

Effect of Paricalcitol on Bone Density After Kidney Transplantation

Analysis of 2 Transplant Centers

Zuzana Žilinská,¹ Ivana Dedinská,² Ján Breza,¹ Ľudovít Laca²

¹Department of Urology With Kidney Transplant Center, University Hospital Bratislava and Medical Faculty of Comenius University, Bratislava, Slovakia

²Surgery Clinic and Transplantation Center, University Hospital in Martin and Jessenius Medical Faculty of Comenius University, Bratislava, Slovakia

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Introduction. The Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines on the management of bone disease in patients with chronic kidney disease recommend periodic measurement of serum calcium, phosphorus, vitamin D, and parathyroid hormone levels after kidney transplantation, with the frequencies that will vary according to the severity of bone disease and graft function. Paricalcitol, a selective vitamin D receptor activator, is indicated in the prevention and treatment of secondary hyperparathyroidism.

Material and Methods. We retrospectively evaluated the effect of treatment with paricalcitol among our kidney transplant recipients. We monitored the effect of paricalcitol on bone density; the plasma levels of parathyroid hormone, calcium, and phosphorus; and proteinuria and calciuria. Comparisons were made between these parameters before treatment and 12 months after treatment.

Results. Eighty-eight kidney transplant recipients with a mean age at the time of transplantation of 47.1 ± 10.5 years were receiving paricalcitol. On average, paricalcitol was included into the treatment for 48 months from transplantation (median, 27 months). The patients had significantly improved bone density ($P < .001$), significantly lower parathyroid hormone levels ($P < .001$), and significantly decreased proteinuria ($P = .02$) after 12 months of treatment. During the treatment with paricalcitol, the immunosuppressive therapy, dose of prednisone, body mass index, and vitamin D levels had not significantly changed. Nor had any significant change occurred to graft function.

Conclusions. Paricalcitol is an effective therapy for secondary hyperparathyroidism in kidney transplant recipients.

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INTRODUCTION

Kidney transplantation is an effective modality for treatment of the end-stage kidney disease. While successful kidney transplantation reverses many problems of uremia which are not corrected by dialysis therapy, osteodystrophy (disorders of bone remodeling and modeling) persist; 90% to 100% of kidney transplant patients have histological

evidence of osteodystrophy and osteopenia (reduced bone mass) following transplantation. Most importantly, the loss of bone mass in the early posttransplant period produces osteopenia and osteoporosis (bone mass reduction more than 2 standard deviations below young adult peak bone mass according to the World Health Organization). In addition, a sizable number of patients suffer

from avascular necrosis, usually in the first 2 years following transplantation.¹

In ideal conditions, any abnormalities of the calcium-phosphate metabolism are adjusted after transplantation. Uremia, calcemia, and production of calcitriol are adjusted; the resistance of the skeleton to parathyroid hormone (PTH) and vitamin D are reduced; and then the level of PTH is decreased.² The persistence and severity of hyperparathyroidism (hyperparathyroidism) after kidney transplantation is relatively frequent and is primarily associated with the timing and its magnitude in the pretransplant period and with presence of parathyroid adenomas.³⁻⁵ Although the pathophysiology of persistent hyperparathyroidism after transplantation is not fully clarified, it is likely related to the presence of parathyroid adenomas in the pretransplant phase whose cells have low density of calcitriol receptors (vitamin D receptors), calcium-sensing receptor in the plasma membrane, and receptors for phosphatonin FGF-23.⁶⁻⁸

Although advances in the management of transplantation have improved its outcome, a high morbidity rate that affects the survival of the graft and the patient still exists, and that is mainly related to cardiovascular disease, rejection, infection, cancer, and bone disease.⁹ The Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines on the management of bone disease in patients with chronic kidney disease recommend for posttransplantation, periodic measurement of serum calcium, phosphorus, vitamin D, and PTH levels with the frequency that will vary according to the severity of bone disease and function of the transplanted kidney.¹⁰ Calcitriol is indicated in the event of hyperparathyroidism, but its use is limited by the value of calcemia. In the event of persisting hyperparathyroidism, the use of nutritional supplements of vitamin D may be an adequate therapy to restore the levels of 25-hydroxyvitamin D.^{11,12}

Paricalcitol, a selective vitamin D receptor activator, is indicated in the prevention and treatment of secondary hyperparathyroidism. Several analyses (however, only in small groups of patients) confirmed that paricalcitol after kidney transplantation reduces the values of PTH, has a positive effect on proteinuria, and is easily tolerated. When compared with any other analogs, paricalcitol causes less significant hypercalcemia

and hyperphosphatemia, which is related to the lower effect on the transport proteins for calcium and phosphorus in the bowels.¹³ There is little information on the use of paricalcitol in patients after kidney transplantation. This study evaluated the effect of treatment with paricalcitol in kidney transplant recipients.

MATERIAL AND METHODS

Study Population

We retrospectively evaluated the effect of treatment with paricalcitol on laboratory and clinical parameters in patients with end-stage kidney disease, after receiving a kidney transplant at the Transplant Center Bratislava and the Transplant Center Martin. The monitored parameters were evaluated at the time of beginning the treatment with paricalcitol and 12 months of treatment with paricalcitol. The patients were at various time periods from kidney transplantation, 48.1 months on average after kidney transplantation.

Data Collection

The following parameters were recorded: age at the time of transplantation, sex, history of rejection (and the type of rejection), treatment of rejection, history of parathyroidectomy, the value of bone density (standard, osteopenia, osteoporosis, or osteomalation), treatment of hyperparathyroidism (calcium carbonicum, paricalcitol, vitamin D, cinacalcet, rocalcrol, bisphosphonate, or any other biologic treatment), type of immunosuppression (tacrolimus, cyclosporine A, mTOR inhibitor, mycophenolate mofetil, and prednisone). We also documented the dose of prednisone and paricalcitol; body mass index; serum creatinine and graft function (using the Chronic Kidney Disease-Epidemiology Collaboration formula); serum levels of PTH, calcium, and phosphorus; and levels of proteinuria and calciuria. The given parameters were identified at the time of the beginning the treatment with paricalcitol and 12 months after treatment with paricalcitol. Bone density was measured in the L3 and L4 vertebral area and assessed by dual-energy radiographic absorption.

Statistical Analyses

We used the certified statistical program MedCalc (version 13.1.2, Ostend, Belgium) for statistical evaluation and applied the following statistical

analyses: the Student *t* test, the chi-square test, and the correlation coefficients. A *P* value less than .05 was considered significant.

Ethics

All procedures performed in the study involving human participants were approved by the ethics standards of the institutional and national research committees and were in compliance with the 1964 Helsinki Declaration and its later amendments.

RESULTS

Eighty-eight kidney transplant recipients were retrospectively identified whose treatment included paricalcitol for a minimum period of 12 months. The cohort was composed of 56 men (63.6%) and 32 women (36.4%). The average age at the time of transplantation was 47.1 ± 10.5 years. On average, paricalcitol was included in the treatment 48 months from transplantation (median, 27 months from transplantation).

The Table summarizes the monitored parameters at the beginning and 12 months of treatment with paricalcitol. Patients treated for a minimum of 12 months had significantly improved bone density and significantly lower PTH and phosphorus levels; On the other hand, the value of calcemia and calciuria had significantly increased (Figures 1 to 4). A significant decrease in proteinuria was also recorded after 12 months of treatment with paricalcitol, corresponding to a significant increase in the value of plasma albumin. Five patients were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, whose proteinuria level was not affected by the use of those medications. After 12 months of treatment, a lower percentage of the patients required vitamin D and calcium carbonate in their treatment regimen.

During the treatment, the dose of paricalcitol had not been changed. Due to certain undesirable gastroenterological effects of treatment with paricalcitol, 2 patients were excluded from

Characteristics at Baseline and 12 Months of Treatment With Paricalcitol

Characteristics	Baseline	12 Months	<i>P</i>
Bone density (standard), %	23.9	55.0	< .001
Osteopenia, %	38.6	14.8	< .001
Osteoporosis, %	40.9	30.7	.16
Osteomalation, %	2.3	0	.16
Treatment with calcium carbonate, %	28.4	5.1	< .001
Calcium carbonate dose, mg/d	1250 ± 1000	1950 ± 1170	< .001
Paricalcitol dose, mg/d	4.2 ± 2.8	4.4 ± 2.9	.64
Treatment with vitamin D, %	90.9	56.7	< .001
Cholecalciferol dose, drops per week	18 ± 10	15 ± 10	.054
Treatment with other medications*, %	15.9	11.4	.39
Treatment with bisphosphonate, %	13.6	11.4	.66
Biologic treatment, %	6.8	6.8	> .99
Treatment with tacrolimus, %	90.9	92.0	.80
Treatment with cyclosporine, %	6.8	5.7	.77
Treatment with mTOR inhibitor, %	4.5	2.3	.43
Treatment with mycophenolate mofetil, %	97.9	100	.18
Treatment with prednisone, %	90.9	85.2	.25
Prednisone dose, mg/d	7.6 ± 3.7	6.9 ± 2.8	.1619
Body mass index, kg/m ²	26.5 ± 4.3	26.9 ± 4.8	.56
Serum creatinine, μ mol/L	170.5 ± 88.4	165.2 ± 90.9	.70
Glomerular filtration rate, mL/s	0.74 ± 0.41	0.84 ± 0.47	.14
Serum albumin, g/L	40.8 ± 5.3	45.1 ± 3.7	< .001
Serum vitamin D, ng/mL	26.3 ± 10.0	29.1 ± 10.4	.07
Parathyroid hormone, pg/mL	256.6 ± 179.2	111.6 ± 59.6	< .001
Serum calcium, mmol/L	2.3 ± 0.2	2.5 ± 0.1	< .001
Serum phosphorus, mmol/L	1.4 ± 0.5	1.0 ± 0.2	< .001
Calciuria, mmol/L	2.7 ± 2.4	4.3 ± 4.1	.002
Proteinuria, g/d	1.113 ± 0.869	0.881 ± 0.548	.02

*Includes cinacalcet, hydrochlorothiazide, and rocaltol.

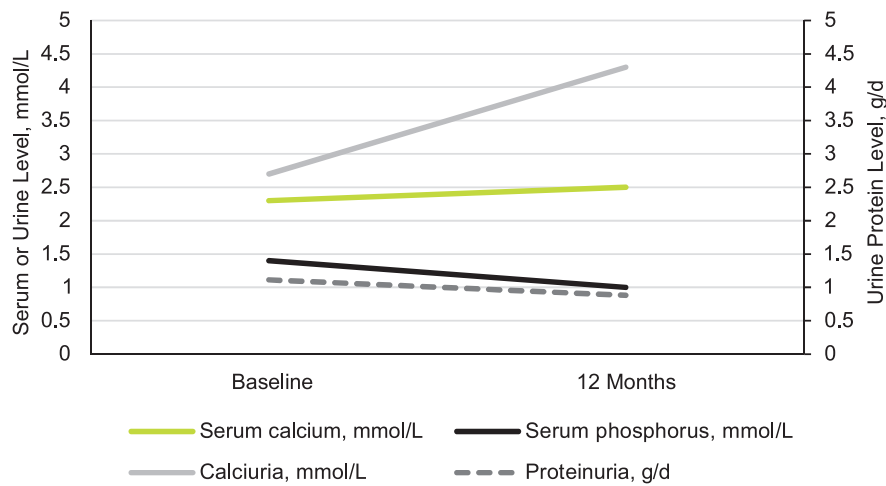


Figure 1. Changes in serum calcium and phosphorus and calciuria and proteinuria during paricalcitol treatment.

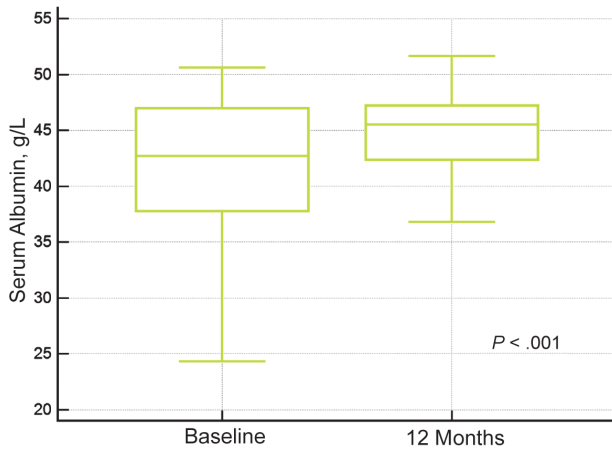


Figure 2. Changes in serum albumin in the paricalcitol-treated patients.

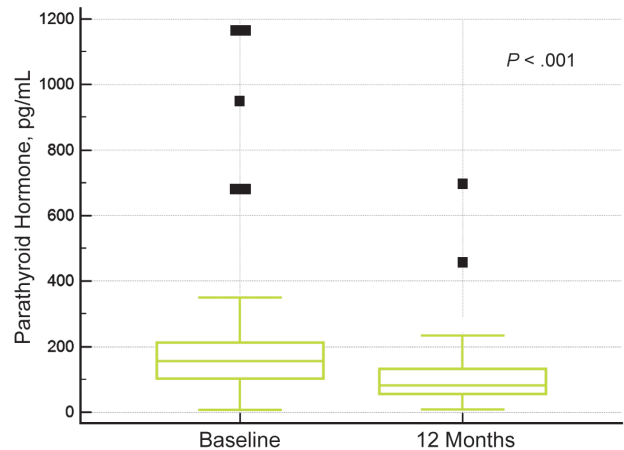


Figure 4. Changes in parathyroid hormone in the paricalcitol-treated patients.

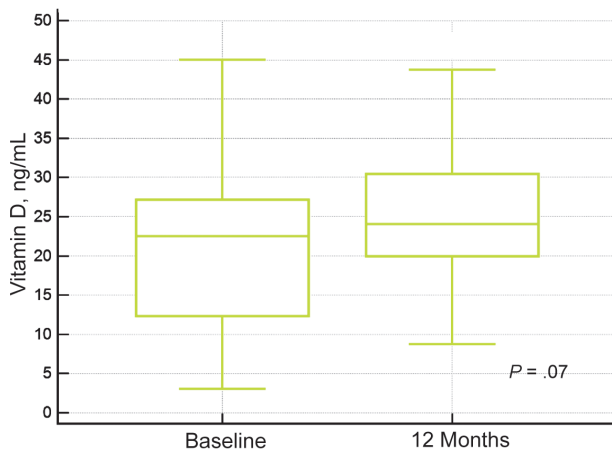


Figure 3. Changes in serum vitamin D in the paricalcitol-treated patients.

monitoring. The other patients tolerated the treatment well, and no other undesirable effects of the treatment with paricalcitol were recorded. During the treatment, there was no significant change in the immunosuppressive treatment, the dose of prednisone, body mass index values, and vitamin D levels. Neither had any significant change occurred in the function of the grafts.

DISCUSSION

Our patients who were treated with paricalcitol after kidney transplantation had significantly decreased values of PTH, and at the same time, during the 12 months of taking paricalcitol, we recorded a significant improvement in the bone density. Amer and colleagues examined the effect

of oral paricalcitol on posttransplant secondary hyperparathyroidism by conducting an open-label randomized trial in 100 incident kidney transplant recipients.¹⁴ Their analysis confirmed that the incidence of hyperparathyroidism after 12 months of treatment with paricalcitol was 29% versus 63% in the control patients, which confirms our findings. Another analysis which confirms our results is a retrospective multicenter study of Borrego Utiel and coworkers.¹⁵ Their analysis with 24-month follow-up contained 69 patients, 12 and more months after kidney transplantation with stable function of the graft, and paricalcitol taken for a minimum of 12 months. The authors recorded a decrease in PTH by 30% versus and recorded no significant changes in the serum values of calcium and phosphorus.¹⁵

In our analysis, we recorded a significant increase of calcemia. However, the value of calcium still remained within the reference range, and no hypercalcemia was recorded. Moreover, the treatment with paricalcitol resulted in an improvement of hypocalcemia that had frequently been observed before the treatment. Finally, the increase of plasma calcium levels related to the significant decrease in the number of patients who also needed to take calcium carbonate in the treatment with paricalcitol.

An interesting and important finding is the significant increase in bone density or significant increase in the number of patients with normal bone density, 12 months after treatment with paricalcitol. In the analysis of 43 patients after kidney transplantation with secondary hyperparathyroidism, Trillini and colleagues confirmed 6 months after treatment with paricalcitol that the serum bone-specific alkaline phosphatase and osteocalcin decreased with paricalcitol therapy only, and that the L3 and L4 vertebral mineral bone density, assessed by dual-energy radiographic absorption, significantly improved with paricalcitol at 6 months.^{12,13}

Another message of our study is that paricalcitol supplementation may reduce urinary protein excretion in the recipients of kidney transplants with secondary hyperparathyroidism. We confirmed the effect of paricalcitol on the decrease of proteinuria, and we also confirmed an increase in the serum value of albumin. The fact that paricalcitol significantly decreases proteinuria in

patients with chronic kidney disease is proven by several analyses.^{16,17} The number of studies on the effect of paricalcitol on proteinuria after kidney transplantation is limited and those are on very small groups. A study carried out on 58 patients who were monitored for a period of 18 months while taking paricalcitol confirmed a significant decrease of proteinuria by more than 50%.¹⁷ In addition to proteinuria, the authors confirmed the effect of paricalcitol on lowering PTH level.¹⁷

Taking paricalcitol was recorded in our analysis without any serious undesirable effects, similar to adverse effects reported also by the abovementioned studies. In our group, paricalcitol was excluded from treatment in only 2 patients due to gastroenterological problems, which represented 2.3% of the patients. No worse (or better) function of the graft was recorded during treatment with paricalcitol.

The limitation of the present study was the heterogeneity of our group in the terms of time from transplantation and retrospective monitoring. In spite of that, our analysis is assessed as a contribution confirming the effect on secondary hyperparathyroidism in the patients after kidney transplantation in a larger group of patients.

CONCLUSIONS

Paricalcitol is an effective therapy for secondary hyperparathyroidism in kidney transplant recipients. We demonstrated a significant decrease in PTH and proteinuria after 12 months of treatment with paricalcitol. The patients treated with paricalcitol for more than 12 months had significantly improved bone density, and paricalcitol was perfectly tolerated without recording any serious undesirable effects.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
doc MUDr Ivana Dedinská, PhD
Surgery Clinic and Transplant Center, University Hospital Martin,
Kollárova 2, 036 01 Martin, Slovak Republic
Tel: +421 43 420 3920
Fax: +421 43 423 0131
E-mail: idedinska@yahoo.co.uk

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