

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

Thesis

Submitted For partial fulfillment of Master Degree in
Internal Medicine

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2017

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبِّحْكَ لَا إِلَهَ إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

حَمْدُ اللَّهِ الْعَظِيمِ

سورة البقرة الآية: ٣٢

Acknowledgment

*First and foremost, I feel always indebted to **ALLAH**, the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Tarek Maged Elsakaty**, Professor of Internal Medicine - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Sherief Sadek Shabana**, Assistant Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I am deeply thankful to **Dr. Hany Haroun Kaiser**, Assistant Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, for his great help, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

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..... | Farnesoid 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 | Hereditary 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 lipoprotein |
| 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- κ B | Nuclear factor kappa B |
| NKT | Natural Killer T |
| OD..... | Optical density |
| PIPLA3..... | Patatin-like phospholipase domain containing 3 |
| PPAR | Peroxisome proliferator-activated receptor- gamma |
| PTX..... | Pentoxifylline |
| 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 element binding 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*).