ASSESSMENT OF THE MYOSTATIN AND VITAMIN D_3 RECEPTOR GENE EXPRESSION IN RELATION TO MUSCLE STATE

Thesis

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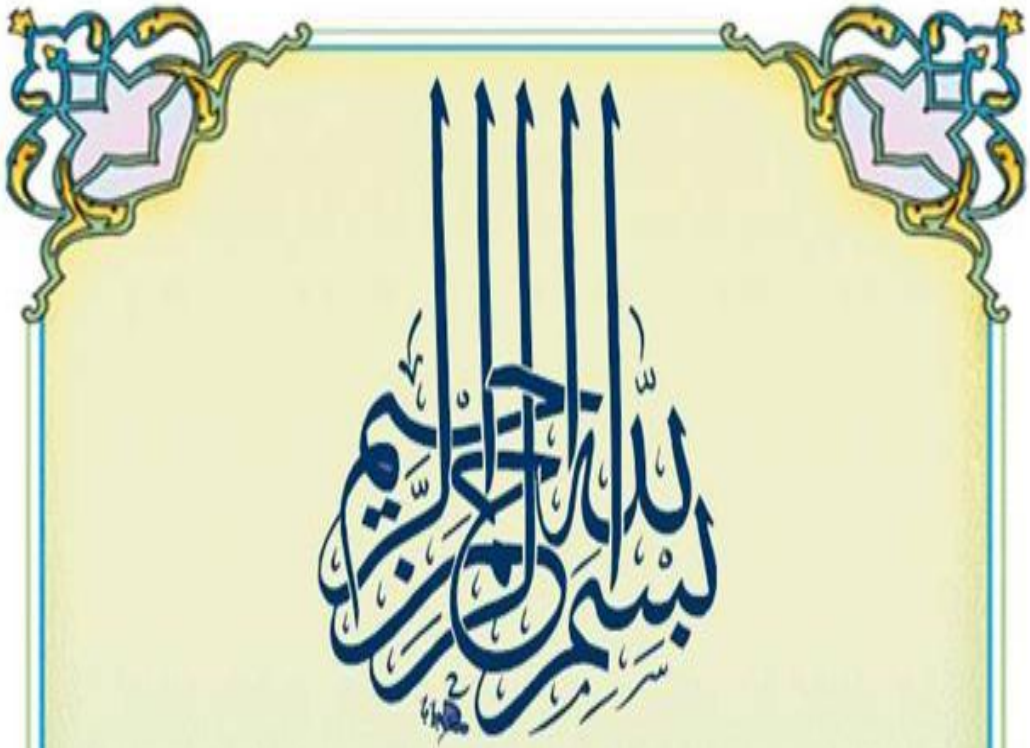

﴿ قالوا سبحانك لا علم لنا الا ما علمتنا

إنك انت العليم الحكيم ﴾

صدق الله العظيم

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Ghada Mohamed Gamal El- Din Ishak

DEDICATION

To My Dear Parents who support and

help me throughout my whole life

To My Dear Brother

Ghada Mohamed Gamal el-din

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Abbreviation	***Meaning***
$1,25(OH)_2$-D_3	1,25-Dihydroxyvitamin D_3.
24, 25 $(OH)_2$ D_3	24, 25 Dihydroxyvitamin D_3.
ACE	Angiotensin-Converting Enzyme.
ActRIIB	Activin Type IIB Receptor.
ADL	Activities of Daily Living.
Akt	Alpha Serine/Threonine-Protein Kinase.
ALK4	Activin-Like Kinase 4.
ALK5	Activin-Like Kinase 5.
AMP	Adenosine Monophosphate.
ATP	Adenosine Triphosphate.
BIA	Bio-Impedance Analysis.
BMI	Body Mass Index.
BMP	Bone Morphogenetic Protein.
bp	Base Pair.
c-Src	Cellular Src.
CT	Computed Tomography.
CVS	Cardio-Vascular System.
CYP2D11	Cytochrome P450 2D11.
CYP2D25	Cytochrome P450 2D25.
CYP2R1	Cytochrome P450 2R1.
DBP	Vitamin D Binding Protein.
DXA	Dual Energy X-Ray Absorptiometry.

Abbreviation	***Meaning***
EDTA	Ethylene-Diamine-Tetra-Acetic Acid.
EWGSOP	The European Working Group On Sarcopenia In Older People.
FLRG	Follistatin Related Gene.
Fst gene	Follistatin Gene.
GASP-1	Growth And Differentiation Factor-Associated Serum Protein 1.
GDF8	Growth And Differentiation Factor 8.
GH	Growth Hormone.
Id	Inhibitor of Differentiation.
IGF-1	Insulin Like Growth Factor-I.
IL-6	Interleukin- 6.
IU	International Unit.
LTBP3	Latent TGF-B Binding Protein 3.
M	Molar.
m	Meter
MAC	Mid-Arm Circumference.
MAMC	Mid-Arm Muscle Circumference.
MgCl2	Magnesium Chloride.
miR-27	Micro RNA-27.
ml	Milliliter.
MRI	Magnetic Resonance Imaging.
mRNA	Messenger RNA.
MSTN gene	Myostatin Gene.

Abbreviation	***Meaning***
mTOR	Mammalian Target of Rapamycin.
PBK	Partial Body Potassium.
PBS	Phosphate Buffer Saline.
PCR	Polymerase Chain Reaction.
pmol	Pico-Mole.
PRT	Progressive Resistance Training.
RAAS	Renin-Angiotensin-Aldosterone System.
RNA	Ribonucleic Acid.
ROC	Receiver Operating Characteristics.
RT-PCR	Reverse Transcription PCR.
RXR	9-Cis-Retinoic Acid Receptor.
siRNA	Small Interfering RNA.
SM	Skeletal Muscle.
T2DM	Type 2 Diabetes Mellitus.
Ta	Annealing Temperature.
Taq	Thermus Aquaticus.
TBK	Total Body Potassium.
Tm	Melting Temperature.
TNFα	Tumor Necrosis Factor-α.
TNFβ	Tumor Necrosis Factor-β.
TUGT	Timed Get Up & Go Test.
UVB	Ultra-Violet B.

Abbreviation	***Meaning***
VDR	Vitamin D Receptor.
VDREs	Vitamin D Response Elements.
VitD	Vitamin D.
µg	Micro-Gram.
µl	Micro Liter.

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INTRODUCTION

A grave change associated with human ageing is progressive decline in skeletal muscle mass, a downward spiral that may lead to decreased strength and functionality. The term sarcopenia (in Greek, sarx for flesh and penia for loss), first proposed by **Rosenberg, 1997** describes the age-related loss of skeletal muscle mass and strength**.**

Sarcopenia has been defined as the loss of skeletal muscle mass and strength that occurs with advancing age **(Morley et al., 2001).** However, a widely accepted definition of sarcopenia suitable for use in research and clinical practice is still lacking.

Ali & Garcia, 2014 found that sarcopenia is increasingly being recognized as a geriatric syndrome and a key public health issue. Starting at the age of 30 years, individuals lose 1–2% of muscle per year, and by the age of 80 years, 30% of the muscle mass is lost.

Geriatric syndromes are common, complex and costly states of impaired health in older individuals. Geriatric syndromes result from incompletely understood interactions of disease and age on multiple systems, producing a constellation of signs and symptoms. Delirium, falls and incontinence are examples of geriatric syndromes **(Inouye et al., 2007)**. It was suggested that it may be likewise helpful to recognize sarcopenia as a geriatric syndrome because this view promotes its identification and treatment even when the exact causes remain unknown **(Cruz-Jentoft et al., 2010)**.

The well-recognized functional consequences of sarcopenia include gait and balance problems and increased risk for fall physical inactivity, decreased mobility, slow gait, and poor physical endurance **(Kim & Choi, 2013)**

Ultimately, these impairments can lead to the loss of physical functional independence. However, sarcopenia may also contribute to an increased risk for chronic diseases such as diabetes and osteoporosis **(Dutta, 1997).**

Emerging evidence has shown that vitamin D administration improves muscle performance and reduces falls in vitamin D-deficient older adults **(Bordelon et al., 2009)**

On the other hand, Myostatin(growth and differentiation factor 8 [GDF8]) is a transforming growth factor- superfamily member with importance as a negative growth regulator for skeletal muscle **(Roth, 2003).**

Mutations in the myostatin gene result in a hypermuscular phenotype in mice **(Mc pherron& Lee, 1997)**.

However, little is known of the underlying mechanism or the role 1,25(OH)2-D3 plays in promoting myogenic differentiation at the cellular and/or molecular level and its relation to myostatin gene expression. **Garcia et al., 2011** declared that addition of vitamin D3 to muscle cell culture decrease expression of myostatin.

The prevalence of falls in older community-dwelling elderly individuals is approximately 30% and such estimate increases to 40% among the "oldest-old" **(Landi et al, 2012a)**

Bahat et al (2010) found that the prevalence of sarcopenia differs between different populations, ages, gender and between settings such as the community and nursing homes **Masanes et al., (2012)** found the prevalence of sarcopenia was 33% in elderly women and 10% for males in healthy community-dwelling elderly in an urban area of Barcelona (Spain). **Tichet et al., (2008)** found the prevalence of sarcopenia was 23.6% in women and 12.5% in men in community-dwelling elderly in France. In Taiwan **Chien et al., (2008)** estimated the prevalence of sarcopenia to be 18.6% and 23.6% in elderly community dwelling women and men respectively.