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

Thesis

Submitted for partial fulfillment of Master Degree
in Internal Medicine

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2014-2015


وأنزل الله عليك
الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن
تَعْلَمُ وكَانَ فَضْلُ
اللَّهِ عَلَيْكَ عَظِيماً
صدق الله العظيم
سورة النساء الآية (١١٣)

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
GHD	Growth hormone deficiency
GHRH	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-cholesterol	Low Density Lipoprotein – 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
T4	Tetra-iodothyronine
WHO	World Health Organisation

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Introduction

Cirrhosis 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

Bones 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 $Ca_3 (PO_4)_2$ (it can exist in a form of hydroxyapatite – $Ca_{10} (PO_4)_6 (OH)_2$, carbonate apatite – $Ca_{10} (PO_4)_6CO_3$ or fluorapatite – $Ca_{10} (PO_4)_6F_2$) ***(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