



# **Evaluation of serum sclerostin level and its correlation with valvular calcification in haemodialysis patients**

*Thesis*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

لَسْبَدَانِكَ لَا عِلْمَ لَنَا  
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

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## Dedication

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## *List of Abbreviations*

Abb.	Full term
$\gamma$ -carboxylation ...	Gamma Carboxylation
ACR.....	Albumin/Creatinine Ratio
ADMA.....	Asymmetrical Di Methy Arginine
AF .....	Atrial Fibrillation
AGEs.....	Advanced Glycation end Products
ALP .....	Alkaline Phosphatase
AMI.....	Acute Myocardial Infarction
ARBs .....	Angiotensin II Receptor Blockers
ATP .....	Adenosine Triphosphate
AV .....	Aortic Valve
A-V .....	Arterio-Venous
AVC.....	Aortic Valve Calcification
BMD.....	Bone Mineral Density
BMP .....	Bone Morphogenetic Protein
CABG.....	Coronary Artery Bypass Graft Surgery
CAC.....	Coronary Artery Calcifications
CAD .....	Coronary Artery Disease
Cbfa1 .....	Core Binding Factor Al
CCB.....	Calciprotein Particles
CHF .....	Congestive Heart Failure
CIMT.....	Carotid Intima-Media Thickness
CK-1 .....	Casein Kinase 1
CKD .....	Chronic Kidney Disease
CV .....	Cardiovascular
CVD .....	Cardiovascular Disease
DKK1 .....	Dickkopf-Related Protein 1
DM .....	Diabetes Mellitus

*List of Abbreviations Cont...*

Abb.	Full term
ECM.....	Extracellular Matrix
EF .....	Ejection Fraction
ELISA .....	Enzyme-Linked Immunosorbent Assay
ePPi.....	Extracellular Pyrophosphate
ER .....	Endoplasmic Reticulum
ESA.....	Erythropoietin Stimulating Agent
ESRD .....	End Stage Renal Disease
EV .....	Extracellular Vesicles
Fet-A.....	Fetuin - A
FGF-23.....	Fibroblast Growth Factor-23
FMC .....	Fetuin-Mineral Complex
FSAP .....	Factor VII-Activating Protease
Fz .....	Frizzled
GFR.....	Glomerular Filtration Rate
GIT.....	Gastrointestinal Tract
GN.....	Glomerulonephritis
GSK3.....	Glycogen Synthase Kinase 3
HD.....	Hemodialysis
HDL .....	High-density Lipoprotein
HOPE.....	Heart Outcomes Prevention Evaluation
HTN .....	Hypertension
IL-1 .....	Interleukin1
IL-6 .....	Interleukin 6
iPTH .....	Intact Parathyroid Hormone
IU/week.....	International Unit Per Week
JUPITER.....	Justification for the Use of statins in Prevention, an Intervention Trial Evaluating Rosuvastatin
kDa .....	Kilodalton

*List of Abbreviations Cont...*

Abb.	Full term
KDIGO.....	Kidney Disease Improving Global Outcomes
Kg.....	Kilogram
KRM.....	Kremen-1
Kt/v .....	K - Dialyzer Clearance of Urea. T - Dialysis Time. V - Volume of Distribution of Urea
LDL.....	Low-Density Lipoprotein
LDL-c .....	Low-Density Lipoprotein-Cholesterol
LRP.....	Low-Density Lipoprotein Receptor-Related Protein
LVH .....	Left Ventricular Hypertrophy
MBD.....	Mineral and Bone Disorder
MGP.....	Matrix Gla Protein
MHD .....	Maintenance Hemodialysis
miRs.....	Micro-RNAs
MM.....	Multiple Myeloma
mRNA .....	Messenger Ribonucleic Acid
MSX2 .....	Msh Homeobox 2
MV .....	Matrix Vesicles
MVC.....	Mitral Valve Calcification
MVSC.....	Multipotent Vascular Stem Cells
NADPH.....	Nicotinamide Adenine Dinucleotide Phosphate
NO.....	Nitric oxide
OPG .....	Osteoprotegerin
OPN .....	Osteopontin
PCI.....	Percutaneous Coronary Intervention
PCK.....	Polycystic Kidney Disease
PCT .....	Proximal Convoluted Tubules
PD .....	Peritoneal Dialysis

## *List of Abbreviations Cont...*

Abb.	Full term
PET scan.....	Positron Emission Tomography SCAN
Pi.....	Inorganic Phosphate
PiT-1 .....	Na-Dependent Phosphate Co-Transporter
PO4 .....	Phosphate
PPi .....	Pyrophosphate
PTH.....	Parathyroid Hormone
PTH1R.....	Parathyroid Hormone Receptor
P-value.....	Probability Value
PVD.....	Peripheral Vascular Disease
RAGE.....	Receptor for Advanced Glycation End-Products
RANK .....	Receptor Activator of Nuclear Factor Kb
RANKL .....	Receptor Activator of Nuclear Factor Kb Ligand
RAS.....	Renin-Angiotensin System
RUNX2 .....	Runt-Related Transcription Factor 2
S.....	Serum
SCD.....	Sudden Cardiac Death
Scl .....	Sclerostin
SD .....	Standard Deviation
SKD.....	Stone Kidney Disease
SM.....	Smooth Muscle
SMC .....	Smooth Muscle Cell
SOST gene .....	Sclerostin Gene
SPSS .....	Statistical Package for the Social Sciences
Streptavidin-HRP .	Streptavidin- Horseradish Peroxidase
TIA.....	Transient Ischemic Attack
TNAP .....	Tissue Nonspecific Alkaline Phosphatase

*List of Abbreviations Cont...*

Abb.	Full term
TNF.....	Tumor Necrosis Factor
TRAIL.....	TNF-Related Apoptosis-Inducing Ligand
TRPV6 .....	Transient Receptor Potential Cation Channel, Subfamily V, Member 6
UF .....	Ultrafiltration
US .....	Ultrasound
USRDS.....	United States Renal Data System
VC .....	Vascular Calcification
VDRAs .....	Vit-D Receptor Agonists
Vit-D .....	Vitamin D
Vit-K .....	Vitamin K
VKA .....	Vitamin K Antagonists
VSMC.....	Vascular Smooth Muscle Cell
Wnt .....	Wingless-Type Mouse Mammary Tumor Virus Integration Site
$\beta$ -Catenin .....	Beta Catenin

## INTRODUCTION

**E**nd Stage Renal Disease (ESRD) patients have a well-recognized increased risk of cardiovascular disease that begins early in the course of chronic kidney disease (CKD) and results in 10-fold or higher cardiovascular mortality rates after the start of renal replacement therapy (*Sarnak, 2003*).

Cardiovascular diseases remain the leading cause of morbidity and mortality in patients of chronic kidney disease, especially in those on dialysis therapy. The risk of cardiovascular death is particularly high 10– 20 times greater than in the general population (*Pencak et al., 2013*).

Vascular calcification (VC) and arterial stiffness have been identified as independent predictors of all-cause and cardiovascular mortality in stage 5 chronic kidney disease (*Sigrist et al., 2007*).

The mechanisms of uremic vascular calcification are multifactorial. Beyond the bone and mineral disturbances, the activation of the Wnt/ $\beta$ -catenin signaling pathway was found to be associated with vascular calcification and may be more profound in uremic conditions (*Chih-Yu et al., 2015*).

Higher serum sclerostin levels are found in haemodialysis patients and are associated with higher bone mineral diseases (*Guillaume et al., 2016*).

Sclerostin is secreted mainly by osteocytes and regulates osteoblast activity. Its concentration is high in prevalent haemodialysis patients and positively associated with age and negatively with parathyroid hormone (*Balemans et al., 2014*).

Plasma concentration of sclerostin increases in haemodialysis patients with secondary hyperparathyroidism treated with cinacalcet. This effect is related to decrease of serum PTH concentration (*Kuczera et al., 2016*).