



FGF-23 Levels before and after Renal transplantation

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Abstract

Background: Fibroblast growth factor 23 (FGF23), a novel bone-derived hormone that inhibits phosphate reabsorption and calcitriol production by the kidney, has uncovered primary regulatory pathways and new systems biology governing bone mineralization, vitamin D metabolism, parathyroid gland function and renal phosphate handling.

Objectives: Our study investigated FGF-23 levels in patients with end-stage renal disease before and after a successful renal transplantation and their probable association with markers of bone and mineral metabolism.

Methods: 40 patients were studied for 6 months and divided into two groups (hemodialysis vs renal transplantat patients).The estimations of serum FGE23 ,calcium, phosphorus, intact parathyroid hormone were performed in both groups . We compared the changes in serum FGF23 ,calcium, phosphorus, and intact parathyroid hormone in renal transplant patients 3 and 6 months after successful renal transplantation.

Results: The serum FGF23 decreased significantly after renal transplantation. i PTH and P levels also decrease significantly after renal transplantation, while Ca increase.

Conclusion: FGF23 are markedly increased in patients with end stage renal disease associated with increase in phosphorous and i PTH levels . FGF-23 levels decrease dramatically after successful renal transplantation and remain within normal limits when graft function is good.

i PTH and P levels also decrease significantly after renal transplantation, while Ca increase.

Key words: FGF-23 , CKD, CRF, Renal transplantation .

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LIST OF ABBREVIATIONS

1,25(OH)₂D	1,25dihydroxy vitamin D
25 (OH)D	25dihydroxy vitamin D
ACEI	Angiotensin converting enzyme inhibitor
ADHR	Autosomal dominant hypophosphatemic rickets
ADMA	Asymmetrical diethylarginine
ADYN	Adynamic bone disease
ANP	Atrial natriuretic peptide
ARF	Acute renal failure
ARHR	Autosomal recessive hypophosphatemic rickets
ASARM	Acidic, serine and aspartate rich motif
AKI	Acute kidney injury
ARHR1and 2	Autosomal recessive hypophosphatemic rickets,type 1and 2
BMP	Bone morphogenetic protein
BMD	Bone mineral density
CAR12	Carbonic anhydrase 12
CaCO₃	Calcium carbonate
CaXPO₄	Calciumxphosphate
CKD	Chronic Kidney disease
CKD-MBD	Chronic kidney disease:Mineral and bone disorder
CrCl	Creatinine clearance
CRF	Chronic renal failure
CRP	C-reactive protein

Abbreviations

CSF	Cerebrospinal fluid
CSR	Calcium-sensing receptor
CV	Cardiovascular
CaSR	Calcium-sensing receptor
cKL	Shedded full-length Klotho
CYP24A1	1,25dihydroxyvitamin D 24-hydroxylase
CYP27B1	25-dihydroxyvitamin D 1-alpha-hydroxylase
DM	Diabetes mellitus
DMP1	Dentin matrix protein 1
ECF	Extracellular fluid
ENPPI	Ectonucleotide pyrophosphate/phosphodiesterase
ESRD	End stage renal disease
FDA	Food and drug administration
FGF23	Fibroblast growth factor 23
FSGS	Focal and segmental glomerulosclerosis
FGF	Fibroblast growth factor
Fgf23^{-/-}	Fibroblast growth factor 23 knockout mice
FGFR	Fibroblast growth factor receptor
FD	Fibrous dysplasia
GALNT3	Polypeptide N-acetylgalactosaminyltransferase 3
GFR	Glomerular filtration rate
GPCR	G-protein coupled receptor
HD	Hemodialysis
HFTC	Hyperphosphatemic familial tumoral calcinosis

Abbreviations

HPTH	Hyperparathyroidism
HPT	High turnover osteodystrophy
HRH	Hyperparathyroidism
IL	Interleukin
Klotho-/-	Klotho knockout mice
Ksp -KL-/-	Distal tubule-specific Klotho knockout mice
KDIGO	Kidney Disease Improving Global Outcomes
LAV	Left atrial volume
LDL	Low density lipoprotein
LTOM	Low turnover osteomalacia
LVH	Left ventricular hypertrophy
LVMi	Left ventricular mass index
MEPE	Matrix extracellular phosphoglycoprotein
MGP	Matrix Gla protein
MUO	Mixed uremic osteodystrophy
NaPi- II	Sodium phosphate cotransporters
NKF	National kidney foundation
NO	Nitric oxide
NPT2a	Sodium phosphate cotransporters
OGD	Osteoglophonic dysplasia
OPN	Osteopontin
PHEX	Phosphate-regulating endopeptidase homolog, X-linked
PHPT	Primary hyperparathyroidism
PRMT	Protein methyltransferase

Abbreviations

PTG	Parathyroid gland
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related peptide
PTH-KL-/-	Parathyroid-specific Klotho knockout mice
PTH1R	Parathyroid hormone 1 receptor
RAAS	Renin-Angiotensin-Aldosterone system
RCT	Randomized controlled study
RGD	Arginine glycine aspartate
RVR	Renal vascular resistance
sFRP4	Secreted frizzled-related protein 4
SIBLING	Small integrin binding ligand N-linked glycoprotein
sHPT	Secondary hyperparathyroidism
TGF-B	Transforming growth factor -3
TIO	Tumor induced osteomalacia
TNF	Tumor necrosis factor
US	United states
USRDS	The united states Renal Data System
VC	Vascular calcification
VDR	Vitamin D receptor
VDRE	Vitamin D receptor element
VSMC	Vascular smooth muscle cell
XLHR	X linked hypophosphatemic rickets

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Introduction and aim of the work

- Our understanding of the dramatic changes in bone and mineral metabolism that occur in patients with chronic kidney disease (CKD) has increased with the discovery of the bone-derived hormone fibroblast growth factor 23 (FGF-23) .

(*Silver J et al,2013*)

-The discovery of fibroblast growth factor 23 (FGF23), a novel bone-derived hormone that inhibits phosphate reabsorption and calcitriol production by the kidney, has uncovered primary regulatory pathways and new systems biology governing bone mineralization, vitamin D metabolism, parathyroid gland function and renal phosphate handling. (*Evenepoel P et al,2007*)

-As our knowledge expands regarding the regulation and functions of FGF23, the assessment of FGF23 will become an important diagnostic marker as well as a therapeutic target for management of disordered mineral metabolism in a variety of acquired and hereditary disorders. (*Stubbs J et al ,2007*)

-Disordered phosphate homeostasis with elevated circulating levels of fibroblast growth factor 23 (FGF23) is an early and pervasive complication of CKD. CKD is

likely the most common cause of chronically elevated FGF23 levels, and the clinical condition in which levels are most markedly elevated.(*Wolf M,2012*)

-Recently, FGF-23 has been suggested to be responsible for the hypophosphatemia and inappropriately low calcitriol levels observed after renal transplantation .

(*Evenepoel P et al,2007*)

Aim of work

The aim of the present prospective study was therefore to investigate FGF-23 levels in patients with end-stage renal disease before and after a successful renal transplantation and their probable association with markers of bone and mineral metabolism.

Chapter One

*Bone and Mineral Metabolism in Chronic
Kidney Disease*

Bone and Mineral Metabolism in Chronic Kidney Disease

The chronic kidney disease-bone and mineral disorders (CKD-MBD) represents a dynamic area of research. Recently, new factors such as FGF-23 have been added to the classic list of regulators of bone metabolism, which include calcium, phosphorus, PTH and calcitriol. (*Mejía N et al,2011*)

Vascular calcification, one of the most important complications of CKD-MBD is regulated by a complex variety of promoters and inhibitors. The relationship between vascular calcification, bone loss and mortality, together with the existence of likely common signaling pathways are subject of interesting investigations. (*Mejía N et al,2011*)

In healthy individuals kidneys regulate calcium and phosphorus homeostasis through tubular reabsorption mechanisms. Patients with chronic kidney disease have seriously compromised homeostatic mechanisms, giving rise to different adaptive changes in calcium (Ca), phosphorus (P), parathyroid hormone (PTH), vitamin D and fibroblastic growth factor (FGF-23) levels. (*Torregrosa JV et al ,2011*)

There are various clinical signs, although secondary hyperparathyroidism (SHPT), fractures, bone pain, vascular calcification and cardiovascular events are highlighted as causing lower quality of life with a high morbidity and mortality. (*KBS,2005*) (*Mejía N et al,2011*)