Preliminary report

Preliminary study of FGF-23 level in post-operative parathyroidectomy in secondary hyperparathyroidism of chronic renal failure patients

Narongkhet Leekatesarakorn*,
Sathit Niramitmahapanya**, Narisa Kengtrong Bordeerat***

Abstract

Introduction: Secondary hyperparathyroidism is a common complication in patients with the end stage renal disease (ESRD), accelerated by hyperphosphatemia. Fibroblast growth factor 23 (FGF-23) has emerged as an important phosphorus-regulating protein for renal phosphate wasting disorders. In ESRD patients, FGF-23 levels are raised with declining kidney function. Objective was to determine and correlate the levels of circulating FGF-23, phosphate, and calcium after total parathyroidectomy in secondary hyperparathyroidism of chronic renal failure patients.

Method: Thirty patients with marked secondary hyperparathyroidism were enrolled. All patients were underwent total parathyroidectomy accompanied by the implantation and their FGF-23 levels were measured at 0, 10, 20, 30, and 40 minutes after parathyroidectomy by means of ELISA assays. Biochemical data including the result of calcium (Ca), phosphate (PO_4), and parathyroid hormone (PTH) were collected from medical records.

Result: FGF-23 levels were significantly decreased at 20 minutes after total parathyroidectomy ($p < 0.05$). FGF-23 levels were significantly correlated with PO_4, ($\rho = 0.64$, $p < 0.05$) Ca ($\rho = 0.51$, $p < 0.05$), and PTH ($\rho = 0.90$, $p < 0.05$) levels. The complete removal of enlarged parathyroid glands significantly reduced circulating FGF-23 levels at 20 minutes. In addition, FGF-23 correlated positively with serum PO_4, Ca, and PTH values in secondary hyperparathyroidism in chronic renal failure patients.

Discussion and Conclusion: Circulating FGF-23 levels may early reflect alterations in ongoing PTH and phosphate balance in patients. Therefore, FGF-23 may be used as the predictive marker for monitoring the successful treatment secondary hyperparathyroidism in chronic renal failure patients.

Key words: End Stage Renal Disease (ESRD), Secondary hyperparathyroidism, Parathyroidectomy, Fibroblast growth factor 23 (FGF-23)

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* Graduate Program in Medical Technology, Faculty of Allied Health Sciences, Thammasat University
** Endocrinology and Metabolism Unit, Internal Medicine Department, Rajavithi Hospital
*** Department of Medical Technology, Faculty of Allied Health Sciences, Thammasat University
Corresponding Author: Narisa Kengtrong Bordeerat, Department of Medical Technology, Faculty of Allied Health Sciences, Thammasat University, Rangsit Center, Pathumthani E-mail: bordeerat@gmail.com

Introduction

The prevalence of patients with end stage renal disease (ESRD) who need dialysis and/or transplantation has more than doubled in Thailand during the past two decades.[1] The onset of ESRD is considered to be the cause of abnormality in phosphate metabolism when renal function declines.[2, 3] Subsequently, disrupted phosphate homeostasis in patients with ESRD also induces secondary hyperparathyroidism. Even though, inappropriate phosphate levels do not appear to be the only mechanism of secondary hyperparathyroidism.

Fibroblast growth factor (FGF-23) is a regulator of phosphate metabolism and is elevated in patients with ESRD. FGF-23 is derived mainly from osteocytes in bone and acts on proximal renal tubules to maintain serum phosphate homeostasis by excreting excess phosphate through the kidney.[4] In ESRD, phosphate retention occurs as functional renal diminished; this stimulates FGF-23 synthesis to increase renal excretion of excess phosphate. In addition, disrupted phosphate homeostasis in patients with ESRD also induces secondary hyperparathyroidism.[5] These high level of circulating FGF-23 is associated with significantly worse clinical outcomes in secondary hyperparathyroidism patients.

FGF-23 levels demonstrate the correlation with serum phosphate, Ca x P and PTH values in patients with secondary hyperparathyroidism. FGF-23 levels are decreased at day 1 and day 3 after total parathyroidectomy because phosphate and PTH level abnormalities may affect the FGF-23 production, secretion and/or degradation.[6] However, there is no report on serum FGF-23 level and their association with calcium level, phosphate level, and parathyroid hormone at various time within an hour after parathyroidectomy in patients with secondary hyperparathyroidism. The present study was designed to test the hypothesis that FGF-23 levels were reduced in circulation of secondary hyperparathyroidism patients after complete a parathyroid glands removal and the association with parathyroid hormone, calcium, and phosphate levels by the time dependent (at 0, 10, 20, 30, and 40 min).

Method

A prospective study of 30 patients who underwent total parathyoidectomy accompanied by implantation, from September 2014 to February 2016 at Rajavithi hospital. Subjects 20 - 70 years of age with end stage renal disease (ESRD) with secondary hyperparathyroidism following criteria of the Kidney Disease Improving Global Outcomes (KDIGO) guideline[7] were included at Rajavithi hospital, Ministry of Public Health, Bangkok, Thailand. The study was reviewed and approved by the Ethical Review Committee for Research in Human Subjects, Rajavithi hospital, Ministry of Public Health, and the Ethical Review Committee for Research in Human Subjects, Thammasat University. Written informed consent was obtained from all patients before participation.

For this study, blood samples were collected at 0, 10, 20, 30, and 40 minutes after parathyroidectomy due to the half-life of FGF-23 (approximately 20 to 40 minutes). FGF-23 was performed with an ELISA kit (Immunotopics International Inc., U.S.A.)[8] that measured intact FGF-23. The precision (coefficient of variation; CV) of intra-assay for FGF-23 at the mean value of 43 pg/mL and 426 pg/mL were 4.1% and 2.0 %, respectively. In addition, the inter-assay for FGF-23 at the mean value of 43 pg/mL and 426 pg/mL were 9.1 % and 3.5%, respectively. Parathyroid hormone (PTH) was measured with chemiluminescence microparticle immunoassay (Abbott Diagnostics, U.S.A.) Serum calcium and phosphate were analyzed by o-Cresolphthalein Complexone (o-CPC) and phosphomolybdate method with routine assays (COBAS INTEGRA 800, Roche Diagnostics Ltd., Switzerland)

Patient characteristics were reported with standard descriptive statistics. All data were analyzed with computer software with comparisons for mean

values performed with ANOVA tests. Correlations between the levels of FGF-23, PTH, calcium, and phosphate were analyzed by analysis of variance linear regression analysis.

Result

Characteristics of the study population

Among the 30 patients, 15 (50%) were men and 15 (50%) were women. Overall mean age of patients was 46.6 ± 12.8 years. Pre operative parathyroid hormone, calcium and phosphate level were presented in Table 1. All patients developed hyperparathyroidism (defined as serum PTH > 65 pg/mL) and hyperphosphatemia (defined as serum phosphate > 4.5 mg/mL).

Table 1 Characteristics and biochemistries data of end stage renal disease (ESRD) patients who had parathyroidectomy

Parameters	n = 30	Mean ± SD	Reference range
Gender			
Male	15 (50%)		
Female	15 (50%)		
Age (year)			
20 - 70		46.6 ± 12.8	
Biochemical parameter (pre-operative)			
Calcium level (mg/dL)		10.50 ± 0.70	8.6 - 10.0
Phosphate level (mg/dL)		6.30 ± 1.55	2.7 - 4.5
PTH level (pg/mL)		1692 ± 666	15 - 65

Circulating FGF-23 levels

A total of 30 subjects were assessed for FGF-23 concentrations by time dependent after parathyroidectomy shown in Figure 1. The data were demonstrated normal distribution in overall and there was statistical significant difference at 20 minutes after surgical removal parathyroid glands. Twenty five subjects (83%) from total indicated that FGF-23 levels were decreased at 20 minutes. The mean pre-operative parathyroid glands FGF-23 level was 3,154.82 ± 1,272.23 pg/mL. Mean FGF-23 levels significantly decreased to 2,570.55 ± 1,240.47 pg/mL at 20 minutes after removal and these levels were still more than 1,000-fold above reference value (reference value of FGF-23 = 0.36 ng/mL). (Table 2) FGF-23 level was increased at 30 minutes and 40 minutes after removal parathyroid glands with 16.4% and 17.1%, respectively.

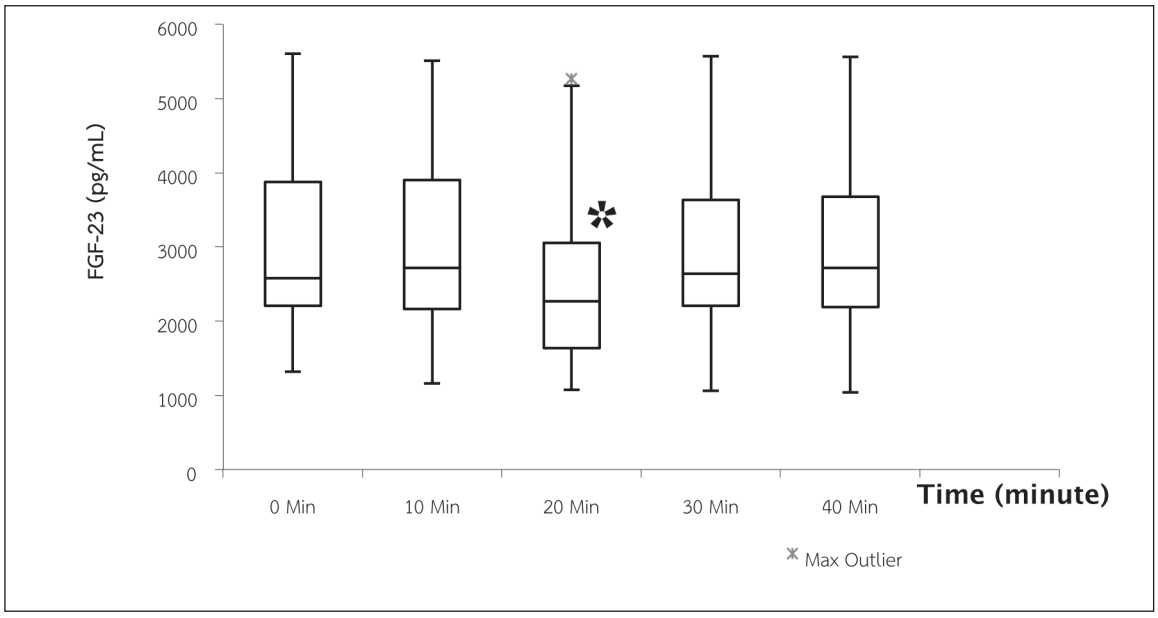

Figure 1 FGF-23 levels after parathyroidectomy by time dependent.

Table 2 FGF-23 levels after surgical removal parathyroid gland by time dependent

Time (minute)	FGF-23 levels (pg/mL) Mean ± SD	p - value
0	3,154.82 ± 1,272.23	-
10	3,018.24 ± 1,280.64	0.340
20	2,570.55 ± 1,240.47	0.038*
30	2,991.72 ± 1,311.39	0.313
40	3,009.71 ± 1,291.78	0.331

* $p < 0.05$

FGF-23 versus PTH, calcium, and phosphate levels in secondary hyperparathyroidism patients

At 20 minutes after parathyroidectomy, FGF-23 level was positively correlated with PTH ($R = 0.902$; $p < 0.05$). A similar relationship was observed for the FGF-23, calcium, and phosphate concentration. There were positively correlated at 20 minutes after removal parathyoid gland ($R = 0.5126$; $p < 0.05$ and $R = 0.643$; $p < 0.05$) (Figure 2).

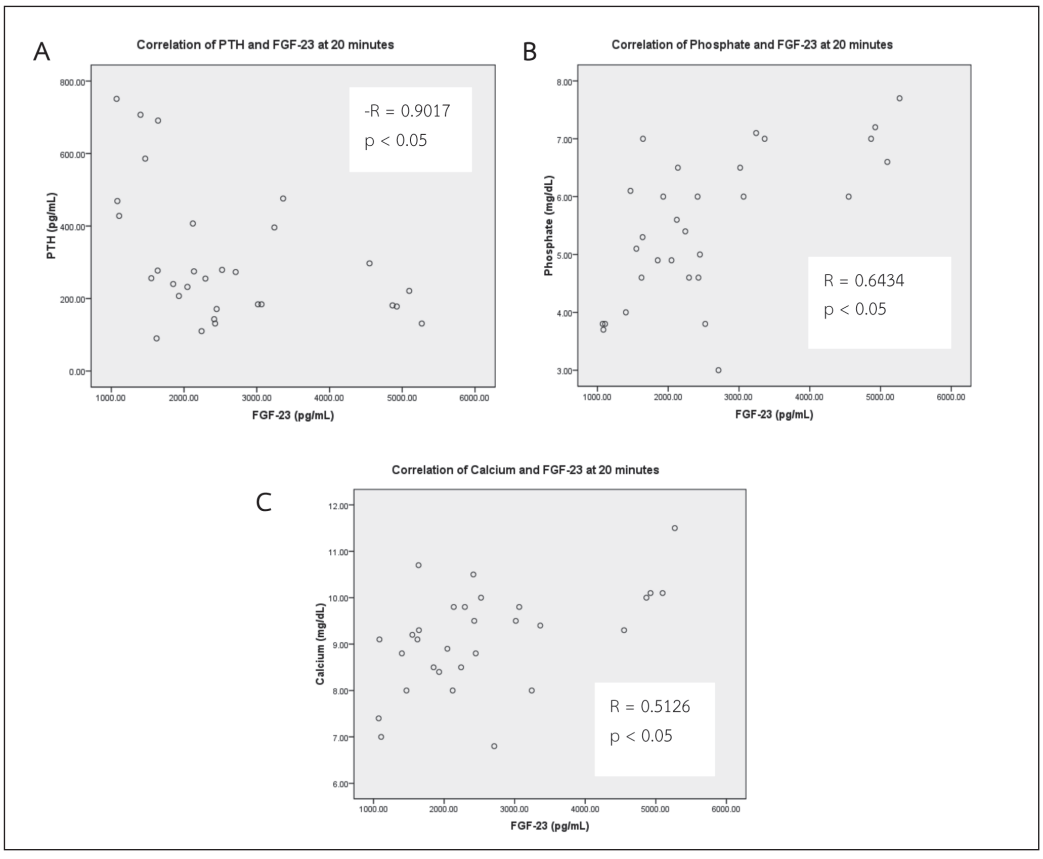

Figure 2 Serum FGF-23 levels at 20 minutes after parathyroidectomy significantly correlated with PTH (A), phosphate (B), calcium (C)

Discussion and Conclusion

This is the first report in Thailand showing the levels of circulating fibroblast growth factor 23 (FGF-23) after parathyroidectomy in secondary hyperparathyroidism patients by time dependent (0 - 40 mins). Plasma FGF-23 levels in patients with secondary hyperparathyroidism after complete ablation of parathyroid glands was significantly decreased at 20 minutes. A dramatic decrease in parathyroid hormone levels after parathyroidectomy seems to trigger a gradual, yet steady, reduction in circulating FGF-23. In addition, the existing evidence that FGF-23 levels are significantly positive correlated with serum PTH, calcium, and phosphate is consistency with ESRD patients who loss kidney function causes abnormal phosphate metabolism, with reflection on parathyroid gland function and bone disease[5]. Several present studies indicate that PTH is not only factor to modulate urinary phosphate excretion but FGF-23 is one of the most candidates for phosphate homeostasis as well. The parathyroid gland is another target for FGF-23. Moreover, there is a strong association between elevated FGF-23 levels and the severity of secondary hyperparathyroidism in chronic kidney disease (CKD). It is also persuasive to presume that FGF-23 may also mediate some of the effects of hyperphosphatemia on the increase in parathyroid gland function in secondary hyperparathyroidism patients.[11, 12] ESRD patients, whose secondary hyperparathyroidism is thought to stimulate constitutive FGF-23 secretion, demonstrate the most dramatically increased FGF-23 levels. The total parathyroidectomy, can reduce the elevation of the circulating of FGF-23 levels because phosphorus and PTH level abnormalities may affect the FGF-23 production, secretion and/or degradation. We revealed that dramatic decline of

FGF-23 level at 20 minutes could be used for medical decision and monitoring for patients after complete parathyroidectomy. However, FGF-23 levels gradually increased at 30 and 40 minutes suggest that FGF-23 have an adaptive response. In patients with ESRD, FGF-23 reaches levels that are subsequent wide variation in the FGF-23 concentration for all time points (SD ± 40% of the mean) may be associated with the high concentration change in hyperparathyroidism patients. One speculation for this finding is that circulating FGF-23 levels reflect systemic calcium and phosphate balance, even after total parathyroidectomy. In this study, a significant association between FGF-23 phosphate and calcium were observed, when intrinsic PTH secretion was essentially deficient. Further studies are needed to define the effects of FGF-23 on parathyroid hormone (PTH) production and secretion especially in patients who were underwent parathyroid removal.

In conclusion, the extremely high FGF-23 levels in renal hyperparathyroidism patients will decrease gradually after parathyroidectomy. Our findings show that the complete removal of parathyroid glands will directly effect to circulating FGF-23 levels and phosphate homeostasis. In addition, FGF-23 level may be used as the predictive marker for monitoring the successful treatment secondary hyperparathyroidism of chronic renal failure patients.

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บทคัดย่อ

การศึกษาเบื้องต้นของระดับ FGF-23 ภายหลังผ่าตัดต่อมพาราไทรอยด์ในผู้ป่วยไตวายเรื้อรังที่มีภาวะ secondary hyperparathyroidism

ณรงค์เขตร หลีเกษรากรณ์*, สถิตย์ นิรมิตรมหาปัญญา, นริสา เก่งตรง บดีรัฐ*****

*บัณฑิตศึกษา สาขาเทคนิคการแพทย์ คณะสหเวชศาสตร์ มหาวิทยาลัยธรรมศาสตร์

**หน่วยต่อมไร้ท่อและเมตาบอลิสม กลุ่มงานอายุรศาสตร์ โรงพยาบาลราชวิถี

***ภาควิชาเทคนิคการแพทย์ คณะสหเวชศาสตร์ มหาวิทยาลัยธรรมศาสตร์

ผู้ให้ติดต่อ: อาจารย์ ดร.นริสา เก่งตรง บดีรัฐ ภาควิชาเทคนิคการแพทย์ คณะสหเวชศาสตร์ มหาวิทยาลัยธรรมศาสตร์ อีเมล: bordeerat@gmail.com

บทนำ: Secondary hyperparathyroidism เป็นภาวะแทรกซ้อนที่พบได้บ่อยในผู้ป่วยไตวายระยะสุดท้าย เนื่องจากผู้ป่วยมีปัญหาเรื่องการควบคุมระดับฟอสเฟตในเลือด ทำให้เกิดการขับฟอสเฟตออกจากร่างกายได้น้อยลง ส่งผลทำให้มีภาวะฟอสเฟตในเลือดสูง fibroblast growth factor 23 (FGF-23) จึงมีบทบาทสำคัญในการควบคุมระดับฟอสเฟตในผู้ป่วย ทั้งนี้ในผู้ป่วยไตวายเรื้อรังระยะสุดท้าย ระดับ FGF-23 จึงเพิ่มขึ้นพร้อมกับการทำงานของไตที่ลดลง วัตถุประสงค์เพื่อศึกษาระดับและความสัมพันธ์ระหว่างระดับ fibroblast growth factor 23 (FGF-23) ฟอสเฟตและแคลเซียมในเลือดของผู้ป่วยไตวายเรื้อรังระยะสุดท้ายที่มีภาวะ secondary hyperparathyroidism ภายหลังได้รับการผ่าตัดต่อมพาราไทรอยด์ออก ณ เวลาที่ต่างกัน

วิธีการศึกษา: ผู้ป่วยไตวายเรื้อรังระยะสุดท้ายที่มีภาวะ secondary hyperparathyroidism จำนวน ๓๐ ราย เข้ารับการผ่าตัดต่อมพาราไทรอยด์ด้วยวิธี total parathyroidectomy ทำการตรวจหาระดับ FGF-23 โดยวิธี ELISA ภายหลังการผ่าตัดต่อพาราไทรอยด์เป็นช่วงเวลา ๐, ๑๐, ๒๐, ๓๐ และ ๔๐ นาที พร้อมกับเก็บข้อมูลผลการทดสอบทางห้องปฏิบัติการ ได้แก่ ระดับพาราไทรอยด์ฮอร์โมน แคลเซียม และฟอสเฟต ตามช่วงเวลาที่กำหนด

ผลการศึกษา: ระดับ FGF-23 ลดลงอย่างมีนัยสำคัญ ($p < 0.05$) ที่เวลา ๒๐ นาทีหลังจากผ่าตัดต่อมพาราไทรอยด์ และระดับ FGF-23 แสดงค่าความสัมพันธ์เชิงบวกกับระดับฟอสเฟต ($\rho = 0.64$, $p < 0.05$) แคลเซียม ($\rho = 0.51$, $p < 0.05$) และฮอร์โมนพาราไทรอยด์ ($\rho = 0.90$, $p < 0.05$) อย่างมีนัยสำคัญ ที่เวลา ๒๐ นาทีภายหลังการผ่าตัด

วิจารณ์ และสรุปผลการศึกษา: จากผลการศึกษานี้พบว่าระดับ FGF-23 จะมีการเปลี่ยนแปลงและสะท้อนถึงสมดุลพาราไทรอยด์ฮอร์โมนและฟอสเฟตของผู้ป่วยหลังการผ่าตัดต่อมพาราไทรอยด์ได้ ดังนั้นระดับ FGF-23 อาจสามารถใช้เป็นตัวบ่งชี้ที่มีประโยชน์กับแพทย์ในการพยากรณ์โรคและตรวจติดตามในการรักษาผู้ป่วยที่ได้รับการรักษาด้วยการผ่าตัดต่อมพาราไทรอยด์

คำสำคัญ: ไตวายเรื้อรังระยะสุดท้าย, Secondary hyperparathyroidism, การผ่าตัดต่อมพาราไทรอยด์, Fibroblast growth factor 23 (FGF-23)