The Correlation Between Visceral Adiposity Index And Liver Fibrosis In Chronic Hepatitis (C) Patients.

Thesis
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BY

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LIST OF ABBREVIATIONS

AFP	Alpha feto-protien
ALT	Alanine transminase
ANA	Anti-nuclear antibody
APRI	AST to Platelet Ratio Index
AST	Aspartate transminase
CD	Cluster of differentiation
CHC	Chronic hepatitis C
DM	Diabetes mellietus
T2DM	Type2 diabetes mellietus
EIA	Enzyme immunoassay
ETR	End-of-treatment response
EVR	Early virological response
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HDL	High density lipoprotien

HSCs	hepatic stellate cells
IFN	Interferon
IU	International unit
NADPH	Nicotinamide adenine dinucleotide phosphate dehydrogenase
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
nm	Nanometer
PCR	Polymerase Chain Reaction
RBV	ribavirin
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic Acid
RVR	Rapid Virological Response
SAD	Sagital abdominal diameter
SLE	Systemic lupus erytheromatus
SVR	Sustained virological response
TG	triglyceride
TMA	Transcription-mediated amplification
TSH	Thyroid stimulating hormone
TNF	Tumor necrosis factor
VAI	Visceral adiposity index
WC	Waist circumference

Introduction

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Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer or life threatening esophageal and gastric varices ***(Ryan and Ray, 2004)***.

Clinical studies suggest a direct association between hepatic fat content and visceral adiposity. For example, imaging modalities as magnetic resonant imaging that estimates abdominal fat in obese and non-obese individuals has found correlations between visceral and liver fat content. Importantly, visceral fat is directly linked to the severity of liver inflammation and fibrosis ***(Sabir and Sermez, 2001)***.

Although waist circumference is often used as a marker of visceral adiposity, it cannot sufficiently discriminate between visceral and subcutaneous fat compartments ***(Adams, 2011)***.

The visceral adiposity index (VAI) – a scoring system based on:
Waist circumference ,body mass index, triglycerides and high density lipoprotein cholesterol(HDL) is a proposed marker of both visceral fat distribution and hepatic fibrosis ***(Petta et al., 2010)***.

Aim of the Work

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To assess the correlation between the visceral adiposity index (VAI) and hepatic steatosis, as well as necroinflammatory activity and liver fibrosis in patients with chronic HCV infection.

Review of Literature

Hepatitis C Virus Infection

Hepatitis C virus (HCV) infection is one of the most serious health problems affecting the liver. More than 180 million individuals worldwide (3% of the world population) are infected with HCV. HCV infection is the cause of approximately 40% of chronic liver disease and is responsible for 8,000 to 10,000 deaths annually ***(Jaecekel et al., 2001*)**. In Egypt, the seroprevalence of HCV infection ranges from 10% to 30% which is 10-20 folds higher than that in the United States ***(Adela et al., 2009)***. In the meantime, HCV infection seroprevalence among Egyptian blood donors ranges from 7-15% compared to 0.3% to 1.5% worldwide ***(Munshi et al., 2009).*** About 15 to 25% of patients with acute hepatitis C infection resolve their infection without further problems , while the remainder develops chronic hepatitis ***(Alavian, 2009)***. Liver cirrhosis as well as hepatocellular carcinoma develops in 10-20% and in 1-5% of HCV-infected patients respectively over a period of 20-30 years ***(Wang &Schreiber, 2003).***

The HCV Virion

HCV is a spherical, enveloped, single-stranded RNA virus of the family Flaviviridae and genus hepacivirus. HCV is a positive- stranded RNA virus of approximately 50 nanometers (nm) in diameter. The positive-stranded RNA of the HCV genome has three potential functions: 1) as a template for synthesis of negative- stranded RNA during replication, 2) as a template for translation of viral proteins, and 3) as genomic RNA to be packaged into new virions ***(Mandell et al., 2000)***.

The virus is surrounded by a nucleocapsid and the RNA is packaged in an envelope, derived from host membranes, into which viral-encoded glycoproteins are inserted. Within infected cells, a polyprotein is cleaved

by both viral and host proteases to produce the protein products of the virus, forming the highly basic core protein. This protein has RNA-binding activity and may undergo a subsequent internal cleavage by an unspecified proteinase ***(Bonkovsky, 2001).***

HCV heterogeneity

The high level of HCV turnover results in a relatively rapid accumulation of mutations within the viral genome. Multiple HCV variants can be recovered from the plasma and liver of an infected individual. Nucleotide sequencing has shown that differences of up to 34% exist between different HCV variants ***(David, 2009)***.

Six major HCV genotypes and numerous subtypes have been identified based on viral genome sequencing. The molecular differences between genotypes are relatively large with a difference of at least 30% at the nucleotide level. HCV exists within infected person as multiple species which are closely related yet have distinct genetic sequences. Viral species represent minor molecular variations with only 1-2% nucleotide heterogeneity. These quasispecies pose a major challenge with respect to the immune-mediated control of HCV, and may be the reason for the difficulty in vaccine production ***(Feldman, 2002)***.

Table (1) HCV Genotypes and subtypes *(Ghany et al., 2009)*.

Genotype	**%**	**Geographical distribution**
Genotype 1a	50-60	most common in the United States (about 75% of cases)
Genotype 1b	15-20	most prevalent in Europe, Turkey, Japan, Taiwan
Genotype 1c	<1	most prevalent in Europe
Genotype 2a/b/c	10-15	Widely distributed
Genotype 3a/b	4-6	India, Pakistan, Australia, Scotland
Genotype 4	<5	Middle East, Africa., **Egypt**
Genotype 5	<5	South Africa
Genotype 6	<5	Hong Kong, Macao

Modes of HCV transmission

1. Transfusion of blood and organ transplantation:

When blood is transfused , transfusion of blood products, or organ transplants without HCV screening from an anti-HCV antibody-positive donor, more than 80% of the recipients will become infected with HCV. Prior to blood screening for anti-HCV antibodies, transmission rates were estimated to be about 17% ***(Munshi et al., 2009).***

Since the advent of routine screening of blood for anti-HCV antibodies, the transmission of HCV by blood product transfusion and organ

transplantation has decreased markedly to less than 4% of the new HCV infections ***(Mandell et al., 2000).***

2. Nosocomial transmission:

Transmission of infection has been well documented in hospitals within certain high-risk groups and in patients undergoing long-term hemodialysis, in whom the annual incidence of HCV infection had decreased from 4.5%─6% (before the introduction of HCV screening and the introduction of universal precautions) to 0.44% after applying of HCV screening. Transmission of HCV from health care providers to patients has also been documented. Needlestick exposure also constitutes a risk factor for the transmission of HCV to health care workers ***(Bonkovsky, 2001)***.

3. Sexual transmission:

Sexual transmission of HCV appears to be uncommon. Spread of HCV to a partner in stable relationship occurs in less than 1% of partners per year ***(Wasley &Alter, 2000).***

4. Vertical transmission:

Maternal-infant transmission is not common. In most studies, less than 5% of infants born to HCV-infected mothers become infected. The disease in newborns is usually mild and free of symptoms. The risk of maternal-infant spread rises with the amount of virus in the mother's blood. Breast-feeding has not been linked to the spread of HCV ***(Wasley & Alter, 2000)***.

5. **Household and interfamiliar spread**:

It is most likely a result of direct, through the skin exposure to the blood of an infected household member. Sharing personal care items that may have come in contact with another person's blood, such as razors or toothbrushes, sharing such items can potentially lead to more exposure to

HCV and infection.

HCV is not spread through casual contact, such as holding hands, coughing, sneezing, kissing, or sharing eating utensils. Neither through food or water ***(sandmann & ploss, 2013)***.

6. **Tattooing**:

Tattooing is associated with two to threefold increased risk of hepatitis C. this can be due to either improperly sterilized equipment or contamination of the dyes being used ***(Jafari et al., 2010).***

Natural history of HCV infection:

Acute HCV infection

After transfusion or accidental needlestick exposure, the incubation period for HCV infection averages 6 to 7 weeks. Among adults with acute HCV infection, only 30% to 40% have symptoms (usually mild) and develop jaundice. In patients in whom jaundice develops, the peak serum bilirubin levels are usually less than 12 mg/dL, and these elevations typically resolve in 1 month. The majority of asymptomatic patients with HCV infection will have fluctuating serum aminotransferase levels. Moreover, in symptomatic patients, 10% to 20% may present with nonspecific symptoms such as fatigue, nausea, and vomiting indistinguishable from symptoms of other types of acute viral hepatitis. In general, HCV accounts for approximately 20% of cases of acute hepatitis. Presentation of hepatitis C as fulminant hepatitis is rare ***(Feldman, 2002)***.

Chronic HCV infection

The development of chronic hepatitis C (CHC) depends on several factors:

The virus itself, the mode of acquisition of infection, and the host immune response ***(Feldman, 2002)***.

A. Viral factors

Approximately 85% of infected patients do not clear the virus by 6 months, and chronic hepatitis develops. Of these, the majority will have elevated or fluctuating serum ALT levels, whereas one third has persistently normal ALT values. Specifically, HCV genotype is a factor that has been implicated in the evolution of CHC. Studies have shown that the HCV genotype 1b is independently associated with development of chronic hepatitis ***(Bonkovsky, 2001).***

B. Mode of HCV acquisition

Large inocula of HCV, as in post-transfusion hepatitis C, are associated with more severe disease. Although the development of cirrhosis was directly correlated with disease duration, cirrhosis was more frequent in blood transfusion recipients than in drug users with similar durations of CHC ***(Bonkovsky, 2001).***

C. Host immune responses

Host immune responses are obviously important factors which influence the development of chronic hepatitis C. Specific HLA alleles have also been associated with differences in the progression of disease ***(Elliot et al., 2006)***.