

Factors Associated With Liver Steatosis In Chronic Hepatitis C Patients

Thesis

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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

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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 ($\beta= 0.13$, $P=0.04$) 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

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,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 proinflammatory 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.