Study of Lipid Profile as Risk Factor for Hepatocellular Carcinoma

Thesis

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William Nasry Shoukry

Contents

List of Abbreviations

AFB1	:	Afla toxin
AFP	:	Alpha-1 fetoprotein
AFP-L3	:	Lens culinaris agglutinin-reactive AFP
AFU	:	α-L-Fucosidase
ALP	:	Alkaline phosphatase
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
BCLC	:	Barcelona Clinic Liver Cancer
BMI	:	Body mass index
BUN	:	Blood urea nitrogen
CETP	:	Cholesteryl ester transfer protein
CEUS	:	Contrast enhanced ultrasound
CGH	:	Comparative genomic hybridization
CKD	:	Chronic kidney disease
CLIP	:	Cancer of the Liver Italian Program
CT	:	Computed Tomography
CTP	:	Child-Turcotte-Pough score
CUPI	:	Chinese University Prognostic Index
CVD	:	Cardiovascular disease
DCP	:	Des-gamma carboxyprothrombin
FAS	:	Fatty acid synthase
FCHL	:	Familial combined hyperlipidemia
FCS	:	Familial chylomicronemia syndrome
FDB	:	Familial defective apoB100
FDBL	:	Familial dysbetalipoproteinemia
FH	:	Familial hypercholesterolemia
FHTG	:	Familial hypertriglyceridemia
GP73	:	Golgi protein 73
GPC-3	:	Glypican-3
GRETCH	:	Groupe D'etude de Traitment du Carcinoma Hepatocellulair
HBs Ag	:	Hepatitis B surface antigen

List of Abbreviations (Cont.)

HBV	:	Hepatitis B virus
HCC	:	Hepatocellular carcinoma
HCV	:	Hepatitis C virus
HD	:	Hemodialysis
HDL-C	:	High-density lipoprotein cholesterol
HGF	:	Hepatocyte growth factor
IEF	:	Isoelectric focusing
IL- 6	:	Interleukin-6
INR	:	International normalized ratio
JIS	:	Japanese Integrated System
LC	:	Liver cirrhosis
LCAT	:	Lecithin-cholesterol acyltransferase
LDL-C	:	Low-density lipoprotein cholesterol
LFT	:	Liver function test
LOH	:	Loss of heterozygosity
LPL	:	Lipoprotein lipase
M-CSF	:	Macrophage colony stimulating factor
MDCT	:	Multidetector row helical computed tomography
MOH	:	Egyptian Ministry of Health
MRI	:	Magnetic Resonance Imaging
NAFLD	:	Nonalcoholic fatty liver disease
NASH	:	Nonalcoholic steatohepatitis
NEFAs	:	Nonesterified Free fatty acids
NS	:	Nephrotic syndrome
OCs	:	Oral contraceptives
PD	:	Peritoneal dialysis
PIAF	:	Platinum, interferon, adriamycin, fluorouracil
PIVKA-II	:	Protein induced by vitamin K absence or antagonist- II

List of Abbreviations (Cont.)

PKC	:	Protein kinase C
PPAR-a	:	Peroxisome proliferators-activated receptor a
PT	:	Prothrombin time
PTT	:	Partial thromboplastin time
RCTs	:	Randomized controlled trials
RF	:	Radio frequency thermal
RILD	:	Radiation induced liver disease
ROS	:	Reactive oxygen species
SCCA	:	Squamous cell carcinoma antigen
SELDI-TOF	:	Surface-enhanced laser desorption/ionization time of flight mass spectrometry
SNP	:	Nucleotide polymorphisms
SOD	:	Superoxide dismutase
SREBP	:	Sterol regulatory element-binding protein
TACE	:	Transcatheter Arterial Chemoembolization
TC	:	Total cholesterol
TG	:	Triglyceride
TGF-β1	:	Transforming growth factor-beta 1
TNF-α, IL-1	:	Tumor necrosis factor
TNM	:	Tumor, Node, Metastasis staging system
TSH	:	Thyroid-stimulating hormone
UCAs	:	Ultrasound contrast agents
US	:	Ultrasound
VEGF	:	Vascular endothelial growth factor
VLDL	:	Very-low-density lipoprotein
VOD	:	Veno-occlusive disease

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Introduction

The liver plays a central role in lipid metabolism, as several pathways are, at least in part, dependent to this site. Major metabolic processes take place at this level, involving the production, transportation and storage of apoproteins and lipoproteins, as well as catabolism of various lipids and excretion of cholesterol and phospholipids. An alteration in liver functions resulting from cellular injury leads to changes in the serum concentration of cholesterol and lipoproteins ***(Vere et al., 2012).***

Lipids are essential for energy homeostasis, reproductive and organ physiology, and other aspects of cellular biology. They are also linked to many pathologic processes, such as inflammation, obesity, and liver disease ***(Skill et al., 2011).***

Lipids might be associated with cancers as they have an integral role in the maintenance of cell integrity. Although, raised lipids are strongly associated with the pathogenesis of coronary heart disease, researchers have also reported an association between plasma/serum lipids and lipoproteins with different types of cancers. The main question is to whether hypolipidemia predisposes to cancer or is an effect of the malignancy. ***(Bielecka-Dabrowa et al.,2011).***

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third cause of cancer-related death worldwide. It has been a major concern in both Western and Asia countries. As known to all, the high prevalence of hepatitis B and C gives rise to the high incidence of HCC. At the same time, so many confounding factors are associated with the occurrence and development of chronic liver diseases. Recently, the relationship between metabolic factors and chronic liver diseases including liver cirrhosis (LC) and hepatocellular carcinoma (HCC) has become a hot topic ***(Zhao et al., 2011).***

Aim of the Work

To determine lipid profiles in hepatocellular carcinoma (HCC) patients compared to other chronic liver diseases and normal subjects.

Hepatocellular Carcinoma

Introduction

Hepatocellular carcinoma (HCC) is a major challenge in contemporary medicine. The incidence of HCC is on the increase and it is becoming more and more significant both clinically and epidemiologically. Now HCC represents the fifth most common cancer in the world and the third most frequent cause of mortality amongst oncological patients ***(Stefaniuk P et al., 2010).***

Hepatocellular carcinoma (HCC) accounts for between 85% and 90% of primary liver cancers. HCC has several interesting epidemiologic features including dynamic temporal trends; marked variations among geographic regions, racial and ethnic groups, and between men and women; and the presence of several well-documented environmental potentially preventable risk factors. Moreover, there is a growing understanding of the molecular mechanisms that induce hepatocarcinogenesis, which almost never occurs in the healthy liver but the cancer risk increases sharply in response to chronic liver injury at the cirrhosis stage ***(El-Serag, 2007).***

Epidemiology

It is responsible for more than 500 000 deaths with over 600 000 new cases yearly worldwide. Incidence rates are different in various countries: highest in South-East Asia and Sub-Saharan Africa (around120/100 000) and lowest in the USA (1.8/100 000) and Western Europe (3-5/100 000) ***(Parkin DM, 2005).***

In Egypt, between 1993 and 2002, there was an almost twofold increase in HCC amongst chronic liver patients (***El-Zayadi AR, 2005).***

In almost all populations, males have higher liver cancer rates than females, with male: female ratios usually averaging between 2:1 and 4:1. At present, the largest discrepancies in rates (4:1) are found in medium-risk European populations. The reasons for higher rates of liver cancer in males may relate to sex-specific differences in exposure to risk factors. Men are more likely to be infected with HBV and HCV, consume alcohol, smoke cigarettes, and have increased iron stores. However, experiments show a 2- to 8-fold increase in HCC development in male mice. These data support the hypothesis that androgens influence HCC progression rather than sex-specific exposure to risk factors ***(El-Serag, 2007).***

HCC incidence rates also vary greatly among different populations living in the same region. For example, ethnic Indian, Chinese, and Malay populations of Singapore had age-adjusted rates ranging from 21.21/ 100,000 among Chinese males to 7.86/100,000 among Indian males between 1993 and 1997. The comparable rates for females were 5.13/100,000 among ethnic Chinese and 1.77/100,000 among ethnic Indians. Another example is the United States where, at all ages and among both sexes, HCC rates are 2 times higher in Asians than in African Americans, whose rates are 2 times higher than those in whites. The reason for this ethnic variability likely includes differences in the prevalence and acquisition time of major risk factors for liver disease and HCC ***(El-Serag, 2007).***

The incidence of HCC increases with age, reaching its highest prevalence among those aged over 65 years. Although HCC is rare before the age of 50 years in North America and Western Europe , a shift in incidence towards younger persons has been noted in the last two decades. HCC tends to occur in the background of cirrhosis of the liver ***(Parikh, 2007).***

Risk factors

1. *Hepatitis B virus*

The WHO has reported HBV to be second only to tobacco as a known human carcinogen . Many studies on HCC risk following chronic HBV infection have been conducted in the East Asian countries, where most patients acquired HBV as newborn infants. The incidence of HCC in HBV-related cirrhosis in this area of the world has been reported to be 2.7%. The annual risk of HCC is 0.5% for asymptomatic HBsAg carriers and 0.8% for patients with chronic hepatitis B, while patients with HBV-cirrhosis have 1000 times higher risk of developing HCC, compared to HBsAg negative individuals ***(Michielsen PP, 2005).***

The mechanisms of carcinogenesis in HBV infection have been extensively studied, and a major factor is chronic necroinflammation with subsequent fibrosis and hepatocyte proliferation. However, HCC may occur in HBsAg carriers without cirrhosis. Both HBV and host hepatocytes may contribute to the final pathogenic outcomes, either individually or synergistically. Therefore, it is reasonable to consider that apart from host factors, viral factors are likely involved in HBV related hepatocarcinogenesis ***(Liu CJ, 2007).***

HCC has been the first human cancer amenable to prevention using mass vaccination programmes. From a global perspective, the burden of chronic HBV infection is expected to decline because of the increasing utilisation of HBV immunization, since the early 1980s ***(Liu CJ, 2007).***

2. Hepatitis C virus

HCV is the most important risk factor for HCC in western European and North American countries, since epidemiological studies have shown up to 70% of patients with

HCC have anti-HCV antibody in the serum. Liver cancer has a higher prevalence in patients with HCV-associated cirrhosis than in non-viral aetiologies of chronic liver disease, while only a few cases of HCV-associated HCC have been reported in the non-cirrhotic liver, indicating that the virus possibly has a mutagenic effect ***(Montalto G, 2002).***

The prevalence of HCV infection varies considerably by geographical region. African and Asian countries reported high HCV infection prevalence rates, while rates in North America, Europe and Australia have usually reported lower rates. Egypt has the highest prevalence of HCV in the world (predominantly genotype 4), which has been attributed to previous public health eradication schemes for schistosomiasis. Even higher HCV infection rates, up to 60%, have been reported in older individuals, in rural areas such as the Nile delta, and in lower social classes ***(Shepard CW, 2005).***

The mechanisms of tumor development in patients with chronic hepatitis C are not known. Although often attributed to the inflammatory effects of chronic hepatitis and fibrogenesis alone, this seems unlikely given the high risk compared with other causes of chronic liver disease. Thus, the virus likely plays some role in the process. This concept is supported by the observation that the risk of HCC remains about 2.5-fold higher in cirrhotic patients who fail to clear HCV with antiviral therapy than in those who eradicate infection ***(Bruno S , 2007)***

3. Role of schistosomiasis

Schistosomiasis is a common parasitic infestation in some parts of the world. In Egypt, Schistosomiasis is a major public health problem and infection with *Schistosoma mansoni* constitutes the major cause of liver disease from 1950s until 1980s. The Egyptian Ministry of Health (MOH) conducted a community-wide therapy campaign using parenteral tarter