



بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / مني مغربي أحمد

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى

مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد





Clinical Value of CASR Gene Polymorphism on Cinacalcet Response in Hemodialysis Patients with Secondary Hyperparathyroidism

Thesis

*Submitted for Partial Fulfillment of Master Degree
in Internal Medicine*

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2022

Acknowledgments

*First and foremost, I feel always indebted to
GOD the Most Beneficent and Merciful.*

*I wish to express my deepest thanks, gratitude and appreciation to **Prof. Dr / Sahar Mahmoud Shawki**, Professor of Nephrology, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

*Special thanks are due to **Ass. Prof. Dr/ Maha AbdELmoneim Behairy**, Assistant Professor of Internal Medicine and Nephrology, Faculty of Medicine, Ain Shams University, for her supervision, continuous help, encouragement throughout this work and tremendous effort she has done in the meticulous revision of the whole work.*

*I am deeply thankful to **Ass. Prof. Dr/ Hoda Ahmed Abdelsattar**, Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her great help, outstanding support, active participation and guidance.*

*Last but not least my sincere thanks and appreciation to **Dr/ Ahmed Yehia Mohamed**, Lecturer of Internal Medicine and Nephrology, Faculty of Medicine, Ain Shams University, for his sincere efforts, fruitful encouragement.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Neveen Nabil Abdelshaheed

List of Contents

Title	Page No.
List of Tables.....	i
List of Figures	iv
List of Abbreviations.....	vi
Introduction	1
Aim of the Work	3
Review of Literature	
Chapter 1: Chronic Kidney Disease – Mineral Bone Disease (CKD- MBD)	4
Chapter 2: Calcium Sensing Receptor (CaSR) Gene Polymorphism	24
Chapter 3: Management of Secondary Hyperparathyroidism (SHPT) in Hemodialysis Patients	37
Patients and Methods.....	56
Results.....	71
Discussion.....	109
Summary	114
Conclusion	118
Recommendation.....	118
References	119
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table 1:	Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012	5
Table 2:	Classification of hyperparathyroidism.....	21
Table 3:	Recommended Levels of Biochemical Parameters in Patients with Chronic Kidney Disease.....	23
Table 4:	Regulators of CaSR.....	29
Table 5:	Pharmacokinetic properties of calcimimetics.....	48
Table 6:	Components of the Reaction Mix in Each PCR Reaction.....	65
Table 7:	Thermal Cycling Protocol.....	66
Table 8:	Relation between Fluorescence Signals and Sequences in Each Sample.....	68
Table 9:	Distribution of the studied cases according to demographic data (n = 50)	72
Table 10:	Distribution of the studied patients according to demographic parameters (n = 50).....	73
Table 11:	Descriptive analysis of the studied patients according to baseline labs (n = 50).....	74
Table 12:	Comparison between laboratory data before and after treatment with cinacalcet (n = 50)	75
Table 13:	Correlation between PTH and different parameters (n = 50)...	76
Table 14:	Descriptive analysis of the studied patients according to delta change and percentage of change (n = 50)	77
Table 15:	Distribution of the studied cases according to % of reduction PTH (n = 50)	78

List of Tables cont...

Table No.	Title	Page No.
Table 16:	Distribution of the studied cases according to PTH post treatment (n = 50).....	79
Table 17:	Distribution of the studied cases according to rs1042636 (n = 50).....	80
Table 18:	Distribution of the studied patients according to CASR gene /SNP rs1802757 (n = 50#)	81
Table 19:	Comparison between Responder and Non responder according to demographic data (n = 50)	83
Table 20:	Comparison between Responder and Non responder according to calcium, phoshous, alkaline phosphatase	84
Table 21:	Relation between rs1042636 and allele with delta change and percentage of change (n = 50)	85
Table 22:	Relation between rs1802757 and allele with delta change and percentage of change (n = 48)	87
Table 23:	Relation between rs1042636 and allele with demographic data (n = 50)	90
Table 24:	Relation between rs1802757 and allele with demographic data (n = 50)	91
Table 25:	Comparison between Responder and Non responder % of reduction PTH according to rs1042636	93
Table 26:	Comparison between Responder and Non responder % of reduction PTH according to rs1802757	95
Table 27:	Comparison between Responder and Non responder PTH post treatment to CASR gene rs1042636	97

List of Tables cont...

Table No.	Title	Page No.
Table 28:	Comparison between Responder and Non responder PTH post treatment to rs1802757.....	99
Table 29:	Distribution of the studied cases according to haplotype (n = 96#).....	101
Table 30:	Comparison between Responder and Non responder % of reduction PTH according to haplotype	102
Table 31:	Comparison between Responder and Non responder PTH post treatment to haplotype.....	104
Table 32:	Relation between Haplotype with delta change and percentage of change alkaline phosphate (n = 96)	106
Table 33:	Univariate and multivariate Logistic regression analysis for the parameters affecting responder (% of delta change of PTH ≥ 20)	107
Table 34:	Univariate and multivariate Logistic regression analysis for the parameters affecting responder (PTH ≤ 600).....	108

List of Figures

Fig. No.	Title	Page No.
Figure 1:	Normal vitamin D metabolism and steps that are affected by high FGF-23 in CKD	8
Figure 2:	The parathyroid–bone–kidney feedback loop	10
Figure 3:	Pathogenesis of secondary hyperparathyroidism (SHP) in chronic kidney disease	11
Figure 4:	Pathogenesis of secondary hyperparathyroidism.....	12
Figure 5:	Receptor resistance in SHP	14
Figure 6:	Regulators of parathyroid cell proliferation in SHP.....	17
Figure 7:	Calcium-sensing receptor (CaR)	26
Figure 8:	Regulation of parathyroid hormone secretion by the calcium-sensing receptor	28
Figure 9:	Effect of calcimimetic on CaSR	30
Figure 10:	Treatment algorithm for secondary hyperparathyroidism (SHPT) in pre-dialysis CKD and dialysis patients.....	38
Figure 11:	Phosphate binders for patients with chronic renal impairment	43
Figure 12:	Vitamin D receptor (VDR) activation.....	45
Figure 13:	Genomic DNA extraction procedure.	63
Figure 14:	Distribution of the studied cases according to rs1042636.....	80
Figure 15:	Distribution of the studied patients according to rs1802757	82
Figure 16:	Relation between rs1042636 and allele with delta change PTH (pg/ml).....	86
Figure 17:	Relation between rs1042636 and allele with percentage of change PTH (pg/ml) (n = 50).....	86
Figure 18:	Relation between rs1802757 and allele with delta change PTH (pg/ml) (n = 50).....	89
Figure 19:	Relation between rs1802757 and allele with percentage of change PTH (pg/ml) (n = 50).....	89

List of Figures cont...

Fig. No.	Title	Page No.
Figure 20:	Comparison between Responder and Non responder % of reduction PTH according to rs1042636.....	94
Figure 21:	Comparison between Responder and Non responder % of reduction PTH according to rs1802757.....	96
Figure 22:	Comparison between Responder and Non responder PTH post treatment to rs1042636.....	98
Figure 23:	Comparison between Responder and Non responder PTH post treatment to rs1802757.....	100
Figure 24:	Distribution of the studied cases according to haplotype.....	101
Figure 25:	Comparison between Responder and Non responder % of reduction PTH according to haplotype.....	103
Figure 26:	Comparison between Responder and Non responder % of reduction PTH according to haplotype.....	105

List of Abbreviations

Abb.	Full term
BMI	Body mass index
CaR.....	Calcium receptor
CASR.....	Calcium sensing receptor
CaXP	Calcium x phosphorous
CDDS	Central dialysis fluid delivery system
CKD	Chronic kidney disease
CT	Confidence interval
CVS.....	Cardio vascular system
CYP3A4	Cytochrome P 3 A4
DCM	Disatolic cardiomyopathy
DM.....	Diabetes mellitus
EDTA.....	Ethylene diamine tetra acetic acid
ESRD.....	End stage renal disease
FAM.....	Fluorescein amidites
FE.....	Fisher exact
FGF.....	Fibroblast growth factor
GFR	Glomerular filtration rate
GN.....	Glomerulonephritis
HBG.....	Hemoglobin
HCV	Hepatitis C virus
HD	Hemodialysis
HTN	Hypertension
IPTH	Intact parathyroid hormones
IQR	Interquatile range
IS	Speaman coefficient
KDIGO	Kidney disease improving global outcomes
Kg/m	Kilogram/meter
LL	Lower limb
MBD	Mineral bone disease
MC	Monte carlo
Mg.....	Milligram
MGB	Minor groove binder
N.....	Number
NFQ	Non flurorescent quencher

List of Abbreviations cont...

Abb.	Full term
OR.....	Odd's ratio
P	Phosphouls
PCKD	Polycytic kidney disease
PTH	Parathyroid hormone
PTx.....	Para thyroectomy
SD	Standard deviation
SHPT.....	Secondary hyperparathyrodism
SNP.....	Single necleotide polymorphysm
TM	Melting temperature
TM	Transmembrane
u	Mann whitney test
UL.....	Upper limb
URR.....	Urea reduction rate
VDR.....	Vitamin D receptor
VDRA.....	Vitamin D activators
X	Chi square test

INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD), associated clinical manifestations, termed CKD– mineral bone disorder (CKD-MBD), include an increased risk of fracture, cardiomyopathy, anemia, pruritus, extra skeletal calcification, increased risks of mortality and morbidity among CKD patients . *(Tabibzadeh et al., 2021).*

Management of secondary hyperparathyroidism can attenuate many of these manifestations. Treatment options include the use of pharmacologic doses of 1, 25 dihydroxy vitamin D (calcitriol) or related analogs, the calcimimetic cinacalcet, and parathyroidectomy *(Kuczera et al., 2013).*

The calcium-sensing receptor (CaSR), a G protein located on the parathyroid gland, is key in the regulation of PTH levels. In hyperplastic parathyroid glands from patients with SHPT, CaSR down regulation has been demonstrated, particularly in glands with nodular hyperplasia, and has been shown to be an important pathogenic contributor to the progression of SHPT *(Rottembourg et al., 2019).*

Cinacalcet is an oral calcimimetic agent available for treatment of SHPT in chronic kidney disease (CKD). Cinacalcet increases the sensitivity of the calcium-sensing receptor (CASR), which are agonists of the calcium receptor induce a conformational change in the calcium receptor, which reduces the

threshold for stimulation by extracellular calcium. Because cinacalcet acts directly on the parathyroid gland to suppress the production and secretion of PTH, the result is a decrease in iPTH the main regulator of PTH secretion, to extracellular ionized calcium ions, resulting in decreased parathyroid hormone (PTH) level. In dialysis patients with SHPT, cinacalcet is efficacious in lowering levels of PTH, serum phosphate, and serum calcium as well as reducing the risks of parathyroidectomy, fractures, and cardiovascular hospitalization (*Warady et al., 2019*).

AIM OF THE WORK

The aim of the present study is to evaluate the frequency of variants of study genes related to PTH regulation (CASR rs 1042636 and CASR rs 1802757) and to assess the effect of these single nucleotide polymorphism on cinacalcet response among prevalent hemodialysis patients with secondary hyperparathyroidism.

CHRONIC KIDNEY DISEASE – MINERAL BONE DISEASE (CKD- MBD)

Definition

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than 3 months, with health implications. CKD is commonly associated with disorders of mineral and bone metabolism manifested by either one or a combination of the following three components:

- Abnormalities of calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and vitamin D metabolism.
- Abnormalities in bone turnover, mineralization, volume linear growth, or strength.
- Extraskeletal calcification.

The workgroup of the Kidney Disease Improving Global Outcomes (KDIGO) recommended the use of the term chronic kidney disease-mineral and bone disorder (CKD-MBD) to describe a systemic disorder that incorporates these abnormalities. Each of these abnormalities is associated with high mortality rates primarily from cardiovascular complications (which is the leading cause of death in patients at all stages of CKD) (*KDIGO CKD-MBD update Work Group, 2017*).