بسم الله الرحمن الرحيم

رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ
الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ
وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ
وَأَصْلِحْ لِي فِي ذُرِّيَّتِي إِنِّي تُبْتُ
إِلَيْكَ وَإِنِّي مِنَ الْمُسْلِمِينَ

صدق الله العظيم سورة الاحقاف
آية (١٥)

# دراسة عن الـ٢٥ هيدروكسى فيتامين د وعامل نمو الألياف ٢٣ فى أمراض الأيض العظامي وعلاقتها بالتكلسات الشريانية فى مرضى الغسيل الكلوى من الأطفال

## رسالة

توطئة للحصول علي درجة الدكتوراه في طب الأطفال

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**كلية الطب – جامعة عين شمس**

**٢٠١٣**

# STUDY OF 25 HYDROXYCHOLECALCIFEROL AND FIBROBLAST GROWTH FACTOR 23 IN METABOLIC BONE DISEASE AND THEIR RELATION TO ARTERIAL CALCIFICATIONS IN CHILDREN ON REGULAR HEMODIALYSIS

Thesis

Submitted for Partial Fulfillment of the MD Degree in

**Pediatrics**

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**Mohamed El-Farsy**

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# List of Abbreviations

| Abb. | Full term |
|---|---|
| *ADHR* | *Autosomal dominant hypophosphatemic rickets* |
| *AH* | *Arterial hypertension* |
| *ARHR* | *Autosomal recessive hypophosphatemic rickets* |
| *ASARM* | *Acidic, serine- and aspartic acid-rich motif* |
| *BMD* | *Bone mineral density* |
| *BMP* | *Bone morphogenic protein* |
| *CaSR* | *Calcium sensing receptor* |
| *Cbfa1* | *Core binding factor 1* |
| *CCA-IMT* | *Common carotid artery-intima media thickness* |
| *CKD* | *Chronic Kidney Disease* |
| *CKD-MBD* | *Chronic Kidney Disease-Mineral and Bone Disorders* |
| *CPM* | *Critical path method* |
| *CRP* | *C-reactive protein* |
| *CVD* | *Cardiovascular disease* |
| *DAG* | *Directed acyclic graph* |
| *DBP* | *Vitamin D binding protein* |
| *DFO* | *Deferoxamine* |
| *DMP-1* | *Dentin matrix protein 1* |
| *DRI* | *Daily recommended intake* |
| *EBCT* | *Electron beam computed tomography* |
| *ELISA* | *Enzyme- linked immunosorbent assay* |
| *ERK* | *Extracellular signal regulated kinase* |
| *ESRD* | *End stage renal disease* |
| *FD* | *Fibrous dysplasia* |
| *FGF23* | *Fibroblast growth factor 23* |
| *FGFR* | *Fibroblast growth factor receptor* |
| *FH* | *Familial hypercholesterolemia* |
| *FMD* | *Flow mediated dilation* |
| *FTC* | *Familial tumoral calcinosis* |
| *GFR* | *Glomerular filtration rate* |
| *GH* | *Growth hormone* |
| *HD* | *Hemodialysis* |
| *HDI* | *High-definition imaging* |
| *HDL* | *High-density lipoprotein* |
| *HRP* | *Horseradish peroxidase* |
| *HS* | *Heparin sulfate* |
| *HT* | *Hypertension* |
| *ICA* | *Internal carotid artery* |

# List of Abbreviations (Cont...)

| Abb. | Full term |
|---|---|
| ***IGF*** | *Insulin growth factor* |
| ***IGFBPs*** | *Insulin growth factor binding proteins* |
| ***IMT*** | *Intima-media thickness* |
| ***iPTH*** | *Intact parathyroid hormone* |
| ***IQR*** | *Inter quartile range* |
| ***kDa*** | *Kilo dalton* |
| ***KDIGO*** | *Kidney Disease Improving Global Outcomes* |
| ***KDOQI*** | *Kidney Disease Outcomes Quality Initiatives* |
| ***Kt/V*** | *K:Dialyzer's clearance, t:time of the session, V: volume of clearance* |
| ***LDL*** | *Low density lipoprotein* |
| ***LVH*** | *Left ventricular hypertrophy* |
| ***MAS*** | *McCune Albright syndrome* |
| ***MEPE*** | *Matrix extracellular phosphoglycoprotein* |
| ***NaPi-2a*** | *Sodium phosphate co-transporter type 2a* |
| ***NMD*** | *Nitrite mediated dilation* |
| ***NSB*** | *Non specific binding tubes* |
| ***OCT*** | *22-Oxacalcitriol* |
| ***PH*** | *Primary hypertension* |
| ***PHEX*** | *Phosphate regulating gene with homologies to endopeptidases on the X-chromosome* |
| ***PTHrP*** | *Parathyroid hormone related protein* |
| ***PWV*** | *Pulse wave velocity* |
| ***RIA*** | *Radio- immunoassay* |
| ***ROD*** | *Renal osteodystrophy* |
| ***RPM*** | *Revolutions per minute* |
| ***Rtx*** | *Renal transplantation* |
| ***SIBLING*** | *Short integrin binding-ligand, N-linked glycoprotein* |
| ***TIO*** | *Tumor induced osteomalacia* |
| ***TOD*** | *Target organ damage* |
| ***VDR*** | *Vitamin D receptor* |
| ***WCSA*** | *Wall cross-sectional area* |
| ***XLH*** | *X-linked hypophosphatemia* |

# INTRODUCTION

Children with chronic kidney disease (CKD) have multiple risk factors for impaired bone development, including abnormal mineral metabolism, secondary hyperparathyroidism, poor linear development, and malnutrition (including vitamin D insufficiency) ***(Helenius et al., 2006).***

Total body stores of vitamin D correlate with $25(OH)D_3$ and not the active, dihydroxylated form. Despite having low affinity for the vitamin D receptor, $25(OH)D_3$ has an important role in regulating PTH due to its higher serum concentration ***(Cozzolino et al., 2006).***

Careful attention to $25(OH)D_3$ (native vitamin D) nutrition is fundamental to the optimal management of renal osteodystrophy. Vitamin D deficiency is prevalent in all children, including those with normal renal function, and the presence of renal insufficiency exacerbates this deficiency ***(National Kidney Foundation "KDOQI", 2005).***

***Ishimura et al. (1999),*** concluded that the treatment with native vitamin D in patients with CKD on regular hemodialysis normalized $1,25(OH)_2D_3$, suggesting that an increase in the substrate concentration maximized 1α-hydroxylase activity.

Fibroblast growth factor 23 (FGF23) is a recently characterized peptide hormone produced mainly in the bone. It

is secreted in response to phosphorus load, and its main function is the promotion of urinary phosphate excretion and the suppression of $1,25(OH)_2D_3$ production in the kidney. As such, FGF23 plays an important role in the maintenance of systemic phosphate homeostasis ***(Fukagawa and Kazama, 2006)***.

Recent investigations have demonstrated that serum FGF23 level can be a useful marker for the prediction of the future development of refractory hyperparathyroidism and the response to vitamin D therapy in chronic kidney disease patients ***(Fukagawa and Kazama, 2006).***

Extra-skeletal calcification, including vascular calcification, is prevalent in adults treated with dialysis, has its origin in childhood, and is associated with significant cardiovascular morbidity and mortality. Vascular calcification in the uremic patients develops primarily in the vascular media. Hypercalcemia, hyperphosphatemia, and elevated levels of the calcium×phosphorus product have all been implicated in the progression of the burden of the extra-skeletal calcification ***(Chertow et al., 2004).***

# AIM OF THE STUDY

- Assess vitamin D stores through $25(OH)D_3$ in pediatric patients on regular hemodialysis.
- Examine the predictive value of fibroblast growth factor 23 for the development of CKD-Mineral and Bone Disorder (CKD-MBD), refractory hyperparathyroidism, and the response to vitamin D therapy in pediatric patients on regular hemodialysis.
- Assess the effect of native vitamin D treatment on CKD-MBD in pediatric patients on regular hemodialysis.
- Evaluation of vascular calcification in children on regular hemodialysis.