#### Serum Sclerostin Level and its Relation to Osteoporosis in Patients with Liver Cirrhosis

#### **Ehesis**

Submitted for partial fulfillment of Master Degree in Internal Medicine

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2014-2015



# Acknowledgments

First and before all, I would like to express my deepest thankfulness and gratefulness to **ALLAH** who gave me the soul and the strength through this work. As our prophet said that who doesn't thank people doesn't thank **ALLAH**.

I am honored to express my deepest appreciation and profound gratitude to **Prof. Dr. Sayed Mohamed Shalaby,** Professor of Internal Medicine, Faculty of Medicine Ain Shams University, whose generous advice; close supervision and kind encouragement have greatly supported me to finish this work.

My best thanks and respect to **Dr. Wael Ahmed Yousry**, Assistant professor of Internal Medicine, Faculty of Medicine Ain Shams University, for his valuable advice and thorough follow up which greatly affected the outcome of this work.

I will be always grateful and appreciating to **Dr. Maha Mohsen Mohamed Kamal,** Assistant professor of Internal
Medicine, Faculty of Medicine Ain Shams University, for her
support and guidance during this work.

I'd like to thank my Father, my Mother, and my Wife for their great support.

Lastly, special thanks to all subjects who participated in this work.

Candidate

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#### **List of Abbreviations**

## Abbr. Full-term

ALP Alkaline phosphatase BMD Bone mineral density BMF Bone Morphogenetic factors BMI Body mass index BMP Bone Morphogenetic protein BMU Bone remodling unit CLD Chronic liver disease CTCK C-terminal cystiene k-not like domain Dexa Dual energy x-ray absorptiometry DM Diabetes Mellitus ELISA Enzyme linked immunosorbent assay FGF Fibroblast growth factor GH Growth hormone
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CTCK C-terminal cystiene k-not like domain  Dexa Dual energy x-ray absorptiometry  DM Diabetes Mellitus  ELISA Enzyme linked immunosorbent assay  FGF Fibroblast growth factor
DexaDual energy x-ray absorptiometryDMDiabetes MellitusELISAEnzyme linked immunosorbent assayFGFFibroblast growth factor
DMDiabetes MellitusELISAEnzyme linked immunosorbent assayFGFFibroblast growth factor
ELISAEnzyme linked immunosorbent assayFGFFibroblast growth factor
FGF Fibroblast growth factor
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GHD Growth hormone deficiency
<b>GHRH</b> Growth hormone releasing hormone
GIOP Glucocorticoid induced osteoporosis
HBsAg Hepatitis B surface Antigen
HBV Hepatitis B Virus
HCC Hepatocellular carcinoma
HCV Hepatitis C Virus
HCV RNA Hepatitis C Virus Ribonucleic Acid
HCVAb Hepatitis B Virus Antibodies
HDL-
cholesterol High density Lipoprotein cholesterol
HRT Hormonal replacement therapy
IGF-1 Insulin-like Growth Factor
IL Interleukin
INF Interferon

## List of Abbreviations (Cont.)

### Abbr. Full-term

LT	Liver transplantation	
LDL-	Low Density Lipoprotein – cholesterol	
cholesterol		
MBD	Metabolic bone disease	
MEN	Multiple endocrine neoplasia	
M-CSF	M-colony stimulating factor	
NIH	National institute of health	
OLT	Orthoptic liver transplantation	
OM	Osteomalacia	
OP	Osteoporosis	
OPG	Osteoprotegrin	
PBC	Primary biliary cirrhosis	
PBM	Peak bone mass	
PDG	Platelet derived growth factor	
PMO	Post menopausal osteoporosis	
PSC	Pimary sclerosing cholangitis	
PTH	Parathyroid hormone	
QCT	Quantitative computerized tomography	
RANKL	Receptor activaror of nuclear factor kb ligand	
SERM	Selective estrogen receptor modulator	
SHBG	Serum hormone binding globulin	
ST	Standard deviation	
TRAP	Tartarate resistant acid phosphatase	
TSH	Thyroid stimulating hormone	
T3	Tri-iodothyronine	
<b>T4</b>	Tetra-iodothyronine	
WHO	World Health Organisation	

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#### Introduction

Virrhosis is scarring of the liver as a result of continuous long term liver damage. Scar tissue replaces healthy tissues in the liver and prevents the liver from working properly. This condition can be fatal when liver decompensate. However, it usually takes years to reach this stage and treatment can help to slow its progression (*Friedman*, 2014).

Each year in the UK, around 4000 people die from cirrhosis and 700 people with this condition need liver transplant to survive (*Friedman*, 2014).

In 2010, Egypt had the highest age standardized cirrhosis mortality rates, 72.2 deaths per 100000. Almost one fifth (18.1 %) of all deaths in males 45 to 54 years old were due to liver cirrhosis (*Lozano et al.*, 2012).

In the early stages of cirrhosis, there are usually few symptoms such as loss of appetite, nausea and abdominal discomfort. In the later stages, symptoms can include: jaundice, hematemesis, oedema, ascites and other symptoms of decompesation (*Friedman*, 2014).

Osteodystrophy is one of the signs of liver cirrhosis (*Goel and Kar*, 2010). In general, maintenance of bone over time requires balance between the formation of new bone tissue and breakdown and removal of old bone tissue. This

balance is maintained by a variety of hormones. One of them is sclerostin (*Van der Horest et al.*, 2007).

Sclerostin is an osteocyte-derived negative regulator of bone formation. Sclerostin inhibits osteoblastic proliferation and differentiation and promotes osteoblast apoptosis (*Toussaint et al., 2010*). Sclerostin exerts its effects by interfering with a process called Wnt signaling, which plays a key role in the regulation of bone formation (*Van der Horest et al., 2007*).

Sclerostin production by the osteocytes is increased by calcitonin and inhibited by parathyroid hormone (PTH) and cytokines including; oncostatin M, cardiotrophin-1 and leukemia inhibitory factor (*Bellido et al.*, 2013).

It is suggested that circulating sclerostin is higher in patients with advanced liver cirrhosis than in healthy persons or patients with early liver cirrhosis. The relationship between circulating sclerostin and liver function indicates a possible role of the liver in sclerostin metabolism (*Collier*, 2007).

#### **Aim of the Work**

The aim of the work is to evaluate serum sclerostin level in relation to osteoporosis in patients with early (Child A) and late (Child B and C) stages of liver cirrhosis and in patients who had underwent liver transplantation.

#### **Physiology of Bone Metabolism**

ones in human body perform many functions as providing support for muscles and protection for the bone marrow, acting as a reservoir of calcium and phosphates (bones influence the metabolism of calcium and phosphates significantly) and releasing phosphate and bicarbonate in the long-term metabolic acidosis (*Buckwalter et al.*, 2012).

#### \*Composition of bone:

#### 1) Cells:

- a) Osteoblasts and osteocytes synthesize new bone tissue
- **b**) Osteoclasts are bone-degrading cells

#### 2) Extracellular matrix:

- **a)** Organic component: collagen type I and non-collagenous proteins (e.g. osteocalcin, protein S)
- **b)** Inorganic component: apatite crystallic form Ca<sub>3</sub> (PO<sub>4</sub>)<sub>2</sub> (it can exist in a form of hydroxyapatite Ca<sub>10</sub> (PO<sub>4</sub>)<sub>6</sub> (OH)<sub>2</sub>, carbonate apatite Ca<sub>10</sub> (PO<sub>4</sub>)<sub>6</sub>CO<sub>3</sub> or fluorapatite Ca<sub>10</sub> (PO<sub>4</sub>)<sub>6</sub>F<sub>2</sub>) (*Raggatt et al., 2010*).

#### a )Osteoblasts:

Osteoblasts originate from mesenchymal cells of bone marrow. They exhibit high proteosynthetic activity and are rich in alkaline phosphatase. Their membranes contain receptors for PTH, calcitriol, growth factors, estrogens etc.

and also mechanoreceptors. Their primary function is bone matter formation, bone mineralization and management of maturation and activity of osteoclasts (*Raggatt et al.*, 2010).

#### b) Osteoclasts:

Osteoclasts are formed from hematopoietic cells (monocyte macrophage lineage). They contain lysosomes filled proteolytic enzymes (collagenase, gelatinase, cathepsins) and acid phosphatase isoenzyme.

Membrane of osteoclasts contains a proton pump (it is able to decrease pH = 7 to pH = 4) and selected receptors (e.g. for calcitonin). Osteoclast activity but at the same time is controlled by signals from osteoblasts. Their primary function is bone resorption (runs parallel to an increased calcemia) (*Raggatt et al.*, 2010).

#### \*Bone remodeling:

Throughout life bone remodeling occurs continuously. It is very important because it allows the adaptation of form and organized structure of bones to biomechanical forces, maintaining the integrity of bone (repair microtraumas) and homeostasis of calcium and phosphates.

People achieve so-called peak bone mass – PBM at age 25. Followed by variable length (average of 5 years) remodeling balance, which means that bone resorption intensity