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Submission date: 18-Mar-2020 12:24PM (UTC+0800)

Submission ID: 1277399157

File name: rathyroidism_A_Case_Series_Focus_on_TRAP5b,_b-ALP,_and_DKK-1.pdf (863.5K)

Word count: 4314

Character count: 22095

Paricalcitol for CKD-MBD Associated with Secondary Hyperparathyroidism: A Case Series Focus on TRAP5b, b-ALP, and DKK-1

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Info Article

Submitted: 6-12-2018

Revised: 9-3-2019

Accepted: 13-3-2019

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ABSTRACT

Chronic kidney disease (CKD) lead to secondary hyperparathyroidism (SHPT) that caused by phosphate retention and hypocalcemia. This condition known as mineral and bone disorder (CKD-MBD). The increase in parathyroid hormone would increase bone turnover that result in an increased risk of bone fractures, and vascular calcification. These will increase the levels of tartrate-resistant acid phosphatase 5b (TRAP5b), and bone-specific alkaline phosphatase (b-ALP), which is a marker of bone turnover, and also dickkopf-related protein 1 (DKK-1), which is an inhibitor of the Wnt pathway. Secondary hyperparathyroidism in CKD also caused by calcitriol deficiency. Paricalcitol is a synthetic calcitriol analogue used to reduce parathyroid hormone (iPTH) with minimal calcemic and phosphatemic activity. Vitamin D receptor activation by paricalcitol will decrease TRAP5b, b-ALP, and DKK-1. In this study we reported 9 cases of CKD-MBD with Hemodialysis (HD) and associated with SHPT. Four of nine cases received 5µg paricalcitol every HD (twice a week) while the others five is not. Level of iPTH, phosphate, calcium, TRAP5b, b-ALP, and DKK-1 were measured before initiation of study and after three months treatment. According to this study, the paricalcitol administration suppresses the increase in iPTH level, bone turnover and vascular calcification showed by decreasing or suppresses the increase b-ALP, TRAP5b, DKK-1 levels without increasing calcium and phosphate levels.

Keywords: secondary hyperparathyroidism, paricalcitol, TRAP5b, b-ALP, DKK-1.

INTRODUCTION

Deranged mineral metabolism in patient with chronic kidney disease (CKD) result not only in bone disease, but a higher risk of cardiovascular disease and reduce survival, through the development of vascular calcification, which is known as CKD-Mineral and Bone Disorder (CKD-MBD). CKD-MBD is a systemic condition that manifests as abnormalities in parathyroid hormone (PTH), calcium, phosphorus and vitamin D; bone abnormalities and extraskeletal calcification which shown by Tartrate-resistant acid phosphatase 5b (TRAP-5b), and bone-specific alkaline phosphatase (b-ALP) (Fukugawa, *et al.*, 2013). In patients with CKD-MBD a calcitriol deficiency leads to the development of secondary HPT (sHPT) both by direct and indirect effects (Llach, *et al.*, 1998). Beside that, calcitriol deficiency also reduces

activity of vitamin D receptor that suppressing dickkopf-related protein 1 (DKK-1) expression (Cianferotti, and Demay, 2007).

Paricalcitol is an analogue of calcitriol that suppresses iPTH secretion while having only minor effects on serum level of calcium and phosphate (Lacy, *et al.*, 2011). Levels of iPTH have a positive correlation with bone turnover rate (ie, both resorption and formation) and vascular calcification (Jilka *et al.*, 2010 and Shetty *et al.*, 2016). So that Paricalcitol therapy in CKD-MBD effectively decreases osteoblast activity (b-ALP level) (Coyne *et al.*, 2013), serum TRAP-5b as a marker of bone resorption and DKK-1 as an inhibitor of Wnt pathway that have a role in vascular calcification. The aim of the study was to analyze changes of serum levels calcium, phosphate, intact parathyroid hormone (iPTH),

Table I. Baseline characteristics of the nine cases

Patient	Sex	Age (yr)	Etiology of ESRD	Body surface area (m ²)	HD Duration (Months)	
Paricalcitol	1	Male	43	NDN	1.84	130
	2	Male	70	DN	1.81	68
	3	Male	62	NDN	1.92	18
	4	Female	64	NDN	1.45	33
Without Paricalcitol	5	Male	50	DN	1.89	42
	6	Male	51	NDN	2.07	54
	7	Female	75	NDN	1.52	19
	8	Male	55	DN	2.14	19
	9	Female	38	DN	1.72	37

DN: Diabetic nephropathy; NDN: Non-diabetic nephropathy

TRAP5b, b-ALP, and DKK-1 on CKD-MBD patient with sHPT who received and without paricalcitol for three months.

MATERIAL AND METHODS

This study was cohort prospective observational to evaluate the effect of paricalcitol in CKD-MBD associated with secondary hyperparathyroidism. The inclusion criteria were hemodialysis patient with end stage renal disease and MBD, age more than 18 years, iPTH serum concentration ≥ 150 pg/mL, calcium serum concentration ≤ 11 mg/dL, phosphate serum concentration ≤ 10.2 mg/dL, with or without paricalcitol therapy. The exclusion criteria was patient with severe liver injury with Child-Pugh Score 10-15. Blood serum withdrawn twice, first before paricalcitol therapy and the second was 3 month after paricalcitol therapy. Analyzed was done for the serum concentration of calcium, phosphate, PTH, b-ALP, TRAP5b, and DKK-1.

Case illustration

In this study we present nine patients who developed CKD-MBD with hemodialysis (HD) at a hospital in Surabaya City, Indonesia. The patients grouped into 2 groups, first group contain 4 patients with paricalcitol therapy and second group contain 5 patients without paricalcitol therapy. Baseline characteristics of nine patients (Table I). Serum level of calcium, phosphate, iPTH, TRAP-5b, b-ALP and DKK-1 were measured twice, before initiation of study (t_0) and after 3 months (t_1). Result of paricalcitol group (Table II) and without paricalcitol group (Table III).

Besides, the correlation test was also performed among serum level of iPTH with TRAP5b, b-ALP, DKK-1 and the correlation of

TRAP5b and b-ALP, TRAP5b and DKK-1, also b-ALP and DKK-1.

Case 1: A 45-year-old man with hypertension, end stage renal disease (ESRD). Level of calcium, phosphate, iPTH, b-ALP, TRAP5B, and DKK-1 decreased after 3 months of paricalcitol. Another therapy was also given to this patient such as risedronate, and lanthanum carbonate; **Case 2:** A 70-year-old man with diabetic nephropathy, hypertension, ESRD. Level of calcium, iPTH, b-ALP, and DKK-1 decreased but level of phosphate, and TRAP5b increased after 3 months of paricalcitol. Another therapy was also given to this patient such as lanthanum carbonate; **Case 3:** A 62-year-old man with hypertension, ESRD. Level of b-ALP, and TRAP5B decreased but level of calcium, phosphate, iPTH, and DKK-1 increased after 3 months of paricalcitol. During treatment level of uric acid also increased from 5.54mg/dL to 7.31mg/dL. Another therapy was also give to this patient such as calcium acetate; **Case 4:** A 64-year-old woman with hypertension, ESRD. Level of calcium, b-ALP, and DKK-1 decreased but level of phosphate, iPTH, and TRAP5b increased after 3 months of paricalcitol. During treatment level of uric acid also increased from 4.83mg/dL to 6.78mg/dL. Another therapy was also given to this patient such as risedronate, and calcium acetate; **Case 5:** A 50-year-old man with diabetic nephropathy, hypertension, end ESRD. Patient has history of GERD with treatment of cisapride. Level of calcium, and DKK-1 decreased but level of iPTH, b-ALP, and TRAP5b increased without change on phosphate level after 3 months. Level of uric acid also increased from 6.75mg/dL to 8.54mg/dL; **Case 6:** A 51-year-old man with hypertension, ESRD. Level of calcium, iPTH, b-ALP, TRAP5b, and DKK-1 increased but level of phosphate decreased after 3 months. Another

Table II Serum levels and changes of calcium, phosphate, iPTH, in paricalcitol group

Patient	Calcium (mg/dL)			Phosphate (mg/dL)			iPTH (pg/mL)		
	t ₀	t ₁	Δ t ₁ - t ₀	t ₀	t ₁	Δ t ₁ - t ₀	t ₀	t ₁	Δ t ₁ - t ₀
1	9.5	9.2	-0.3	5.84	5.74	-0.10	627.3	578.7	-48.6
2	10.8	10.3	-0.5	6.21	6.64	0.43	544.4	378.4	-166.0
3	8.0	8.1	0.1	4.94	5.69	0.75	751.8	816.8	65.0
4	9.4	8.3	-1.1	2.55	4.15	1.60	542.4	1165.0	622.6
Mean	9.4	9.0	-0.4	4.88	5.56	0.67	616.5	734.7	118.2
SD	1.1	1.0	0.5	1.65	1.03	0.71	98.5	338.2	349.2

therapy was also given to this patient such as calcium acetate; **Case 7:** A 75-year-old woman with hypertension, ESRD. Level of calcium, phosphate, and b-ALP decreased but level of iPTH, TRAP5b, and DKK-1 increased after 3 months. Another therapy was also given to this patient such as risedronate, and calcium acetate; **Case 8:** A 55-year-old man with diabetic nephropathy, hypertension, ESRD. Level of phosphate, iPTH, b-ALP, TRAP5B, and DKK-1 increased but level of calcium decreased after 3 months; **Case 9:** A 38-year-old woman with diabetic nephropathy, hypertension, ESRD. Level of iPTH, b-ALP, TRAP5B, and DKK-1 increased but level of calcium and phosphate decreased after 3 months. Another therapy was also given to this patient such as calcium acetate.

RESULTS AND DISCUSSION

Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) is a systemic disorder of mineral and bone metabolism due to CKD manifested by abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism, abnormalities in bone turnover, mineralization, volume, linear growth, or strength, vascular or other soft tissue calcification (KDIGO, 2013). As kidney function continues to decline and the GFR falls less than 30 mL/min/1.73m² (0.29 mL/s/m²), phosphorus excretion continues to decrease and calcitriol production decreases, causing PTH levels to begin to rise significantly, leading to sHPT (Dipiro, 2013).

The excessive production of PTH leads to hyperplasia of the parathyroid glands, which decreases the sensitivity of the parathyroid glands to serum calcium levels and calcitriol feedback, further promoting sHPT. Most dramatic consequence of sHPT is alterations in bone turnover and the development of renal osteodystrophy (ROD) (Dipiro, 2013). Paricalcitol is a synthetic vitamin D analog which binds to and

activates the vitamin D receptors (VDR) in kidney, parathyroid gland, intestine and bone, thus reducing PTH levels and improving calcium and phosphate homeostasis (Lacy, et al., 2011).

Level of iPTH in circulation reflects bone turnover, a better correlation of iPTH with bone turnover markers especially TRAP5b and b-ALP has been reported (Fukugawa, et al., 2013). DKK-1 change in CKD is not only influenced by iPTH but also by inflammation cytokines such as IL-6 and TNF-α (Lee and Kalluri, 2010; Yao et al., 2011; Yeremenko et al, 2015). Administration of paricalcitol could reduce iPTH level which affected decline bone turnover marker and inhibit Wnt pathway (He et al., 2011; Cozzolino et al., 2014).

Table II, III, IV and V showed that before initiation of study (t₀) serum levels of calcium and phosphate were in normal range, while serum levels of iPTH, TRAP5b, b-ALP, and DKK-1 increased from normal range. This is in accordance with the pathophysiology of CKD-MBD. There were a homeostatic between calcium and phosphate by increasing PTH that will increase the impact on bone turnover, and also decrease of VDR activity. Those caused increase of TRAP5b, b-ALP and DKK-1 (Fukugawa et al., 2013; Cianferotti and Demay, 2007; Saliba and El-Haddad, 2009).

Generally, after three month from initiation of study there were no changes on serum levels of calcium and phosphate in 2 groups, while in paricalcitol group iPTH and TRAP5b increased although not as much as in without paricalcitol group. b-ALP and DKK-1 increased in without paricalcitol group while decreased in paricalcitol group.

The selectivity of paricalcitol in VDR has a little effect on absorption of calcium and phosphate in intestine (Lacy et al., 2011; Slatopolsky et al., 2003). Other factors which affected levels of

Table III Serum levels and changes of b-ALP, TRAP5B, and DKK-1 in paricalcitol group

Patient	b-ALP (U/L)			TRAP5B (U/L)			DKK-1 (pg/mL)		
	t ₀	t ₁	Δ t ₁ - t ₀	t ₀	t ₁	Δ t ₁ - t ₀	t ₀	t ₁	Δ t ₁ - t ₀
1	35.3	29.1	-6.2	7.3	8.2	0.9	2871	2275	-596
2	22.6	21.0	-1.6	4.9	5.0	0.1	679	666	-13
3	31.7	23.3	-8.4	6.8	6.6	-0.2	1444	2096	652
4	92.1	89.7	-2.4	4.9	8.1	3.2	2239	1302	-937
Mean	45.4	40.8	-4.6	6.0	7.0	1.0	1808	1585	-224
SD	31.6	32.8	3.2	1.2	1.5	1.5	953	744	697

iPTH: Intact parathyroid hormone; TRAP5b: Tartrate-resistant-acid-phosphatase 5b; b-ALP: Bone specific alkaline phosphatase; DKK-1: Dickkopf-related protein 1; t₀: time before initiation of study; t₁: 3 months after initiation of study; Δ t₁- t₀: Change from t₀ to t₁

Table IV Serum levels and changes of calcium, phosphate, iPTH in without-paricalcitol group

Patient	Calcium (mg/dL)			Phosphate (mg/dL)			iPTH (pg/mL)		
	t ₀	t ₁	Δ t ₁ - t ₀	t ₀	t ₁	Δ t ₁ - t ₀	t ₀	t ₁	Δ t ₁ - t ₀
5	9.4	9.2	-0.2	6.70	6.70	0	1212.0	1284.0	72.0
6	8.5	9.1	0.6	9.00	8.20	-0.80	1066.0	1254.0	188.0
7	9.0	8.7	-0.3	4.26	3.94	-0.32	694.5	929.0	234.5
8	8.1	8.0	-0.1	2.89	3.53	0.64	199.6	474.5	274.9
9	8.7	8.4	-0.3	8.25	6.56	-1.69	186.7	393.3	206.6
Mean	8.7	8.7	-0.1	6.22	5.79	-0.43	671.8	867.0	195.2
SD	0.5	0.5	0.4	2.60	1.98	0.88	475.9	420.1	76.2

Table V Serum levels and changes of b-ALP, TRAP5B, and DKK-1 in without-paricalcitol group

Patient	b-ALP (U/L)			TRAP5B (U/L)			DKK-1 (pg/mL)		
	t ₀	t ₁	Δ t ₁ - t ₀	t ₀	t ₁	Δ t ₁ - t ₀	t ₀	t ₁	Δ t ₁ - t ₀
5	88.5	128.9	40.4	10.1	15.8	5.7	2061	1640	-421
6	52.4	79.3	26.9	4.8	7.0	2.2	3851	5928	2077
7	61.5	54.0	-7.5	3.1	6.7	3.6	1129	1776	647
8	48.9	72.9	24.0	4.8	5.9	1.1	1622	1747	125
9	19.2	29.7	10.5	1.6	3.6	2.0	1492	2037	545
Mean	54.1	73.0	18.9	4.9	7.9	2.9	2031	2626	595
SD	24.9	36.7	18.2	3.2	4.7	1.8	1071	1852	929

iPTH: Intact parathyroid hormone; TRAP5b: Tartrate-resistant-acid-phosphatase 5b; b-ALP: Bone specific alkaline phosphatase; DKK-1: Dickkopf-related protein 1; t₀: time before initiation of study; t₁: 3 months after initiation of study; Δ t₁- t₀: Change from t₀ to t₁

calcium and phosphate are diet intake and other therapies associated with CKD-MBD such as phosphate binder and bisphosphonate (KDIGO, 2009; NKF, 2013).

Phosphate binder used in this study is calcium and lanthanum based. The mechanism of phosphate binder is binding phosphate from food intake in intestine. The risk of hypercalcemia in calcium-based phosphate binder is higher than do lanthanum-based (Salusky, 2006). Meanwhile administration of bisphosphonate such as risedronate will reduce bone resorption so that no caused by increasing level of calcium and phosphate (Martin, *et al.*, 1998; Toussaint, *et al.*,

2009). In paricalcitol therapy there were 2 cases with increase level of iPTH level. This is due the paricalcitol doses have not optimal yet. In this study the evaluation of calcium, phosphate, iPTH, TRAP5b, b-ALP, and DKK-1 was done before initiation and after three months without dose titration of paricalcitol, so the 30% targeted-decrease iPTH was not achieved. According to the recommendation for doses titration of paricalcitol, dose is increased by 0.04μg/kg (maximum 16.8μg) to be adapted levels of iPTH and calcium periodically. If iPTH levels decrease <30% and calcium <11.5mg/dL, the paricalcitol dose should be increased (Lacy, *et al.*, 2011; Martin, *et al.*, 1998).

The elevation of iPTH levels stimulates osteoclast reflected by the elevation of TRAP5b (Saliba and El-Haddad, 2009). This results were shown in case 1 and 2 -paricalcitol group, level of TRAP5b was still high. In case 4 the elevation of TRAP5b was influenced by the elevation of iPTH and also patient has a history hyperuricemia. In this condition level of TRAP5b increased (Zhao, *et al.*, 2012).

Reduction level of iPTH serum is followed by decrease of bone turnover (Martin, and Gonzales, 2007). Actually, in paricalcitol group two cases declined of b-ALP level although the iPTH level increased. This is due to the suppression effects of paricalcitol in osteoblast by Wnt/ β -catenin pathway, induced the inhibition in osteoblast proliferation and differentiation (He, *et al.*, 2011; Peterlik, and Cross, 2013). Meanwhile decrease of b-ALP in one case (without paricalcitol group) is caused by risedronate therapy during the study. The similarity of chemical structure between risedronate and pyrophosphate is underlining the inhibition mechanism of bone matrix mineralization (propagation of hydroxyapatite crystal), and finally could suppress b-ALP levels (Nancollas, *et al.*, 2006; Bilezikian, *et al.*, 2008; Recker, *et al.*, 2008).

Decrease of activity stromal VDR due to calcitriol deficiency caused the elevation of DKK-1. Administration of paricalcitol was aimed to reduce DKK-1 by activation of VDR (Cianferotti, and Demay, 2007).

In case 3, after paricalcitol therapy the level of DKK1 increased, it may be caused by the elevation of uric acid (Zhao, *et al.*, 2012). However, the elevation of uric acid is not always increase DKK-1 level, as in case 4. This is because of other factors such as risedronate which had effect in reducing DKK-1 (Memon, *et al.*, 2013). Furthermore, case 5 (without paricalcitol group) patient has history of gastro-esophageal reflux disease (GERD) with administration of cisapride that may reduce DKK-1 (Storr, *et al.*, 2000; Lyrus, *et al.*, 2014).

Figure 1-3 showed there were positive correlation between iPTH and b-ALP, TRAP5b, DKK-1. Figure 4 showed there was positive correlation between TRAP5b and b-ALP. Secondary hyperparathyroidism on CKD-MBD caused high turnover metabolic bone disease (Martin and Gonzales, 2007; Malluche, *et al.*, 2012) and vascular calcification (Marinou, *et al.*, 2012; Druke and Massy, 2016) Characterization of high turnover metabolic bone disease begins with increased

osteoclast activity and followed by increased activity of osteoblast (Dimkovic, 2001). Figure 5 and 6 showed no correlation between DKK-1 and TRAP5b; DKK-1 and b-ALP. This results maybe caused by level of DKK-1 is not only influenced by iPTH level but also by inflammation cytokines such as IL-6 and TNF- α (Cianfero, 19 and Demay, 2007; Yao, *et al.*, 2011; Yermenko, *et al.*, 2015).

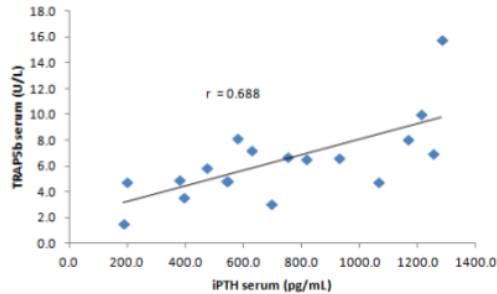


Figure 1. Correlation between serum level iPTH and TRAP5b

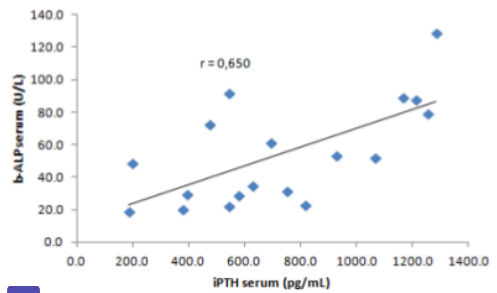


Figure 2. Correlation between serum level iPTH and b-ALP

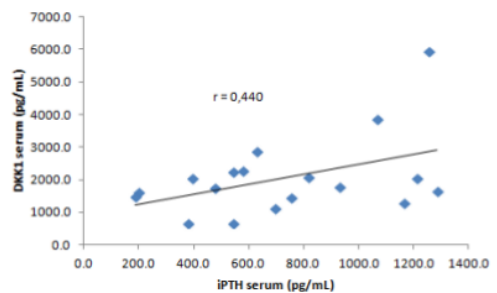
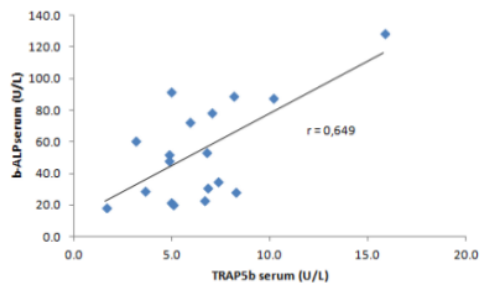
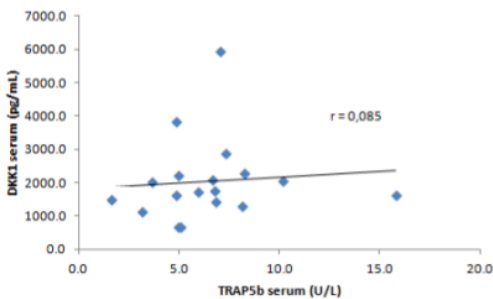


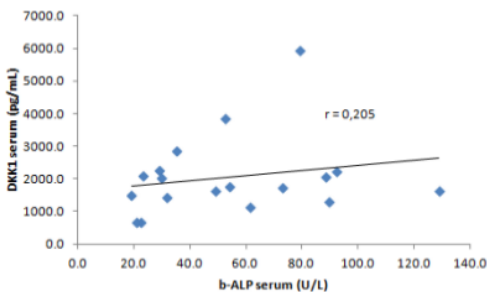
Figure 3. Correlation between serum level iPTH and DKK-1



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Figure 4. Correlation between serum level TRAP5b and b-ALP



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Figure 5. Correlation between serum level TRAP5b and DKK-1



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Figure 6. Correlation between serum level b-ALP and DKK-1

Of the overall results suggesting the use of paricalcitol suppresses iPTH increase without effecting an increase in serum calcium and phosphate. Paricalcitol administration decrease in marker bone turnover suppression b-ALP and TRAP5b, where in paricalcitol group there was a smaller increase TRAP5b compared to the group without paricalcitol. Paricalcitol decreased DKK- 1, a marker of vascular calcification.

The limitations of our study were variation of the patient's comorbid i.e diabetes mellitus type 2 and hypertension that can affect the result, variation of therapy regimen for CKD-MBD i.e phosphate binder and calcium supplement, variation of patient daily activity and food. To ensure these results are needed more samples.

CONCLUSION

The paricalcol administration suppresses the increase in iPTH level, bone turnover and vascular calcification showed by decreasing or suppresses the increase b-ALP, TRAP5b, DKK-1 levels without increasing calcium and phosphate levels.

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