# Value of Serum Leptin Level in Patients with Decompensated Liver Cirrhosis and Hepatocellular Carcinoma

Thesis
Submitted for Partial Fulfillment of MSc Degree in
Internal Medicine

Presented by
## Ahmed Ibrahim El Said Mandour
M.B.B.Ch
Misr University for Science and Technology

Supervised by
## Prof. Amal shawky Bakir
Professor of Gastroenterology and Hepatology

## Prof. Reham Ezzat Al Swaff
Assistant Professor of Gastroenterology and Hepatology

## Dr. Hany Samir Rasmy
Lecturer of Gastroenterology and Hepatology

Faculty of Medicine
Ain Shams University
2016

قَالُوا

سُبْحَانَكَ لَا عِلْمَ لَنَا

إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ

الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

# Acknowledgment

First thanks to **ALLAH** to whom I relate any success in achieving any work in my life.

I wish to express my deepest thanks, gratitude and appreciation to *Prof. Amal shawky Bakir,* Professor of Gastroenterology and Hepatology for her meticulous supervision, kind guidance, valuable instructions and generous help.

Special thanks are due to *Prof. Reham Ezzat Al Swaff,* Assistant Professor of Gastroenterology and Hepatology for her sincere efforts, fruitful encouragement.

I am deeply thankful to *Dr. Hany Samir Rasmy,* Lecturer of Gastroenterology and Hepatology for his great help, outstanding support, active participation and guidance.

*Ahmed Ibrahim El Said Mandour*

# List of Contents

# *List of Tables*

# *List of Tables* **cont...**

# *List of Figures*

| Fig. No. | Title | Page No. |
|---|---|---|

# List of Abbreviations

| Abb. | Full term |
|------|-----------|
| AFP | Alpha fetoprotein |
| AFU | Alpha-L-fucosidase |
| AKI | Acute kidney injury |
| ALT | Alanine transaminase |
| AST | Aspartate transaminase |
| BCLC | Barcelona-Clinic Liver Cancer |
| BCP | Basal core promoter |
| BMI | Body mass index |
| CDC | Centers for Disease Control and Prevention |
| CHB | Chronic hepatitis B |
| CLD | Chronic liver disease |
| COX | Cyclooxygenase |
| DCP | Des-gamma-carboxyprothrombin |
| DM | Diabetes mellitus |
| EMT | Epithelial–mesenchymal transformation |
| FDG | Fluorodeoxyglucose |
| GGT | $\gamma$-glutamyl transferase |
| GPC3 | Glypican-3 |
| HCC | Hepatocellular carcinoma |
| HCV | Chronic hepatitis C infection |
| HE | Hepatic Encephalopathy |
| HOMA-IR | Homeostatic model assessment of insulin resistance |
| HPA | hypothalamo- pituitary- adrenal axis |
| HRS | Hepatorenal syndrome |
| HSCs | Histiocytes |
| htert | Human telomerase reverse transcriptase |
| INR | International normalized ratio |
| IR | Insulin resistance |
| KCs | Kupffer cells |
| LEPR | Leptin receptor gene |
| LPS | Lipopolysaccharides |
| LR | Leptin receptor |

# *List of Abbreviations* **cont...**

| Abb. | Full term |
|------|-----------|
| MRI | Magnetic resonance imaging |
| MS | Metabolic syndrome |
| NASH | Nonalcoholic steatohepatitis |
| Ob | Obese |
| OBR | The leptin receptor |
| PET | Positron Emission Tomography |
| PIVKA-II | Proteins induced by vitamin K absence |
| PMN | Polymorphonuclear leucocytes |
| PT | Prothrombin time |
| RFA | Radiofrequency ablation |
| SBP | Spontaneous Bacterial Peritonitis |
| SEER | Surveillance, Epidemiology and End Results |
| T.B , D.B | Total and direct bilirubin |
| TACE | Transcatheter arterial chemoembolization |
| TERT | Telomerase reverse transcriptase |
| TG | Triglycerides |
| TGF | Tumor growth factor |
| VEGF | Vascular endothelial growth factor |

# Abstract

All participants were subjected to history taking, clinical examination, laboratory investigations, abdominal ultrasonography, and measurement of fasting serum insulin and serum leptin levels.

This study revealed highly significant higher serum leptin; fasting insulin and HOMA-IR were found in patients with HCC than in cirrhotic HCV patients.

These results strongly points to the potential role of leptin and leptin resistance in the pathogenesis of HCC.

There is direct relationship between leptin and insulin resistance, so that an increase in blood leptin concentration can lead to insulin resistance.

The aim of this study is to determine the value of serum leptin assessment in patients with HCV related liver cirrhosis and patients with hepatocellular carcinoma.

**Key words:** Magnetic resonance imaging- Metabolic syndrome - Nonalcoholic steatohepatitis- Positron Emission Tomography- Radiofrequency ablation

# INTRODUCTION

**H**epatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer death *(Bosch et al., 2004).*

The association of metabolic syndrome (MS) with malignancy attracted more and more attentions. As inevitable consequence of insulin resistance (IR), hyperinsulinemia plays an important role in occurrence and prognosis of cancer *(Chung et al., 2004).* In the liver, inflammatory and angiogenic changes due to insulin resistance and fatty liver disease are associated with an increased incidence of liver cancer. Regardless of underlying liver disease, cirrhosis remains the most important risk factor for HCC although cases of HCC arising without cirrhosis raise the possibility of a direct carcinogenesis secondary to nonalcoholic fatty liver disease (NAFLD) *(Rosmorduc and Fartoux, 2012).*

Leptin, the product of the obese (*ob*) gene, mainly produced by adipose tissues and, to a lesser extent, by tissues such as the skeletal tissue and placenta. Leptin is a pro-angiogenic, pro-inflammatory and mitogenic factor, the actions of which are reinforced through crosstalk with IL-1 family cytokines in cancercenogenesis *(Perrier et al., 2009).*

Leptin is best known as a regulator of food intake and energy expenditure via hypothalamic-mediated effects. It is

currently appreciated that this adipokine has many additional effects, often as a consequence of direct peripheral actions. These include angiogenesis, hematopoiesis, and various effects on the reproductive, cardiovascular and immune systems. More importantly, a study considered leptin as a fibrogenic factor in all types of chronic liver disease *(Marra, 2002)*. Based on analysis of liver tissue samples, somatic mutations accumulate in leptin receptor gene (LEPR) in cirrhotic liver with chronic HCV infection. These mutations could disrupt LEPR signaling and increase susceptibility to hepatocarcinogenesis *(Ikeda et al., 2014).*

# AIM OF THE STUDY

The aim of this study is to determine the value of serum leptin level in patients with HCV related decompensated liver cirrhosis and hepatocellular carcinoma and to correlate this level with metabolic profile in these patients.

Chapter I

# HEPATOCELLULAR CARCINOMA

## Epidemiology

**H**epatocellular carcinoma (HCC) is the most common type of liver cancer, and the second common type of cancers affecting the Gastrointestinal tract, after gastric cancer *(Zhu et al., 2013).*

The incidence of HCC ranges from <10 cases per 100,000 population in North America and Western Europe as well as in Iran, Iraq and India to 50– 150 cases per 100,000 population in parts of Africa and Asia **(Figure 1)** *(Jemal et al., 2011).*
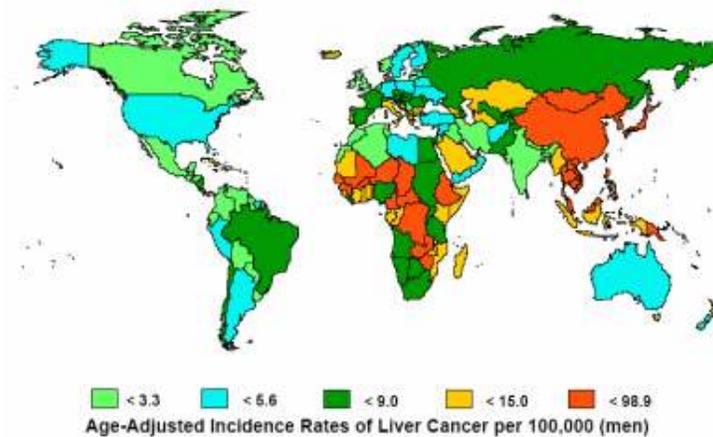


**Figure (1):** Worldwide incidence of HCC *(Jemal et al., 2011).*

Liver cancer incidence rates and death rates are increasing in many parts of the world, including North America, Latin America, and central Europe. In an analysis of data reported to the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Database of the National Cancer institute in the united states, liver cancer incidence rates increased by 3.1 percent per year from 2008 to 2012 *(Ryerson et al., 2016).*

*Egypt* is now plagued by the highest prevalence of HCV in the world (predominantly genotype 4), with estimates ranging from 6 to 28% and a reported average of 13.8%. investigations in Egypt have also shown the increasing importance of HCV infection in the etiology of HCC *(Elizabeth et al., 2009).*

Nearly half of the data on HCC in Africa came from Egypt *(Ezzat et al., 2005).* Over the last decade, a considerable increase was observed in the proportion of chronic liver disease Egyptian patients with HCC (from 4 %to 7.2%) *(Abdel-Hamid et al., 2011).*

## Etiology of HCC

World-wide, hepatitis B and C are the most important factors for the development of hepatocellular cancer. However, other factors contribute for the development of HCC, The