بسم الله الرحمن الرحيم

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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

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Neveen Nabil Abdelshaheed

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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 thyrodectomy
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).***