SERUM HEPCIDIN LEVEL AND IRON PROFILE IN OBESE PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE

Thesis

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Mohammed Mokhtar Abdel-Hakim

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List of Abbreviations

Abb.	Full term
AA	Amino acids
AASLD	American Association for the Study of Liver Diseases
ACG	American College of Gastroenterology
AI	Anemia of inflammation
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ApoB	Apolipoprotein B
APOC3	Apoprotein C3
APRI	AST/Platelets ratio index
ARBs	Angiotensin receptor blockers
ARFI	Acoustic radiation force impulse imaging
AST	Aspartate transaminase
BARD	BMI, AST/ALT ratio, DM score
Bax	Bcl-2-associated X protein;
BM	Bone marrow
BMI	Body mass index
CAP	Controlled attenuation parameters
CCHREBP	Carbohydrate-responsive element binding protein
CK-18	Cytokeratin 18
CP	Ceruloplasmin
CRN	Clinical research network
CSI	Chemical shift imaging
CT	Computed tomography
DcytB	Duodenal cytochrome b
DIOS	Dysmetabolic iron overload syndrome
DMT-1	Divalent metal transporter-1
DNL	de novo lipogenesis

List of Abbreviations (Cont...)

Abb.	Full term
DRG	Diagnosis related group
ELF	Enhanced liver fibrosis panel
FDA	Food and drugs administration
FFA	Free fatty acids
FGF 21	Fibroblast growth factor 21
FIB-4	Fibrosis 4 score
FLI	Fatty liver index
FPN	Ferroportin
FXR	Farsenoid X receptor
GCKR	Glucokinase (hexokinase 4) regulator
GGT	Gamma-glutamyl transferase
H, E	Hematoxylin and eosin
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High density lipoprotein
HFE	Hemochromatosis gene
HH	Heridetary hemochromatosis
HJV	Hemojuvelin
HMG-COA	Hydroxy-3-methyl-glutaryl-coenzyme A reductase
HP	Hepcidin
IL-6	Interleukin-6
IR	Insulin resistance
IRE	Iron response element
IRIDA	Iron-refractory iron-deficiency anemia
IRP	Iron regulatory protein
JNK	Jun N-terminal kinase

List of Abbreviations (Cont...)

Abb.	Full term
LAP	Lipid Accumulation Product
LDL	Low density lipoprotien
LEAP-1	Liver-expressed antimicrobial peptide 1
LPS	Lipopolysaccharide
LRH-1	Liver receptor homolog 1
LXR	Liver X receptor
LYPLAL1	Lysophospholipase-like1
MDB	Mallory-Denk bodies
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCAN	Gene encoding neurocan
NF-κB	Nuclear factor kappa B
NKT	Natural Killer T
OD	Optical density
PlPLA3	Patatin-like phospholipase domain containing 3
PPAR	Peroxisome proliferator-activated receptor-gamma
PTX	Pentoxyfilline
RBC	Red blood cell
ROS	Reactive oxygen species
RTE	Real time shear wave elastography
SFA	Saturated fatty acid
SNP	Single nucleotide polymorphism
SREPB-1	Sterol regulatory elementbinding protein 1
T2DM	Type 2 diabetes mellitus

List of Abbreviations (Cont...)

Abb.	Full term
TF	Transferrin
TfR2	Transferrin receptor 2
TG	Triglycerides
TGF-β	Transforming growth factor beta
TLR-4	Toll-like receptor-4
TMPRSS6	Transmembrane protease, serine 6
TZD	Thiazolidinediones
U. S	United States
UDCA	Ursodeoxycholic acid
UPR	Unfolded protein response
USG	Ultrasonography
VAT	Visceral adipose tissue
VLDL	Very low-density lipoprotein
WC	Waist circumference
WHR	Waist to Hip ratio

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) describes a spectrum of liver clinico pathological changes extending from simple steatosis through non-alcoholic steatohepatitis (NASH) to fibrosis ***(Farrell and Larter, 2006).***

It is the most common cause of chronic liver injury worldwide. It has been documented in 10 to 15 percent of normal individuals and 70 to 80 percent of obese individuals ***(Bellentani et al., 2000).*** NAFLD has doubled during last 20 years and it is the leading cause of liver disease in the western countries, but recent data confirmed that NAFLD play an equally important role worldwide ***(LaBrecque et al., 2014).***

It was initially believed that NAFLD is a completely benign disorder; but histological follow-up studies showed that progression to fibrosis occurs in about one third of patients ***(Bellentani et al., 2000).*** On the other hand, approximately 7% of patients with NASH will progress to cirrhosis within 3 years ***(Wong et al., 2010).*** It is currently the third most common cause of liver transplantation and is projected to be the leading cause in 2020 ***(McCullough, 2011).***

In addition, several prospective studies showed that NASH is independently associated with increased mortality, from both liver disease-related and cardiovascular causes ***(Ekstedt et al., 2006).***

Liver biopsy remains the golden standard for the diagnosis of NAFLD and for distinguishing simple steatosis from NASH. However, biopsy is an invasive method carrying a small but not negligible risk of Complications ***(Myers et al., 2008).*** So ultrasonography is accepted as an initial screening for fatty liver because it is noninvasive, inexpensive, and widely available ***(Palmentieri et al., 2006).*** A Japanese study conducted on the general population shows that ultrasound scanning has a sensitivity of 94% and a specificity of 84% for detecting liver steatosis ***(Angulo et al., 2007).***

In addition, it has been shown that adipose tissue expresses hepcidin, a key regulator of iron homeostasis, and this expression is enhanced in massively obese patients with NAFLD ***(Bekri et al., 2006).***

The liver has important role in the regulation of iron homeostasis. Primarily, it is one of the major storage sites of iron. Additionally, it produces transferrin, iron carrier glycoprotein in the plasma and hepcidin, the key hormone regulating the systemic iron homeostasis ***(Park et al., 2001).***

Hepcidin controls plasma iron concentration and tissue distribution of iron by inhibiting intestinal and macrophage iron efflux. Iron *per se* has also been shown to modulate hepcidin levels, thus hepcidin is now considered as the iron regulatory hormone ***(Kemna et al., 2007).***

Aim of the Work

The aim of the work is to assess serum hepcidin level and iron profile in obese patient with NASH and compare the results with normal age and sex matched individuals.

Chapter 1

NONALCOHOLIC FATTY LIVER DISEASE

Introduction

Nonalcoholic fatty liver disease (NAFLD) is describes a spectrum of liver clinico pathological changes extending from simple steatosis through non-alcoholic steatohepatitis (NASH) to fibrosis and is defined strictly as fat accumulation of >5% of the liver weight on histology. However, in clinical practice and for epidemiological reasons, it is the presence of fatty liver at ultrasonography (USG) in the absence of known secondary causes of fatty liver ***(Farrell and Larter, 2006).***

It is the most common cause of chronic liver injury worldwide; it has been documented in 10 to 15 percent of normal individuals and 70 to 80 percent of obese individuals ***(Bellentani et al., 2000).***

The prevalence of NAFLD has doubled during last 20 years and it is the leading cause of liver disease in the western countries, but recent data confirmed that NAFLD play an equally important role worldwide and it is the third most common risk factor for HCC after viral infection and alcohol ***(LaBrecque et al., 2014).***