



STUDY OF THE POLYMORPHISM *BsmI* AND *TaqI* IN VITAMIN D RECEPTOR GENE IN EGYPTIAN PATIENTS WITH CHRONIC KIDNEY DISEASE

Thesis

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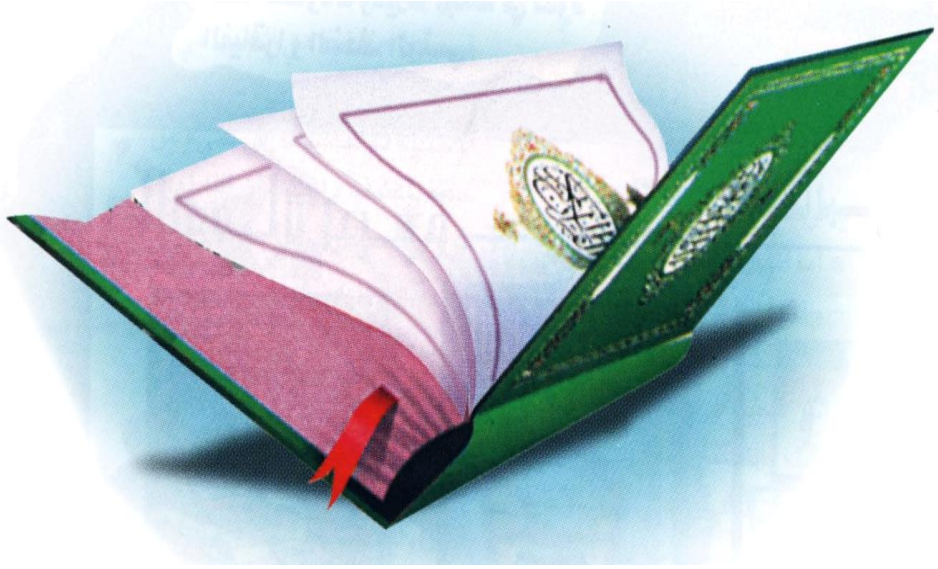
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

إِنَّا فَتَحْنَا لَكَ فَتْحًا مُبِينًا



صدق الله
العظيم

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List of Abbreviations

<i>Abb.</i>	<i>Full term</i>
25-OH VIT D	25- -hydroxy vitamin D
AAS	Atomic absorption spectrophotometry
ACR	Albumin / creatinine ratio
AE	Acridinium ester
AER	Albumin excretion rate
AMP	2amino-2-methyl-1-propanol
bALP	Bone alkaline phosphatase
BCP	Bromocresol purple
BGP	Bone gla protein
BMD	Bone mineral density
bp	Base pair
Ca	Calcium
CaR	Calcium sensing receptors
CDC	Centres for disease control and prevention
Cdx	Caudal-related homeodomain protein
CI	Confidence intervals
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease –mineral bone disorder
Conc	Concentration
CPBA	Competitive protein binding assay
Cr	Creatinine
CT	Computed tomography
CTX	Products of type I collagen C-telopeptide
CVD	Cardiovascular disease
DBD	DNA binding domain
DM	Diabetes mellitus
DNA	Deoxy ribonucleic acid
DHPLC	Denaturing high-performance liquid chromatography
dNTPs	Deoxynucleotide triphosphates
DXA	Dual X-ray absorptiometry
EDTA	Ethylene diamine tetra-acetic acid
eGFR	Estimated glomerular filtration rate
EGIPT-CKD	Egypt Information, Prevention, and Treatment of Chronic Kidney Diseases Program
EIA	Enzymatic assay
ELISA	Enzyme-linked immunosorbent assay
ESRD	End-stage renal disease

List of Abbreviations cont...

<i>Abb.</i>	<i>Full term</i>
FBG	Fasting blood glucose
FGF23	Fibroblast growth factor 23
FITC	Anti-fluorescein labeled
GFR	Glomerular filtration rate
GLDH	Glutamate dehydrogenase
HCC	Hepatocellular carcinoma
HPLC	High-performance liquid chromatography
HVDRR	Hereditary vitamin D-resistant rickets
ICTP	Products of type I collagen C-telopeptide
ID-MS	Isotope dilution–mass spectrometry
iPTH	Intact Parathyroid hormone
IQR	Inter-quartile range
IRMA	immunoradiometric assay
ISE	Ion-selective electrodes
K/DOQI	Kidney Disease Outcome Quality Initiative
KCl	Potassium Chloride
kda	Kilo Dalton
KDIGO	Kidney Disease Improving Global Outcomes
KDIGO-MBD	Kidney Disease Improving Global Outcomes- Mineral Bone Disease
LBD	Ligand-binding domain
LC/MS	Liquid chromatography mass spectrometry
LVH	Left ventricular hypertrophy
MA	Microalbuminuria
MDRD	Modification of diet in renal disease formula
MgCl₂	Magnesium Chloride
MS	Mass spectrometry
NA	Nucleic acid
NGS	Next-generation" or "second-generation" sequencing
NKDEP	National Kidney Disease Education Program
NKF	National kidney foundation
NTX	Products of type I collagen N-telopeptide
OC	Osteocalcin
OR	Odds ratio

List of Abbreviations cont...

<i>Abb.</i>	<i>Full term</i>
PCR- RFLP	Polymerase chain reaction-restriction fragment length polymorphism
Pcr	Plasma creatinine
PCR	Polymerase Chain Reaction
Pi	Phosphorus
PICP	Procollagen type 1 C propeptides
PINP	Procollagen type 1 N propeptide
PMP	Paramagnetic particles
QCT	Quantitative computed tomography
RANKL	Receptor activator of nuclear factor κ -B ligand
RFLP-PCR	Restriction fragment length polymorphism-polymerase chain reaction
RFLPs	Restriction Fragment Length Polymorphisms
RIA	Radioimmunoassay
RO	Renal Osteodystrophy
RT	Room temperature
RXR	Retinoid X receptor
SNP	Single nucleotide polymorphism
SPSS	Statistical package for the social science
T.Bil	Total Bilirubin
TAE	Tris-acetate EDTA buffer
TBE	Tris-borate EDTA buffer
TRAP5b	Tartrate resistant acid phosphatase
Ucr	Urinary creatinine
UK	United Kingdom
URL	Upper reference limit
UTR	Untranslated region
UV	Ultraviolet
V	Volume of urine
VDDR2A	Vitamin D-dependent rickets type 2A
VDR	Vitamin D receptor
VDRE	Vitamin D response elements
WHO	World health organization

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem and a leading cause of morbidity and mortality worldwide, accounting for 60% of all deaths, affecting 5–10% of the world population with an ever-increasing prevalence. Estimated Prevalence of CKD (Stages 3-5) in the World is nearly 200-333 million (*Kidney Disease Improving Global Outcomes (KDIGO), 2012*), while the prevalence of end-stage renal disease patients in Egypt per million population is about 522 (*Soliman et al., 2012*).

Chronic kidney disease mineral and bone disorders (CKD-MBD) is a common complication of CKD and an important cause of morbidity and decreased life quality (*Delanaye et al., 2014*). CKD-MBD comprises a group of inter-related abnormalities of either one or a combination of the following: *i*) serum bone biomarkers: calcium, phosphorus, parathyroid hormone (iPTH), or vitamin D metabolism, *ii*) bone: bone turnover, mineralization, volume, linear growth or strength and *iii*) the vasculature: arterial calcification (*Al Rukhaimi et al., 2014*). It is clinically detectable as early as stage (2) CKD. Up-to 20% of death in dialysis patients may be associated with poorly controlled CKD-MBD, illustrating the importance for its management efficiently (*Evenepoel et al., 2015*).

Serum levels of 25-hydroxy vitamin D and iPTH provide an accurate picture of bone turnover and mineralization states. Therefore, they could be used with other serum bone biomarkers as non-invasive sensitive bone markers to help management of MBD in CKD patients as recommended by the Kidney Disease Improving Global Outcome- mineral and bone disorders (KDIGO.MBD) (*Sprague et al., 2015*).

The kidney is the main site for the conversion of 25-hydroxyvitamin D to circulating 1, 25-dihydroxyvitamin D. Vitamin D receptor (VDR) is a transcription factor that mediates the genomic effects of vitamin D. It is activated by 1, 25-dihydroxyvitamin D to induce/repress genes that maintain mineral homeostasis and skeletal integrity, and prevent secondary hyperparathyroidism, hypertension, immune disorders, renal and cardiovascular damage as the VDR is widely expressed in many tissues and cells such as heart, kidney, immune cells, brain and muscle (*Dusso, 2011; Zhou et al., 2014*).

The VDR gene is located on chromosome 12q12.14. The VDR-regulated gene products tightly coordinate intestinal calcium and phosphate absorption, bone metabolism, renal calcium and phosphate reabsorption, and parathyroid function to prevent or slow the development of secondary hyperparathyroidism, phosphate retention, and soft-tissue calcifications (*Khadijeh et al., 2014*).

There have been several VDR gene polymorphisms named according to the restriction sites, such as VDR *BsmI* (*rs1544410*), *FokI* (*rs2228570*), *ApaI* (*rs7975232*) and *TaqI* (*rs731236*). The VDR gene polymorphisms have been shown to drive the progression toward secondary hyperparathyroidism and influence the response to calcitriol and the survival in CKD patients (*Zhou et al., 2014*).

Due to the complex role played by vitamin D in kidney disease, the genotyping for VDR variants in CKD patients has been regarded as a way for improving the management of the disease, given that some VDR genotypes have been proven to influence the responsiveness to therapeutical approaches (*Santoro et al., 2015*).