The study of insulin resistance and its relation to serum osteocalcin among Diabetic patients with chronic HCV infection

Thesis

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LIST OF ABBREVIATIONS

Akt/PKB	Akt Protein Kinase B
ATP	Adenosine Tri-Phosphate
bFGF	basic Fibroblast Growth Factor
BGP/BGLAP	Bone Gamma-carboxyglutamic acid protein
BMP	Bone Morphogenetic Protein
BMD	Bone Mineral Density
BMI	Body Mass Index
CHC	Chronic Hepatitis C
DCCT	Diabetes Control and Complications Trial
DNA	Deoxyribonucleic Acid
Elisa	Enzyme Linked Immunosorbent Assay
FBG	Fasting Blood Glucose
FFA	Free fatty acids
FPI	Fasting Plasma Insulin
GDM	Gestational Diabetes Mellitus
GLUT4	Glucose Transporter-4
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinome
HCV	Hepatitis C Virus
HCV RNA	Hepatitis C Virus Ribonucleic Acid
HCVAb	Hepatitis B Virus Antibodies
HDL-cholesterol	High density Lipoprotein cholesterol

LIST OF ABBREVIATIONS (CONT.)

HIV/AIDS	Human Immuno-deficiency Virus / Acquired Immune Deficiency Syndrome
HOMA	The Homeostatic Model Assessment
HOMA-IR	The Homeostatic Model assessment to detect Insulin Resistance
IFNAR2c	Interferon Receptor Chain 2
IGF-1	Insulin-like Growth Factor
IGFBP-2	Insulin Growth Factor Binding Protein-2
IL-6	Interleukin-6
IRs	Insulin Receptors
IRS	Insulin Receptor Substrate
IR	Insulin Resistance
JAK	Janus Kinase
LDL-cholesterol	Low Density Lipoprotein - cholesterol
MAPK/ERK	Mitogen-Activated Protein Kinase/ The Extracellular signal Regulated Kinase
NAFLD	Non-Alcoholic fatty Liver Disease
NGSP	National Glycohemoglobin Standardization Program
OC	Osteocalcin
OGTT	Oral Glucose Tolerance Test
OV	Oesophageal varices
PAI-1	Plasminogen activator inhibitor-1
PEG-IFN	Pegylated interferon
PI3K	Phosphatidyl-Inositol-3-Kinase
PKA	Protein Kinase A
PKC	Protein Kinase c

LIST OF ABBREVIATIONS (CONT.)

PTH	Parathyroid hormone
ROS	Reactive Oxygen Species
Runx2	Runt Realted Transcription Factor2 on Chromosome17 for protein coding
SOCS-3	Suppressor Of Cytokines-3
STAT	Signal transducer and activator of transcription
SVR	Sustained Virological Response
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
TGF-β	Transforming growth factor-β
TNF-α	Tumor Necrosis Factor-α
Twist2	Twist basic helix-loop-helix transcription factor 2 on chromosome 1 for protein coding
TYK2	Tyrosine kinase 2
VDR	Vitamin D Receptors
β –cell	Beta cells of pancreas

Introduction

Introduction

Kanazawa, (2011) showed that osteocalcin functions as a hormone that regulates glucose metabolism and fat mass. Also **Zhou, et al., (2009)** suggested that osteocalcin can increase β-cell proliferation, insulin secretion, and insulin sensitivity by increasing adiponectin gene expression.

Clinical observations showed that serum osteocalcin levels are significantly lower in type-2 diabetic patients, and become normal following improvement of glycemic control **(Oz, et al., 2006).**

Circulating osteocalcin levels have been reported to be inversely associated with measures of insulin resistance (fasting insulin and glucose levels and homeostasis model assessment of insulin resistance [HOMA-IR]) and adiposity (body mass index [BMI]) and fat percentage ***(Kindblom et al., 2009).***

A population-based study in an HCV hyperendemic area revealed that chronic HCV infection was associated with severe insulin resistance and with mild atherosclerosis, suggesting a unique characteristic of HCV-related metabolic abnormality ***(Miyajima, et al., 2012).***

There is no evidence based data that is published studying the relation between serum osteocalcin and glucose homeostasis with chronic liver disease and HCV chronic active hepatitis.

Aim of the work

The study of insulin resistance and its relation to serum osteocalcin among Diabetic patients with chronic HCV infection.

Chapter I: Osteocalcin

Introduction

Osteocalcin is a 49-amino acid bone matrix non-collagen protein expressed mainly by osteoblasts **(Ferron, et al., 2010).** It is also known as "bone gamma-carboxyglutamic acid protein (BGP) and is the most abundant noncollagenous protein of bone matrix **(Razzaque. 2011).** Studies have verified that adipose tissue could regulate bone remodeling through the adipokine leptin by acting on osteoblasts **(Elefteriou, et al., 2005).** Osteocalcin has been recognized as a bone-derived hormone to regulate energy metabolism. Osteocalcin knockout mice exhibited glucose intolerance, increased fat mass, insulin resistance, decreased expression of insulin target genes in liver and muscle, and decreased adiponectin gene expression in adipose tissue **(Lee, et al., 2007).** Administration of recombinant osteocalcin increased insulin secretion, decreased blood glycaemia and weaken the development of obesity. In an in vivo study, when wild-type mice were given osteocalcin through implanted pumps (~3 ng/h), results indicated significantly lower blood glucose levels compared with placebo **(Ferron, et al., 2008).**

- ***Osteocalcin expression, synthesis and release:***

  The BGLAP gene encoding for OC is expressed efficiently in osteoblasts and odontoblasts, and more weakly in the ovaries, prostate, testes, skeletal muscle, thyroid and other tissues **(Jung, et al., 2001).** Once transcribed, osteocalcin undergoes posttranslational modifications within the osteoblast before its secretion**.** Vitamin D stimulates directly osteocalcin transcription (in fact the gene has a "vitamin D responsive element") while vitamin K regulates carboxylation processes. In addition, various growth factors, hormones, or cytokines can modulate osteocalcin production through signaling pathways or interacting with

transcription factors that act on osteocalcin gene promoter region (BGLAP gene in chromosome 1q25–q31) **(Villafan-Bernal, et al., 2011).**

Carboxylated Gla residues are involved in calcium and hydroxyapatite binding, allowing osteocalcin deposition in mineralized bone matrix **(Razzaque. 2011).** Levels of undercarboxylated osteocalcin are influenced by vitamin K status, whereas total circulating concentrations of osteocalcin are influenced by bone cells activity independent of vitamin K **(Booth, et al., *2013*).**

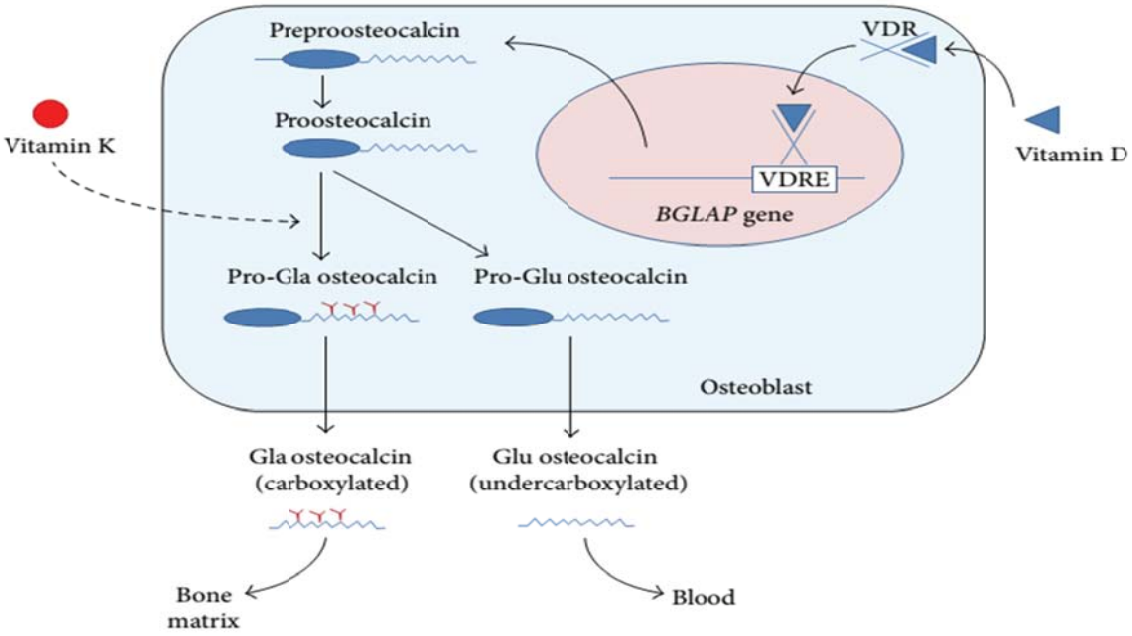

Figure 1: Osteocalcin synthesis in osteoblasts.

VDR: Vitamin D Receptors, BGLAP gene: Bone Gamma Carboxyglutamic acid containing Protein **(Aurora Patti, et al., 2013).**