Disrupted Tubular PTH/PTH1R Signaling Is a Possible Candidate for Postsurgical Kidney Injury in Patients with Advanced Hyperparathyroidism

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OBJECTIVES

Parathyroidectomy (PTX) alleviates various clinical manifestations including hypercalcaemia, caused by primary hyperparathyroidism (PHPT) or tertiary hyperparathyroidism (THPT).

However, little is known about the relation between post-surgical robust PTH reduction and perisurgical renal tubular cell viability. We hypothesized that steep decline of PTH action may trigger tubular cell instability, resulting in possible kidney injury after PTX. We conducted both clinical and experimental studies, regarding how presurgical renal tubular cell function was affected after PTX.

METHODS

Patients

We examined consecutive 52 patients with advanced PHPT or THPT who underwent PTX in our center between June 2015 and May 2017.

Their clinical data including urinary liver-type fatty acid binding protein (L-FABP), known as a tubular biomarker for acute kidney injury (AKI), were obtained from patient charts.

Serological and urinary laboratory findings were compared before and after PTX.

Calcium supplementation protocol after PTX

Postsurgical calcium supplementation was meticulously designed and performed by giving Alfa calcidol and calcium carbonate, aiming to maintain serum calcium at the lower half of the normal range.

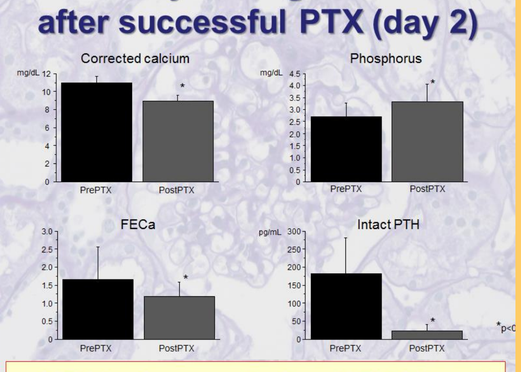
Experimental model

A rat model of hypoparathyroidism with or without chronic kidney disease was produced using the methods described elsewhere (Iwasaki et al; Bone 81:247-254, 2015). Briefly, 13 week-old male Sprague–Dawley rats weighing approximately 350g underwent thyroparathyroidectomy (TPTX) and/or 5/6 subtotal nephrectomy (NX). As control, a group that underwent TPTX alone was also included. Indicated TPTX rats were given continuous infusion of a physiological level of 1–34 PTH (0.1 μg/kg/h, Peninsula laboratories, Talyo Way, San Carios, CA) using a subcutaneously implanted Alzet osmotic mini-pump (Model 2002; Alza Corp., Palo Alto, CA; pumps exchanged every two weeks), and subcutaneous L-thyroxin (Sigma Chemical Company, St. Louis, MO) 4 μg/kg body weight thrice weekly, beginning on the second day after TPTX.

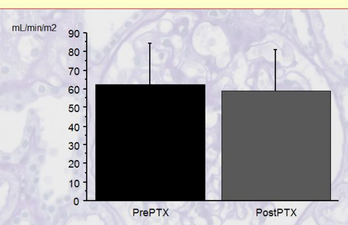
Immunofluorescence technique

Polyclonal antibody against PTH 1 receptor (PTH1R) was purchased from abcam (Cambridge, UK). Immunohistochemical fluorescence is described elsewhere (Kikkawa Y, et al; J.Biol.Chem 277:44864–44869, 2002). Briefly, IgG purified from antiserum was labeled with a biotinylation kit (GEHealthcare, Little Chalfont,UK). Primary antibody-conjugated second- ary antibodies were purchased from Life technologies (Carlsbad, CA). Metalloproteinase inhibitor (BB-94) was purchased from Tocris Bioscience (Ellisville, MO).

Laboratory findings before and after successful PTX (day 2)

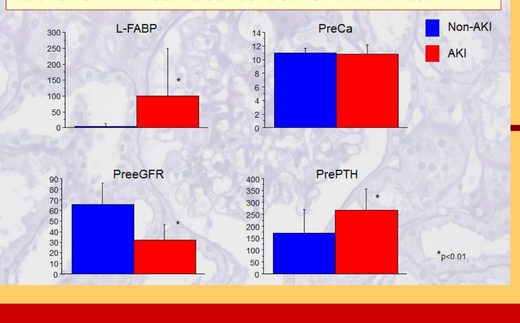


eGFR before and after PTX (day 2)

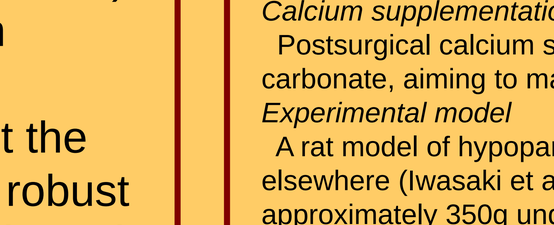


Overall patients who underwent PTX maintained clinically favorable kidney function postsurgically. However, 5 patients had elevated creatinine level, greater than 0.5mg/dL after PTX, which met KDIGO-defined AKI criteria within 48 hours postsurgically.

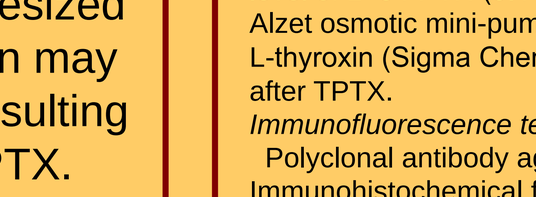
Patients with elevated L-FABP levels before PTX tended to suffer AKI after PTX



Kidney transplant recipients with marked IFTA had lower kidney function (AKI) after PTX, regardless of meticulous postsurgical calcium supplementation

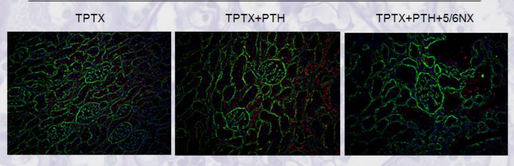


Reduced PTH 1 receptor (PTH1R, red) immunoreactivity in 5/6NX tubular cells



Chronic kidney model rats possibly had lower PTH/PTH1R signaling after TPTX.

Reduced klotho (red) immunoreactivity in 5/6NX tubular cells



Chronic kidney model rats had lower klotho expression after TPTX.

RESULTS

Patient Profile and Biochemistry

Variables	
Gender (m/f)	13/39
Age (years)	59±14
Hyperparathyroidism	
Sporadic	43
MEN1	2
Tertiary	7
Corrected calcium (mg/dL)	11±0.71
Phosphorus (mg/dL)	2.7±0.59
eGFR (mL/min)	62.5±22.0
intact PTH (pg/mL)	181±100

Expressed as mean± SD

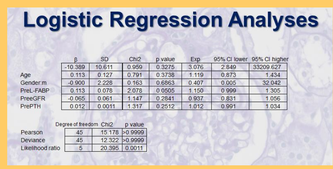
Urinalysis

Variables	
L-FABP (μg/gCr)	13.2±51.9
Beta2-microglubulin (mg/gCr)	802±2575
UACR (mg/gCr)	80.3±297

Expressed as mean± SD

L-FABP; L-type fatty acid binding protein
UACR; urinary albumin creatinine ratio

Logistic Regression Analyses



	β	SD	Chi2	p value	Exp	95% CI lower	95% CI higher
	-10.389	10.611	0.959	0.3275	3.076	2.849	33209.627
Age	0.113	0.127	0.791	0.3738	1.119	0.873	1.434
Gender:m	-0.900	2.226	0.163	0.6863	0.407	0.005	32.042
PreL-FABP	0.113	0.078	2.078	0.0905	1.150	0.999	1.305
PreeGFR	-0.065	0.061	1.147	0.2841	0.937	0.831	1.056
PrePTH	0.012	0.0011	1.317	0.2512	1.012	0.991	1.034

	Degree of freedom	Chi2	p value
Pearson	45	15.178	>0.9999
Deviance	45	12.322	>0.9999
Likelihood ratio	5	20.395	0.0011

Logistic regression analyses revealed that elevated L-FABP before PTX was a borderline risk factor for AKI after PTX.

DISCUSSIONS

- Elevated L-FABP is a potential risk factor for AKI after PTX, even though PTX recovers calcium/phosphorus milieu.
- Blunted PTH action may deteriorate kidney function after PTX, possibly through PTH/PTH1R signaling pathway. Klotho may be involved in that mechanism.
- Direct PTH supplementation is a possible promising approach to avoid acute/subacute kidney injury after PTX. Intervention study is rigorously needed to prove this hypothesis.

CONCLUSIONS

Presurgical tubular cell viability is critical for stable kidney function although serum calcium levels are normalized after PTX. It is strongly recommended to examine renal biomarkers that evaluate tubular function including L-FABP before PTX. Damaged tubular PTH/PTH1R signaling may be the underline mechanism of kidney injury after PTX, possibly through klotho-linked pathyway.

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DOI: 10.3252/pso.eu.54ERA.2017
ePosters supported by F. Hoffmann- La Roche Ltd.