Factors Associated With Liver Steatosis In Chronic Hepatitis C Patients

Thesis
Submitted for partial fulfillment of the Master degree in Tropical Medicine

BY
Ahmed Mohamed Yaseen
(M.B.B.Ch Cairo University)

Under the Supervision of

Dr. Hanan Abd El Haleem Marzouk.
Assistant Professor of Tropical Medicine
Faculty of Medicine
Cairo University

Dr. Mohamed Mohamed Tawfik.
Assistant Professor of Tropical Medicine
Faculty of Medicine
Beni Suef University

Dr. Olfat Gamil Shaker.
Professor of Medical Biochemistry
Faculty of Medicine
Cairo University

Faculty of Medicine
Cairo University
2006

ACKNOLEGMENT

" He , and will always be, Allah who always blessed my work and who sent me those who were of help "

I would like to thank ***ALLAH*** *a lot for his kindness, patience and strength he gave to me to achieve this work and made me able to finish it.*

I wish to express my sincere gratitude to ***Dr. Hanan Abdel Haleem Marzouk,*** *Assistant professor of Tropical Medicine, Faculty of Medicine, Cairo University. She patiently gave me much of her time, experience, knowledge, directions, supervision and support that can not be expressed by words. From her, I learnt the way of scientific research.*

My great appreciation and thanks are for ***Dr. Mohammed Mohammed Tawfik,*** *Assistant professor of Tropical Medicine, Faculty of Medicine, Beni Suef University, for his continuous advice through this work.*

I am so grateful to ***Dr. Olfat Gameel Shaker,*** *Professor of Medical Biochemistry, Cairo University who gave me much of her support.*

Words stand short to express my deep appreciation for the ***staff members*** *of the Tropical Medicine Department and* ***my colleagues*** *by whom all, I was very much impressed by the noble characters , generous attitude and kind sympathy.*

Special thanks to ***Bilharzial Liver Unit*** *and* ***Dr. Gamal Esmat*** *Professor of Tropical Medicine, Faculty of Medicine, Cairo University and the director of the unit who provided us with financial and scientific support.*

My great appreciation are for ***Dr. Rasha Ahmed*** *lecturer of Tropical Medicine, Faculty of Medicine, Cairo University, for her continuous advice through this work.*

I also thank ***Dr.Sahar Talaat,*** *Assistant professor of pathology, Faculty of Medicine, Cairo University, who was of great help for this study.*

I am much grateful to ***Dr. Wafaa El Akel*** *for her great help for this study.*

Ahmed Yasin

Table of Contents

List of abbreviations

ALD: Alcoholic Liver Disease

A2M: Alfa 2 Macroglobulin

ALP: Alkaline phosphatase

ALT: Alanine transaminase

Apo : Apolipoprotein

AST: Aspartate transaminase

ATP: Adenosine Triphosphate

BMI: Body Mass Index

CAGE: Cut down, Annoyed, Guilty and Eye opene

CPT –1: Cytoplasm Transfer Protein 1

DM: Diabetes Mellitus

EGr-1: Early Growth response-1 transfer factor

EIISA: Enzyme Linked Immune Assay

GGT: Gamma Glutamyl Transferase

3GP: Glycerol 3 Phosphate

HAI: Histologic activity index

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HCC: Hepatocellular carcinoma

H&E: Haematoxyline and Eosin

HDL: High Density Lipoprotein

HIV: Human immune deficiency virus

HOMA: Homeostasis Model Assessment Method

HPG: Hexose Phosphate Glutamyl Transferase

IFN: Interferon

IL-: Interleukin

IR: Insulin Resistance

LFTs: Liver Function Tests

MRI Magnetic resonance imaging

MTP: Microsomal Triglyceride Transfer Protein

NAD: Nicotinamide Adenine Dinucleotide

NADH: Reduced form of NAD

NAFLD: Non Alcoholic Fatty Liver Disease

NASH: Non Alcoholic Steatohepatitis

NHW: Non Hispanic World

NIH: National Institute of Health

Ob: Obesity

OB-R: Obesity Receptor

OR: Odd Ratio

PCR: Polymerase chain reaction

PEG: Pegylated

PEG-OB: Pegylated recombinant native human leptin

RNA: Ribonucleic acid

SR: Sustained Response

TGF: Transforming growth factor

TGs: Triglycerides

TNF: Tumor necrosis factor

U/S: Ultrasonography

VLDL: Very Low Density Lipoprotein

WHO: World Health Organization

List of tables

A-Tables of the review and methods

B-Tables of the results

.

List of figures

A-Figures of the review

B-Figures of the results

ABSTRACT:

Background :

Liver steatosis is a common finding in patients infected with hepatitis C virus (HCV). Host and viral factors have been associated with steatosis , but their relative contributions have not been clearly addressed. It has been suggested that steatosis plays a role in the progression of liver fibrosis.

Aim:

To assess factors associated with steatosis in Egyptian patients with chronic HCV infection and to assess the impact of insulin resistance levels (as HOMA score) and Leptin levels on liver steatosis, relative to other factors.

Patients and methods :

This study was conducted on fifty five cases of chronic HCV hepatitis as well as fifteen healthy subjects without evidence of chronic liver disease. They were clinically assessed and investigated (Laboratory including complete blood count, liver biochemical profile, lipid profile, fasting blood glucose, serum insulin, HOMA IR and serum leptin , imaging by abdominal ultrasonography and Histopathologically according to modified Knodell score). Body mass index was assessed. Logistic regression and multivariate analysis were used to identify variables independently associated with steatosis.

Results:

The frequency of hepatic steatosis was 54.5%. In univariate analysis, steatosis was associated with elevated BMI (P= 0.007), age (P= 0.008), high serum triglycerides (P= 0.005) and high fibrosis stage (P= 0.03). Multivariate analysis revealed that BMI is a good predictor for steatosis (β= 0.13 , P=0.04) while age and triglyceride are no more predictors (P= 0.06 and 0.09 respectively). Serum leptin was significantly higher in chronic HCV patients with steatosis than control group (17.05±17.69 ng/ml *vs* 7.44±7.95 ng/ml in the control group, P value <0.02). Serum leptin level in Chronic HCV patients with steatosis was relatively higher than Chronic HCV patients without steatosis, but the difference did not reach a statistical significance. There was no statistically significant difference between the studied groups as regard fasting blood sugar, serum insulin and insulin resistance.

Conclusion:

Hepatic steatosis is common in patients with chronic HCV hepatitis. Factors associated with hepatic steatosis are BMI, age of the patient, serum TGs and stage of fibrosis. BMI is the only predictor of hepatic steatosis. There is no significant correlation between IR, leptin and incidence of hepatic steatosis.

Key Words :

Liver steatosis

Hepatitis C patients

Insulin resistance

Introduction

Hepatitis C virus infection is characterized by a high rate of developing chronic disease (observed in 75-85% of patients) and exposes the patient to the risk of chronic active hepatitis with progression to cirrhosis and hepatocellular carcinoma. Cirrhosis develops in about 25% of patients.***(WHO,2002).***

Steatosis was recently identified as a risk factor for progression to extensive fibrosis (***Cholet et al.,2004***).Liver steatosis is a common finding in patients infected with hepatitis C virus (HCV). Host and viral factors have been associated with steatosis, but their relative contributions have not clearly addressed (***Gordon et al.,2005*).**Pathology studies show that from 40-86% of HCV infected patients will develop liver steatosis (***Mihm et al., 1997***).Several studies have demonstrated a significant relationship between steatosis and elevated Body Mass Index (BMI**) *(Monto et al.,2002).***In HCV infected patients ,when risk factors of steatosis such as obesity, dyslipidemia, alcohol ,diabetes or drugs are excluded, the high prevalence of steatosis persists suggesting that HCV itself may be a risk factor for steatosis (***Andinolfi et al.,2001***).

Two main mechanisms have been proposed to account for the high prevalence of steatosis in chronic hepatitis C. Firstly ,in patients infected with genotype 3, the degree of steatosis is correlated with the level of viral load***, (Adinolfi et al .,2001***) suggesting that HCV could alter fatty acid metabolism and/or export in hepatocytes (***Perlemuter,2002***).Secondly

,type 2 diabetes and more generally insulin resistance is highly frequent in chronic HCV infection. Recently, ***Fartoux et al.,2005*** concluded that insulin resistance is the cause rather than the consequence of steatosis in genotype 1 patients and that increased circulating insulin is a risk factor for fibrosis through insulin resistance induced steatosis.

In chronic hepatitis C ,we need to clearly understand the basic pathophysiologic mechanisms involving potential viral polyprotein modulation of cellular lipid metabolism along with the relative contribution of body fat distribution, the anti oxidant system and possibly any genetic predisposition to the development of steatosis. Are there common links between the host, viral and other environmental factors that predispose to steatosis (***Patel et al.,2003***).One of such common links may be Leptin; a peptide which regulates food intake and energy expenditure. Leptin levels are increased in most cases of obesity, indicating Leptin insensitivity or resistance **(*Patel et al., 2003***).Recent evidence suggests that Leptin promotes insulin resistance and alters insulin signaling leading to increased intracellular fatty acids. Furthermore, Leptin amplifies select proinflamatory responses **(*Loffreda et al.,1998***) and mediates hepatic fibrogenesis during chronic liver injury. ***Romero Gomez et al.(2003)*** reported that increased serum leptin levels, higher degree of fibrosis and genotype 3 were independent variables associated with steatosis in patients with chronic HCV infection.