disease progression but also a marker of cardiovascular risk[3]. Treatments that reduce proteinuria are considered beneficial to improve both kidney and cardiovascular risks in DKD patients[4]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) have proven renal protective effects that can decrease proteinuria and slow the subsequent loss of glomerular filtration rate (GFR) or retard progression of kidney disease[5].

However, DKD patients who have received ACEI and/or ARBs cannot completely avoid proteinuria and also have annual renal event rates of 15% or more[6]. Other treatments that can further reduce proteinuria may provide important ways to decrease the burden of kidney disease in diabetic patients. Previous studies suggest that vitamin D treatment may reduce proteinuria and has the potential to delay the progression of renal disease[7,8]. Recent randomized trials have shown that the vitamin D analogue, 19-nor-1-alpha-di hydroxyvitamin D2 (paricalcitol), can reduce proteinuria in patients with chronic kidney disease, including those with diabetes mellitus[7-9]. Calcitriol is an active vitamin D treatment that showed a modest antiproteinuric effect in patients with IgA nephropathy[7]. The purpose of the present study was to

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evaluate the efficacy of oral calcitriol in reducing proteinuria in type 2 diabetic mellitus (T2DM) patients with DKD.

Material and Method

This was a 16-week, open-label, prospective randomized controlled trial of oral calcitriol in T2DM patients with DKD. The ethical committee approved the present study and all patients signed an informed consent. At the out-patient departments of Rajavithi Hospital (Bangkok) and Banphaeo Hospital (Samutsakorn), patients with T2DM were recruited during February 2010 to August 2010. Eligible patients were patients at least 18 years of age who had a diagnosis of T2DM (American Diabetes Association's criteria)[10], stable clinical symptoms and treatment for diabetes and hypertension of at least 3 months, no previous vitamin D therapy, an estimated glomerular filtration rate (eGFR) of more than 15 ml/min/1.73 m^2 (calculated by using the 4-variable Modification of Diet in Renal Disease Study equation[11]) and a urinary protein to creatinine ratio (UPCR) of more than 1 g/g in 2 consecutive urine samples within 3 months of recruitment. Exclusion criterias were serum calcium (adjusted for serum albumin) greater than 10.0 mg/dl, serum phosphate greater than 5.2 mg/dl, uncontrolled blood pressure greater than 160/100 mmHg, pregnancy, breast feeding, active infection, malignancy or heart failure.

Patients were randomized into 2 groups. The calcitriol group received oral calcitriol (Rolcaltrol, Roche Pharmaceuticals, Switzerland), 0.25 mcg twice weekly added to the standard treatment and the control group received the standard treatment only. Through randomized visits, patients in the calcitriol group received oral calcitriol of 0.25 mcg weekly for 2 weeks. If their clinical and laboratory tests were stable after two weeks of low dose oral calcitriol treatment, the dose of oral calcitriol was increased to 0.50 mcg twice weekly and this regimen continued for 16 weeks. In the control group, patients received standard treatment for 16 weeks. Patients were followed for a total of six study visits: one screening, randomizing visit and then subsequently at 2, 4, 8, 12 and 16 weeks. Clinical status and laboratory tests were assessed on every visit. Fasting venous blood samples for plasma creatinine, calcium, phosphate, intact parathyroid hormone (iPTH), albumin, fasting blood sugar and HbA1c and spot urine samples for UPCR were performed at each visit. Serum and urine creatinine concentrations were measured by buffered kinetic Jeffe' reaction using a COBAS INTEGRA 800® analyzer (Roche Diagnostics, Indianapolis, IN, USA). The urinary protein concentration was determined using a turbidimetric method. Throughout the present study, all patients received the standard treatment for T2DM. Antihypertensive agents other than ACEI or ARBs were adjusted to maintain target blood pressures of 130 mmHg or less systolic and 80 mmHg or less diastolic. If patients had abnormal clinical symptoms that related to research medication or a corrected serum calcium level greater than 11.0 mg/dl, the medication was stopped and the subject was discontinued from the present study. Pill counts indicated mean adherence to the treatment regimen of greater than 90% in the calcitriol group. The primary outcome was determined by change of proteinuria and GFR levels between the baseline and week 16 measures in the calcitriol and control groups. Significant antiproteinuria was defined as a decrease in proteinuria by greater than 30%, a reduction beneficial by reducing both kidney risks[4,12]. Significant antiproteinuria over time between the two groups was one of the secondary end points.

Continuous variables are reported as mean $\pm$ standard deviation. Categorical variables are reported as frequency and percentage. Group comparisons were performed by independent sample t-test and Chi-square test. The sample size (assuming a 10% dropout rate) was estimated to yield a power of 95% to achieve a significance level of 0.05 using analysis of covariance. All statistical tests were conducted at a significance level of alpha = 0.05. Statistical analysis was performed using SPSS for Windows software, version 17.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Fig. 1 shows a diagram of the present study. A total of 99 patients were randomly assigned to either calcitriol (n = 51) or control group (n = 48). Five patients in the calcitriol group and three patients in the controls refused to participate or were inconvenient to follow-up. Patients in the calcitriol (n = 46) and control group (n = 45) attended throughout the present study. Baseline characteristics of the population are listed in Table 1; there were no significant differences between groups at baseline. Urinary protein excretion was normally distributed at baseline.

Fig. 2 shows mean UPCR of both study groups from baseline to week 16. At randomization, the mean UPCR was 3.7 $\pm$ 2.2 g/g in the calcitriol group and 3.4 $\pm$ 2.1 g/g in the control group. At week 16, the mean UPCR was 2.9 $\pm$ 1.7 g/g in the calcitriol group and 3.5 $\pm$ 2.3

Table 1. Demographics and patient characteristics

Characteristics	Control group (n = 45)	Calcitriol group (n = 46)	p-value
Age (years)	61.80 ± 11.90	59.70 ± 8.50	0.340
Female (%)	28 (62.2)	20 (43.5)	0.070
Duration of DM (years)	10.40 ± 5.90	11.90 ± 8.70	0.330
Systolic blood pressure (mmHg)	132.80 ± 16.40	134.10 ± 13.40	0.680
Diastolic blood pressure (mmHg)	70.60 ± 11.20	73.10 ± 11.70	0.310
ACE-inhibitors and/or ARBs (%)	24 (53.3)	28 (60.9)	0.450
Statins (%)	30 (66.7)	33 (71.7)	0.600
Laboratory values			
Hemoglobin (g/dl)	11.38 ± 1.80	11.35 ± 1.90	0.930
HbA1c (%)	7.03 ± 0.70	6.88 ± 0.80	0.380
Serum creatinine (mg/dl)	1.99 ± 0.70	2.13 ± 0.80	0.380
eGFR MDRD formula (ml/min/1.73 m^2)	36.51 ± 16.50	37.93 ± 18.30	0.700
Mean UPCR (g/g)	3.39 ± 2.10	3.73 ± 2.20	0.460
Serum total cholesterol (mg/dl)	180.36 ± 52.22	187.17 ± 51.01	0.810
Serum calcium (mg/dl)	9.24 ± 0.50	9.14 ± 0.50	0.390
Serum phosphorus (mg/dl)	3.81 ± 0.60	4.03 ± 1.10	0.270
iPTH (pg/ml)	63.44 ± 34.20	61.48 ± 35.10	0.780

Note: Results presented as mean ± SD
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; UPCR, urine protein-creatinine index; iPTH, intact parathyroid hormone
p > 0.05 for all comparisons between the two groups

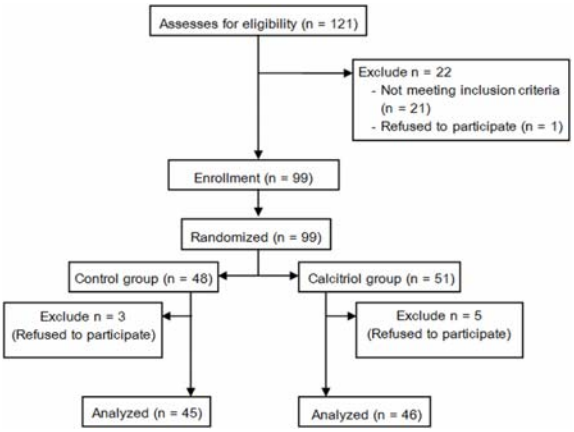

Fig. 1 Flow diagram of study

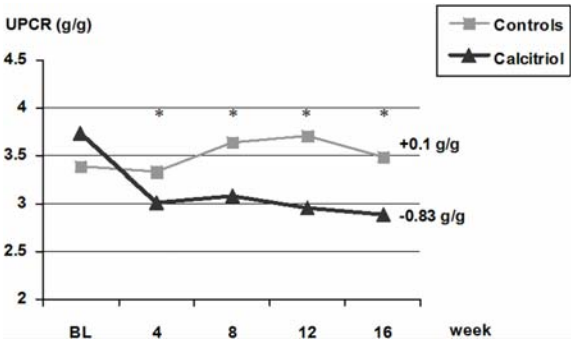

Fig. 2 Mean UPCR of both groups from baseline to week 16th. There was a significant decrease in UPCR from baseline to the last evaluation in the calcitriol group, BL, baseline, * = p < 0.05

g/g in the control group. In the calcitriol group, UPCR significantly decreased after the first 4 weeks of treatment.

Fig. 3 shows percent change of UPCR in both groups from baseline to week 16. Percent change of UPCR in the calcitriol group had also significantly decreased after the first 4 weeks of treatment. Changes in UPCR from baseline to the last evaluation were -18.7% for the calcitriol group and +9.9% for the control group (p = 0.004).

Fig. 4 shows the number of patients with a 30% or more decrease in proteinuria, or clinically significant antiproteinuria. Clinically significant antiproteinuria occurred in 43.5% of the calcitriol group and 11.1% of controls (p < 0.01).

Fig. 5 shows mean eGFR of both groups from baseline to week 16. At baseline, mean eGFR was 36.5 ± 16.5 ml/min/1.73 m^2 and 37.9 ± 19.3 ml/min/1.73 m^2 in the control and calcitriol groups, respectively. At 16-weeks after treatment, mean eGFR was 35.5 ± 17.6 ml/min/1.73

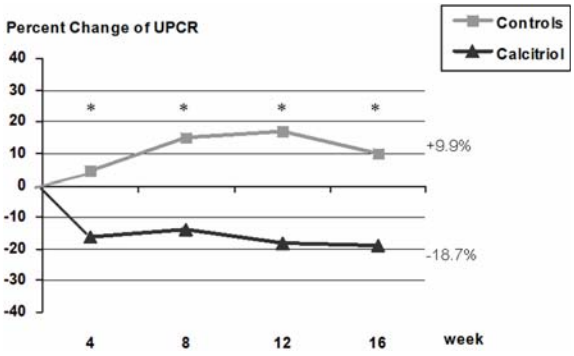

Fig. 3 Percent change of UPCR of both groups from baseline to week 16th. There was a significant decrease in percent change of UPCR from baseline to the last evaluation in the calcitriol group ($p < 0.05$), BL, baseline, * = $p < 0.05$

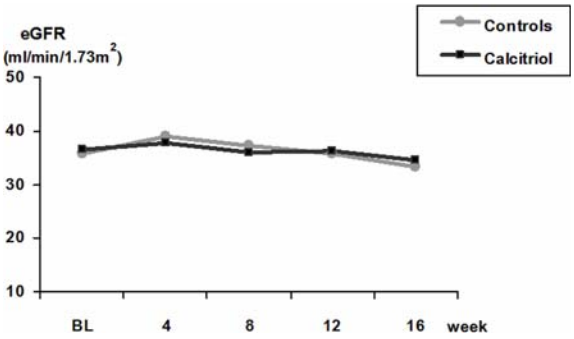

Fig. 5 Mean eGFR (ml/min/1.73m^2) of both groups from baseline to week 16. There are no significant differences

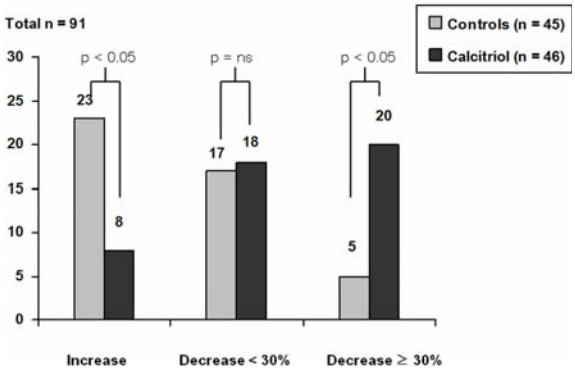

Fig. 4 A 30% or more decrement in proteinuria or clinical significant antiproteinuria occurred in 43.5% patients of the calcitriol group (20 of 46) and 11.1% patients of controls group (5 of 45; $p < 0.01$)

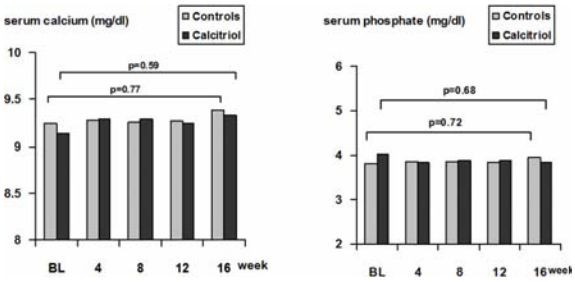

Fig. 6 Mean serum calcium and phosphate levels in controls and calcitriol groups. There are no significant differences, BL, baseline

m^2 and 36.9 $\pm$ 19.8 ml/min/1.73 m^2, respectively. There was no significant difference between mean eGFR from baseline to last evaluation in either group or between the two groups ($p = 0.83$).

Fig. 6 shows that neither mean serum calcium or phosphate level was significantly different for either group throughout the study. No episode of hypercalcemia or hyperphosphatemia was detected. Serum iPTH levels from baseline to week 16 in both groups were not significantly different (63.4 $\pm$ 34.2 to 70.9 $\pm$ 31.7 pg/ml in the control group and 61.4 $\pm$ 35.1 to 67.1 $\pm$ 48.4 pg/ml in the calcitriol group, $p = 0.17$). Mean systolic and diastolic blood pressure did not change significantly throughout the course of the present study in either group. Neither was there any significant change in overall serum albumin or HbA1c level throughout the present study period.

There were six adverse events in the control group and four adverse events in the calcitriol group. In the control group, there were five cases of upper respiratory tract infection and one case of hospitalization due to hyperglycemia. In the calcitriol group, there were two cases of upper respiratory tract infection, one case of abnormal sweating and one case of hospitalization due to congestive heart failure. These adverse events were assessed as unrelated to the research medication when they occurred during the study period.

Discussion

Active vitamin D is a potent regulator of cell differentiation and immune system function. It regulates mesangial cell smooth-muscle phenotypes in a TGF beta mediated manner, ameliorates glomerular injury and decreases proteinuria in diabetes mode[13,14]. In subtotally nephrectomized rats, vitamin D decreased podocyte loss and podocyte hypertrophy[15] and it prevented progressive glomerulosclerosis without adversely affecting calcium and phosphate metabolism[16]. The protective effect was a result of blockade of the compensatory renin increase by the

vitamin D analogue, leading to more effective renin angiotensin aldosterone system (RAAS) inhibition. Antihypertensive drugs using inhibitors of the RAAS such as ACEI and ARBs can reduce proteinuria and improve cardiovascular and renal outcomes[17]. More recent has been the recognition of the interaction of vitamin D with the RAAS[10]. Li YC[18] has demonstrated that vitamin D is a potent negative endocrine regulator of the RAS as a suppressor of renin biosynthesis. Vitamin D suppresses renin expression independently of its effect on calcium metabolism, the volume and salt sensing mechanisms or angiotensin II feedback regulation. Calcitriol is the natural activator of the vitamin D receptor and it is produced by the kidney, but plasma calcitriol concentration declines with reduced eGFR. In patients with chronic kidney disease (CKD), lower calcitriol concentrations strongly correlate with diabetes, higher UPCR and lower eGFR[19]. Calcitriol supplements may be given to DKD patient with higher UPCR and lower eGFR.

In the present study, patients with T2DM with high UPCR and low eGFR received oral calcitriol, 0.25 mcg twice weekly, added to standard treatment, and were compared with patients who received standard treatment only. Twice weekly oral calcitriol therapy had a significant antiproteinuric effect in these patients. Proteinuria decreased in the calcitriol group more than the control group. Clinically significant antiproteinuria occurred more in the calcitriol group than in the control group. The renal function or eGFR was unchanged in calcitriol and control groups. Serum calcium, phosphate and iPTH levels in both groups were not significantly different throughout the present study. Serious adverse effects were not different in the two groups. Calcitriol treatment reduced proteinuria in patients with DKD without serious adverse events. This result confirms findings in previous studies. There are few published studies of renoprotection by vitamin D and vitamin analogue among patients with CKD not on dialysis. Agarwal R[8] analyzed data from randomized controlled trials comparing paricalcitol with placebo for the treatment of hyperparathyroidism in CKD. Urine dipstick for proteinuria was the assessment tool. A significant decrease in proteinuria occurred in 51% of the paricalcitol group with 0.5 μg calcitriol, twice weekly for 12 weeks in ten patients with immunoglobulin A nephropathy. Proteinuria decreased after treatment without a change in renal function or blood pressure. Alborzi P[9] studied twenty-four patients with CKD randomly assigned to treatment with placebo or paricalcitol, 1 or 2 mcg/d for 1 month. At 1 month, the treatment to baseline ratio of proteinuria was 1.35 (95% CI: 1.08 to 1.69; $p = 0.01$) with placebo, 0.52 (95% CI: 0.40 to 0.69; $p < 0.001$) with a 1-mcg dose and 0.54 (95% CI: 0.35 to 0.83; $p = 0.01$) with a 2-mcg dose. These studies suggested benefits from vitamin D for the treatment of proteinuria in patients with CKD or DKD. Reduction of proteinuria through vitamin D might be an important means to retard progression of kidney disease and decrease risk of cardiovascular events in these patients.

Limitations of the present study include small sample size and short time to observe the best outcomes such as mortality, hospitalizations or progression to ESRD. Vitamin D level was not evaluated. The appropriate dosage of calcitriol for maximum antiproteinuria remained undetermined in the present study. Future larger studies such as a double-blind, randomized controlled trial would be helpful for this purpose.

Conclusion

The present study shows that treatment with active vitamin D calcitriol led to a significant decrease in proteinuria in T2DM patients with DKD without serious adverse effects. In DKD patients with uncontrolled proteinuria, calcitriol may be helpful to reach antiproteinuria goals.

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Potential conflicts of interest

None.

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การรับประทาน calcitriol เพื่อรักษาโปรตีนในปัสสาวะในผู้ป่วยโรคไตจากเบาหวาน: การศึกษาแบบเปิดที่มีการควบคุมและสุ่ม

อุดม ไกรฤทธิชัย, รุ่งระวี มหรรณพกุล, สกานต์ บุนนาค

ภูมิหลัง: *การเสื่อมของโรคไตจากเบาหวานสัมพันธ์กับปริมาณโปรตีนในปัสสาวะ การศึกษาก่อนหน้านี้พบว่าการให้วิตามินดีช่วยลดโปรตีนในปัสสาวะและช่วยชะลอการเสื่อมของไตได้*

วัตถุประสงค์: *ต้องการประเมินผลของการรับประทาน calcitriol ในการลดโปรตีนในปัสสาวะในผู้ป่วยโรคไตจากเบาหวานชนิดที่สอง*

วัสดุและวิธีการ: *การศึกษาแบบเปิดที่มีการควบคุมและสุ่มนาน 16 สัปดาห์ ในผู้ป่วยโรคไตจากเบาหวานชนิดที่สอง จำนวน 91 ราย ที่มีหน้าที่ไตมากกว่า 15 ml/min/1.73 m^2 และมี urine protein to creatinine ratio (UPCR) มากกว่า 1 g/g ผู้ป่วยจะถูกสุ่มออกเป็นสองกลุ่ม คือ กลุ่มได้รับ calcitriol 0.5 mcg รับประทานสองครั้งต่อสัปดาห์ (n = 46) หรือกลุ่มควบคุมที่ได้รับการรักษาตามมาตรฐาน (n = 45) โดยมีการวัดผลจากการเปลี่ยนแปลงของ UPCR ระหว่างเริ่มต้นและ16 สัปดาห์หลังการรักษาของทั้งสองกลุ่ม*

ผลการศึกษา: *เมื่อเริ่มสุ่มพบว่าผู้ป่วยกลุ่ม calcitriol จะมี UPCR 3.7 $\pm$ 2.2 g/g และกลุ่มควบคุมมี UPCR 3.4 $\pm$ 2.1 g/g ภายหลัง16 สัปดาห์ของการรักษาผู้ป่วยกลุ่ม calcitriol จะมี UPCR 2.9 $\pm$ 1.7 g/g และกลุ่มควบคุมมี UPCR 3.5 $\pm$ 2.3 g/g ส่วนร้อยละการเปลี่ยนแปลงของ UPCR ระหว่างเริ่มต้นและ16 สัปดาห์หลังการรักษาพบว่าผู้ป่วยกลุ่ม calcitriol และกลุ่มควบคุมเท่ากับ -18.7% และ +9.9% ($p < 0.01$) ตามลำดับ ผู้ป่วยที่มีการลดลงของโปรตีนในปัสสาวะมากกว่า 30% ในผู้ป่วย กลุ่ม calcitriol และกลุ่มควบคุมเท่ากับ 43.5% และ11.1% ($p < 0.01$) ตามลำดับ หน้าที่ไตและความดันโลหิตไม่เปลี่ยนแปลงทั้งสองกลุ่ม ไม่พบภาวะแทรกซ้อนรุนแรงในผู้ป่วยทั้งสองกลุ่ม*

สรุป: *Calcitriol สามารถลดโปรตีนในปัสสาวะในผู้ป่วยโรคไตจากเบาหวานโดยไม่พบภาวะแทรกซ้อนรุนแรง*