The American Journal of Surgery 218 (2019) 609–612

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Changes in serum FGF23 and Klotho levels and calcification scores of the abdominal aorta after parathyroidectomy for secondary hyperparathyroidism

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ARTICLE INFO

Article history:
Received 3 October 2018
Received in revised form
11 December 2018
Accepted 13 December 2018

Keywords:
FGF23
Klotho
Calcification scores of abdominal aorta
Secondary hyperparathyroidism
Parathyroidectomy plus autotransplantation

ABSTRACT

Background: Changes of calcification scores of the abdominal aorta (CSAA) after total parathyroidectomy plus autotransplantation (TPX + AT) for symptomatic secondary hyperparathyroidism (SSHP) have never been reported.

Methods: Forty-nine patients who successfully underwent TPX + AT for SSHP were enrolled; 13 patients who had regular hemodialysis were enrolled as controls.

Preoperatively, patients' age, gender, and duration of dialysis were recorded. Serum Ca, P, alkaline phosphatase (Alk-ptase), intact parathyroid hormone (iPTH), vitamin D, FGF23, and Klotho levels, and CSAA were measured. One year postoperatively, these data were measured again. In the control group, these data were recorded and measured before and one year later.

Results: Serum iPTH, Alk-ptase and FGF23 levels and CSAA of the study group were significantly higher than those of the control group.

One year postoperatively, serum Ca, P, Alk-ptase, iPTH, and FGF23 levels and CSAA were significantly lower than those before surgery. Except for FGF23 levels, other items of the control group did not change significantly one year later, whereas the study group decreased CSAA more than the control group.

Conclusion: One year postoperatively, CSAA decreased.

Introduction

Fibroblast growth factor-23 (FGF23) and the Klotho endocrine axis have an important role in mineral metabolism.[1] FGF23 increases in the blood of chronic kidney disease patients, and elevation of FGF23 levels is associated with higher vascular and aortic calcification in hemodialysis patients.[2,3] Klotho deficiency and high circulating FGF23 levels precede symptomatic secondary hyperparathyroidism (SSHPT) in chronic kidney disease patients.[1] Among patients with preserved left ventricular ejection fraction, serum Klotho levels are negatively associated with diastolic dysfunction.[4] Renal insufficiency leads to decreased Klotho levels and impaired phosphate excretion.[5] The presence of aortic calcification assessed by radiography of the lateral abdomen is also associated with increased cardio-vascular mortality.[6]

In this study, we measured serum FGF23 and Klotho levels and calcification scores of the abdominal aorta (CSAA) before and 1 year after total parathyroidectomy plus autotransplantation (TPX + AT) for SSHPT to evaluate the changes.

Materials and methods

From August 2015 to July 2016, among 55 patients with SSHPT, 49 patients who were successfully underwent TPX + AT for SSHPT, were enrolled in this prospective cohort study. We excluded patients of surgical failure and patients on peritoneal dialysis.

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https://doi.org/10.1016/j.amjsurg.2018.12.026
0002-9610/

Thirteen patients who had had regular hemodialysis for more than 8 years at our dialysis center were enrolled as the control group. In the study group, the patients had to discontinue all calcitriol, sevelamer and cinacalcet one month before surgery; in the control group, 9 patients took calcitriol, 5 took sevelamer and 2 took cinacalcet regularly.

Preoperatively, patients' age, gender, duration of dialysis, and symptoms such as skin itching, bone pain, general weakness, and insomnia were recorded, and serum Ca, P, alkaline phosphatase (Alk-ptase), intact parathyroid hormone (iPTH), vitamin D, FGF23, and Klotho levels were checked; lateral view radiography of the abdominal aorta at levels of the first through fourth lumbar vertebrae (L1–L4) was conducted to calculate calcification scores.[6–8] These data were checked one year after a successful operation in the study group or 1 year later in the control group. The indications for surgery with SSHPT were iPTH levels over 800 pg/mL, Ca levels over 10.1 mg/dL, and P levels over 4.7 mg/dL. During surgery, total parathyroidectomy and bilateral thymectomy were performed plus autotransplantation of 120 mg of diffuse hyperplastic parathyroid tissue to the subcutaneous tissue of the forearm, without formation of an arteriovenous fistula. A successful operation was defined as iPTH levels less than 72 pg/mL within one week after surgery.[9] After successful surgery, intravenous calcium gluconate (2–8 g/day), oral calcium carbonate (2–8 g/day), and calcitriol (0.5–4 μg/day) were provided if patients' serum calcium levels were below 7.6 mg/dL. Calcitriol was not regularly given three months after surgery if patients' serum Ca levels were above 7.6 mg/dL. A radiographic examination of the lateral abdomen was obtained for each patient in a standing position at 70 kV, and the abdominal 24-point scoring system was applied.[6] Abdominal calcification at levels of L1–L4 vertebrae was evaluated by one of the authors (W-T Chen), who was a senior radiologist and was completely blind to patients' data. Scores were assigned from 0 to 3 (0, none; 1, small; 2, moderate; 3, large) according to the size of each abdominal aortic calcified plaque identified before surgery and one year postoperatively (Fig. 1.).

Serum iPTH levels were measured with chemiluminometric technology using the Centaur intact PTH kit (Tarrytown, NY 10591–5097, USA). Serum vitamin D levels were measured with the Advia Centaur Vitamin D Total kit (Siemens Healthcare Diagnostics, Inc., East Walpole, MA, USA). Serum FGF23 levels were measured with the enzyme-linked immunosorbent assay (ELISA) using the RayBio® Human FGF23 ELISA Kit (RayBiotech, Inc. Norcross, GA 30092, USA). Serum Klotho levels were measured with the ELISA using the Human Soluble-α-Klotho Assay Kit-IBL (Gunma 375–0005, Japan). Serum Ca, P, and Alk-ptase levels were measured with the colometric method as our routine examinations. Symptoms of the control group were recorded, and serum Ca, P, Alk-ptase, iPTH, vitamin D, FGF23, Klotho levels and CSAA were checked at baseline and 1 year later. The study was approved by the institutional review board (103–7444A3) of the Chang Gung Memorial Hospital, and informed consent was obtained from patients who served as subjects of the investigation.

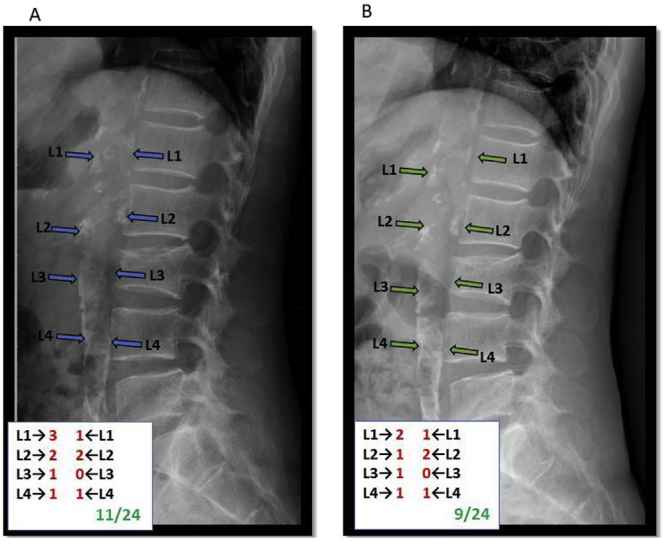

Fig. 1. Lateral lumbar spine X-ray with images of calcification in the abdominal aorta of one patient in the study. The calcification scores of the abdominal aorta were 11/24 (A) before surgery and 9/24 (B) one year after parathyroidectomy.

Statistical analysis

Data were expressed as median with range (interquartile range [IQR]). Nonparametric analysis with X^2 test, Wilcoxon signed-rank test, and Mann-Whitney *U* test were performed, if necessary. All analyses were performed with the SPSS version 22 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered significant.

Results

The patients of the study group had more symptoms than the patients of the control group (all $p < 0.001–0.0013$) (Table 1), and patients' age, gender, duration of dialysis, serum Ca, P, and Klotho levels, and CSAA were not significantly different between the two groups. Serum iPTH, Alk-ptase and FGF23 levels, of the study group were significantly higher than those of the control group (Table 1).

One year after surgery, in the study group, serum Ca, P, Alk-ptase, iPTH, and FGF23 levels, and CSAA were significantly lower, but serum vitamin D and Klotho levels were significantly higher than those before surgery (Tables 2 and 3).

Except for FGF23 levels, which were significantly decreased, serum Ca, P, Alk-ptase, iPTH, vitamin D, and Klotho levels, and CSAA in the control group did not change significantly after one year (Tables 2 and 3). Decreases in serum Ca, P, Alk-ptase, iPTH, vitamin D, and FGF23 levels, and CSAA, but increases in Klotho levels of the study group were significantly more than those of the control group after one year (Tables 2 and 3).

Discussion

SSHPT is a common complication of patients with end-stage renal failure who are undergoing maintenance dialysis. Secondary hyperparathyroidism may be associated with a number of unfavorable outcomes, such as uremic bone disease, vascular calcification, and death.[10–12] Despite the supplements of an active form of vitamin D, phosphate binders, and calcimimetics in the medical management of SSHPT, about 8.0–14.2 cases per 1000 patient-years need parathyroidectomy.[13–16] FGF23 is a phosphaturic hormone, synthesized and secreted by osteoblasts, whereas Klotho, which is a coreceptor for FGF23, was identified in a mouse model showing hyperphosphatemia and multiple aging-like traits.[17,18]

A paradigm of FGF23 excess and Klotho deficiency was proposed in patients with chronic renal failure undergoing regular dialysis. FGF23 stimulated left ventricular hypertrophy, and loss of Klotho augmented fibrosis, endothelial dysfunction, and vascular calcification.[17] Vascular calcification including aortic calcification was highly prevalent in dialysis patients and disorders of mineral metabolism were reported as risk factors for vascular calcification.[19–21] Abdominal aortic calcific deposits were an important predictor of vascular morbidity and mortality[22] and also

Table 1
Age, gender, duration of dialysis, and symptoms, and preoperative serum Ca, P, alkaline phosphatase (Alk-ptase), intact parathyroid hormone (iPTH), vitamin D, FGF23, and Klothos levels, and calcification scores of the abdominal aorta. Comparison between study and control groups.

[normal range]	Study Group N = 49	Control Group N = 13	*p*
Age (years)	59 (52–65)	61 (52–69)	0.527
Gender (M; F)	17:32	5:8	1.0[a]
Bone pain	38	3	<0.001[a]
Skin itching	34	2	0.001[a]
Insomnia	27	2	0.004[a]
General weakness	26	1	0.013[a]
Ca [7.9–9.9 mg/dL]	10.3 (9.7–10.9)	10.1 (9–10.2)	0.163
P [2.4–4.7 mg/dL]	5.9 (4.6–6.8)	5.8 (4.1–6.2)	0.243
Alk-ptase [28–94 U/L]	140 (108–206)	100 (66–133)	0.009
iPTH [14–72 pg/mL]	1188 (917–1712)	649 (245–958)	<0.001
Vitamin D [≧30 ng/mL]	24.8 (18.7–33.5)	33 (27.4–40.6)	0.019
FGF23 [ng/mL]	54.5 (44.9–78.4)	35 (31.6–50.3)	0.002
Klotho [pg/mL]	703 (632–779)	642 (545–761)	0.118
Duration of dialysis (years)	8 (5–12)	10 (9.7–10.9)	0.165
Abdominal aorta 24-Score System	4.0 (1–11) (N = 39)	3.5 (0–15.5) (N = 12)	0.696

All data = median (interquartile range).
Mann-Whitney *U* test.
[a] X2-test.

Table 2
Changes of serum Ca, P, alkaline phosphatase (Alk-ptase), intact parathyroid hormone (iPTH)), vitamin D, FGF 23 and Klotho levels before (Pre OP) and 1Y after surgery (Post OP). Comparison between study and control groups.

[normal range]	Study Group N = 49			Control Group N = 13			p^b between differences
	Pre OP Post OP 1Y	p^a	Difference	Baseline At 1Y	p^a	Difference	
Ca. [7.9–9.9 mg/dL]	10.3 (9.6–10.9) 9.2 (6.2–9.8)	<0.001	1.0 (0.3–2.3)	10.1 (9.0–10.2) 10.1 (8.2–10.4)	0.098	0.2 (−0.2–0.6)	0.027
P [2.4–4.7 mg/dL]	5.9 (4.6–6.8) 4.7 (3.7–5.6)	<0.001	1.1 (0.2–2.0)	5.8 (4.1–6.2) 5.1 (4.2–6.2)	0.695	0.2 (−1.1–0.7)	0.036
Alk-p tase [28–93 U/L]	140 (108–206) 75 (51–112)	<0.001	59 (23–136)	100 (66–133) 106 (73–149)	0.463	−7 (-25–13.5)	0.001
iPTH [14–72 pg/mL]	1188 (917–1712) 48.1 (10.9–118)	<0.001	1079 (816–1621)	649 (245–958) 384 (154–782)	0.311	47 (-120-428)	<0.001
Vitamin D [≧30 ng/mL]	24.8 (18.7–33.5) 33.7 (24.5–43.5)	<0.001	−7.9 (−16.4 to −1.6)	33 (27.4–40.6) 31.5 (26–42)	0.552	−7 (−5.6–1.4)	0.015
FGF23 [ng/mL]	54 (44.9–74.8) 42 (32.3–45)	<0.001	11.9 (5.8–33)	35 (31.6–50.3) 31.9 (30–43)	0.023	2.3 (0.4–7.0)	0.014
Klotho [pg/mL]	703 (632–779) 820 (639.5–1016.8)	<0.001	−124 (-238–1.7)	642 (545–761) 600 (551–662)	0.249	38 (-46-99)	0.001

All data = median (interquartile range).
[a] Wilcoxon Signed-Ranks test within group.
[b] Mann-Whitney *U* test between groups.

associated with increased risk of congested heart failure.[23] At baseline, serum iPTH, Alk-ptase and FGF23 levels were higher in the study group than those in the control group; serum Ca, P, and Klotho levels and patients' age, gender, duration of dialysis and CSAA were not significantly different between the two groups. One year after surgery, in the study group, serum Ca, P, Alk-ptase, and FGF23 levels and CSAA were significantly lower than those before surgery, while serum vitamin D and Klotho levels were significantly higher than those before surgery. The higher vitamin D levels might be due to regular treatment of hypocalcemia with calcitriol after TPTX + AT. In the control group, only serum FGF23 levels were significantly lower after 1 year, and other items were not significantly changed. We speculated that the changes in FGF23 levels of the control group might due to cinacalcet or sevelamer,[24,25] regularly prescribed in 7 patients in the control group.

In a previous study of ours, due to a small number of patients (No = 46), we found there was no change in FGF23 and Klotho levels 3 months after TPX + A in hemodialysis patients given calcium supplements and vitamin D analogue. However, serum FGF23 levels negatively correlated with serum calcium levels at pre-operation, day 5 and day 90 after parathyroidectomy.[26] In another previous report, before surgery of SSHPT, serum FGF23

Table 3
Changes of calcification scores of the abdominal aorta before surgery (pre OP) and 1Y after surgery (Post OP). Comparison between study and control groups.

	Study Group N = 39			Control Group N = 12			p^b between differences
	Pre OP Post OP 1Y	p^a	Difference	Baseline At 1Y	p^a	Difference	
Abdominal aorta 24-Score System	4 (1–11) 3 (1–11)	0.003	0 (0–1)	3.5 (0–15.5) 4.0 (0–14.8)	0.317	0 (−0.75-0)	0.019

All data = median (interquartile range).
[a] Wilcoxon Signed-Ranks test within group.
[b] Mann-Whitney *U* test between differences.

levels were markedly elevated, whereas serum Klotho levels were moderately decreased.[27] Parathyroidectomy resulted in significantly reductions of serum Ca, P, Alk-ptase, FGF23, and iPTH levels. The serum Klotho levels were reduced from baseline immediately after parathyroidectomy; however, the levels increased progressively, reaching 34% above the postoperative levels at 3 months after surgery.[27] Our recent results that serum FGF23 levels decreased, but serum Klotho levels increased, one year after parathyroidectomy were compatible with this report. Changes of CSAA after parathyroidectomy have never been reported before. Decreases of CSAA in this study group were significantly more than the control group.

Limitation

The limitation of this study is a small number of patients especially in the control group. We have found that it is quite difficult for us to recruit patients for the control study. Further studies to enroll more patients in either study or control groups are suggested.

Conclusion

TPX + AT for SSHPT can decrease serum FGF23 levels and CSAA, but increase serum Klotho levels one year postoperatively.

Conflicts of interest

All authors declare no conflicts of interest.

Sources of financial support

The study was supported by the Ministry of Science and Technology 04-2314-B-182A-127 of Taiwan.

This study was approved by Institutional Review Board 103-7444A3 of The Chang Gung Memorial Hospital.

Acknowledgements

We thank Miss Chih-Yun Lin and the Biostatics Center, Kaohsiung Chang Gung Memorial Hospital for statistic work.

References

1. Evenepoel P, Rodriguez M, Ketteler M. Laboratory abnormalities in CKD-MBD: markers, predictors, or mediators of disease? *Semin Nephrol*. 2014;34(2):151–163 [Review].
2. Jean G, Terrat JC, Vanel T, et al. High levels of serum fibroblast growth factor(FGF-23) areassociated with increased mortality in long haemodialysis patients. *Nephrol Dial Transplant*. 2009;24(9):2792–2796.
3. Nasrallah MM, El-Shehaby AR, Salem MM, et al. Fibroblast growth factor-23 (FGF-23) is independently correlated to aortic calcification in haemodialysis patients. *Nephrol Dial Transplant*. 2010;25(8):2679–2685.
4. Okamoto Y, Fujita S, Morita H, et al. Association between circulating FGF23, α-Klotho, and left ventricular diastolic dysfunction among patients with preserved ejection fraction. *Heart Ves*. 2016;31(1):66–73.
5. Omata M, Fukagawa M, Kakuta T. Vascular calcification - pathological mechanism and clinical application - . Vascular calcification in chronic kidney disease-mineral and bone disorder (CKD-MBD). [Review] (Japanese). *Clin Calcium*. 2015;25(5):645–653.
6. Okuno S, Ishimura E, Kitatani K, et al. Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. *Am J Kidney Dis*. 2007;49(3):417–425.
7. Kauppila LI, Polak JF, Cupples LA, et al. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. *Atherosclerosis*. 1997;132(2):245–250.
8. Hong D, Ruan Y, Pu L, et al. Both pelvic radiography and lateral abdominal radiography correlate well with coronary artery calcification measured by computed tomography in hemodialysis patients: a cross-sectional study. *Hemodial Int*. 2016;20(3):399–406.
9. Okada M, Tominaga Y, Yamamoto T, et al. Location frequency of missed parathyroid glands after parathyroidectomy in patients with persistent or recurrent secondary hyperparathyroidism. *World J Surg*. 2016;40(3):595–599.
10. Ganesh SK, Stack AG, Levin NW, et al. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*. 2001;12(10):2131–2138.
11. Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol*. 2002;39(4):695–701.
12. Block GA, Hulbert-Shearon TE, Levin NW, et al. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31(4):607–617.
13. Malberti F, Marcelli D, Conte F, et al. Parathyroidectomy in patients on renal replacement therapy: an epidemiologic study. *J Am Soc Nephrol*. 2001;12:1242–1248.
14. Slinin Y, Foley RN, Collins AJ, et al. Clinical epidemiology of parathyroidectomy in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *Hemodial Int*. 2007;11(1):62–71.
15. Chuang CH, Wang JJ, Weng SF, et al. Epidemiology and mortality among dialysis patients with parathyroidectomy: Taiwan National Cohort Study. *J Nephrol*. 2013;26(6):1143–1150.
16. Foley RN, Li S, Liu J, et al. The fall and rise of parathyroidectomy in U.S. hemodialysis patients, 1992 to 2002. *J Am Soc Nephrol*. 2005;16(1):210–218.
17. Olauson H, Vervloet MG, Cozzolino M, et al. New insights into the FGF23-Klotho axis. *Semin Nephrol*. 2014;34(6):586–597 (Review).
18. Donate-Correa J, Mora-Fernández C, Martinez-Sanz R, et al. Expression of FGF23/KLOTHO system in human vascular tissue. *Int J Cardiol*. 2013;165(1):179–183.
19. Chertow GM, Raggi P, Chasan-Taber S, et al. Determinants of progressive vascular calcification in haemodialysis patients. *Nephrol Dial Transplant*. 2004;19(6):1489–1496.
20. Davies MR, Hruska KA. Pathophysiological mechanisms of vascular calcification in end-stage renal disease. *Kidney Int*. 2001;60(2):472–479.
21. Taniwaki H, Ishimura E, Tabata T, et al. Aortic calcification in haemodialysis patients with diabetes mellitus. *Nephrol Dial Transplant*. 2005;20(11):2472–2478.
22. Wilson PW, Kauppila LI, O'Donnell CJ, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation*. 2001;103(11):1529–1534.
23. Walsh CR, Cupples LA, Levy D, et al. Abdominal aortic calcific deposits are associated with increased risk for congestive heart failure: the Framingham Heart Study. *Am Heart J*. 2002;144(4):733–739.
24. Lin HH, Liou HH, Wu MS, et al. Long-term sevelamer treatment lowers serum fibroblast growth factor 23 accompanied with Klotho levels in chronic hemodialysis patients. *Nephrology*. 2014;19(11):672–678.
25. Sprague SM, Wetmore JB, Gurevich K, et al. Effect of cinacalcet and vitamin D analogs on fibroblast growth factor-23 during the treatment of secondary hyperparathyroism. *CJASN*. 2015;10(6):1021–1030.
26. Liao SC, Moi S, Chou FF, et al. Changes in serum concentrations of fibroblastic growth factors 23 and soluble Klotho in hemodialysis patients after total parathyroidectomy. *BioMed Res Int*. 2016;6453803:2016.
27. Takahashi H1, Komaba H, Takahashi Y, et al. Impact of parathyroidectomy on serum FGF23 and soluble Klotho in hemodialysis patients with severe secondary hyperparathyroidism. *J Clin Endocrinol Metab*. 2014;99(4):E652–E658.