High circulating D-dimers as a predictor for hepatocellular carcinoma and ascites in liver cirrhosis

THESIS

Submitted for partial fulfillment of Master degree in internal medicine

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List of Abbreviations

AA..... Amino acid
AASLD..... American Association for the Study of Liver Disease
Ab..... Antibody
ACG ……. American College of Gastroenterology
AFP …… Alpha fetoprotein
AILD..... Autoimmune liver disease
ALP..... Alkaline phosphatase
ALT ..... Alanine amino transferase
AMA..... antimitochondrial antibody
ANA ……..Antinuclear antibody
AST..... Aspartat amino transferase
AUC…… Area under the curve
AzBF..... Azygous vein blood flow
b.i.d ..... bis in die (twice a day)
°C ..... degree celsius
CBC..... Complete blood cell count
CC..... Cryptogenic cirrhosis
CDC ..... Centers for Disease Control and Prevention
CI ...…… Confidence interval
cm..... centimeter
CMV ..... Cytomegalovirus
CO ..... cardiac output
CT..... Computed tomography
DD …….. D-dimer
DNA ..... Deoxyribnucleic acid
DPAS ..... periodic acid-Schiff stain after diastase digestion
Ds-DNA..... Double stranded DNA
e.g..... example
ELISA …… enzyme-linked immunosorbant assay
ES..... Endoscopic sclerotherapy
FHVP ..... Free hepatic vein pressure
GABA..... Gamma amino butyric acid
GIT ..... Gastrointestinal tract
gm..... gram
GV..... Gastric varices
HBF ..... Hepatic blood flow
HBsAg..... Hepatitis B surface antigen
HBV ..... Hepatitis B virus

HCC..... Hepatocellular carcinoma
HCV..... Hepatitis C virus
HDV..... Hepatitis D virus
5-HT 5-hydroxytryptamine
HVPG..... hepatic venous pressure gradient
i.e..... that is to say
Ig A..... Immunoglobulin A
INF-γ ..... gamma interferon
INR..... International normalized ratio
IOVP..... intravascular oesophageal pressure
ISDN..... isosorbide dinitrate
Is-5-Mn ..... isosorbide-5 mononitrate
I V. ..... Intravenous
K..... potassium
Kcal ..... kilocalorie
Kgm..... kilogram
kPa..... kilo pascal
LCAT..... Lecithin cholesterol acyltransferase
LKM-1 Ab.....…….Liver-kidney Microsomal antibody
MAP..... Mean arterial pressure
Max ..... Maximum
MCV ..... mean corpuscular volume
MLP..... Mosaic pattern
mmHg ..... millimeters murcury
MOHP ..... Ministry of Health Planning
MRI ..... Magnetic Resonance Imaging
MSBD ..... Maximum spleen bipolar diameter
Na..... sodium
NAFLD ..... Nonalcoholic fatty liver disease
N_0 .... Number
NOV ..... No oesophageal varices
NIEC..... North Italian Endoscopic Club
NTG..... nitroglycerin
OV..... Oesophageal varices
OT..... Octreotide
PAS..... periodic acid-Schiff stain
PAT..... Parenteral antischistosomal therapy
PDGF ..... Platelet derived growth factor
PHG…….. Portal Hypertensive Gastropathy
Plt ..... Platelet
PT ..... Prothrombin time
PTE..... Percutaneous Transhepatic Embolization

PTFE..... polytetrafluoroethylene
PVD ..... Portal vein diameter
PVL..... Portal vein ligation
PVP..... Portal vein pressure
REE ..... Resting energy expenditure
RNA ..... Ribonucleic acid
ROC ……. (Receiver operator characteristic curve
S.Alb ..... Serum albumin
SBP ..... spontaneous bacterial peritonitis
SD..... Standard deviation
SGOT..... Serum glutamic oxaloacetic transaminase
SGPT..... Serum glutamic pyruvic transaminase
S. japonicum..... Schistosoma Japonicum
SLA..... soluble liver antigen
SMA..... smooth muscle antibody
SPSS …… statistical program for social science
ST…….....Somatostatin
Tbil ..... Total bilirubin
TGLVP..... triglycyl-lysine vasopressin
TIPS..... transjugular intrahepatic portal systemic shunt
US..... Ultrasound
USA..... United States of America
VP ..... vasopressin
vs..... versus
WHO..... World Health Organization
WHVP..... Wedge hepatic vein pressure
γ -globulin..... gamma globulin
γ -GT..... gamma glutamyl transferase

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High circulating D-dimers as a predictor for hepatocellular carcinoma and ascites in liver cirrhosis

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Abstract

Hemostasis is a dynamic process resulting from the balance between procoagulant and anticoagulant factors, the liver is the site of production of most proteins which favor and inhibit the process of coagulation and fibrinolysis.

Main objective of this study was to evaluate the relationship between the presence of ascites and/or hepatocellular carcinoma (HCC) with hyperfibrinolytic state in liver cirrhosis measuring the circulating levels of D-dimer in patients with and without ascites and HCC, and to assess the effect of ascites resolution in the plasma concentration of D-dimers.

50 cases with liver cirrhosis were selected, 25 of them had ascites we evaluated the biochemical parameters for all patients, including: total bilirubin, SGOT, SGPT, alkaline phosphatase, serum albumin, prothrombin time, INR, CBC, alpha fetoprotein and plasma levels of D-dimer. All patients were classified according to Child-Pugh's

criteria. Also, abdominal ultrasonography was done for the presence of ascites, and any hepatic focal lesions.

We found that plasma D-dimer levels above the normal range were found in 35/50 patients (70%). D-dimer above normal values were more frequent in group A (25/25) than in group B (10/25). D-dimer mean values were higher in group A (3.3 ± 2 ng/ml) than in group B (1.5 ± 1 ng/ml). In all patients of group A after aspiration of ascetic fluid mean D-dimer values decreased in 5 patients with high basal levels, returning to normal range in 15 and remains high in 5 patients (HCC was discovered in them). In these patients, D-dimer values after aspiration of ascites were not significantly different from those found in patients without ascites, group B. In patients without ascites, group B, high D-dimer levels were associated with presence of HCC.

By using the **ROC** curve, the cut off value for plasma D-dimer for detection of malignancy was **3.9**, Sensitivity is **72%** and Specificity is **80%.**

INTRODUCTION

Hemostasis is a dynamic process resulting from the balance between procoagulant and anticoagulant factors ***(Agarwal et al., 2000)*** the liver is the site of production of most proteins which favor and inhibit the process of coagulation and fibrinolysis.

Patients with liver cirrhosis may develop a serious coagulopathy whose origin is commonly ascribed to a defective hepatic synthesis of clotting factors ***(Steib et al., 1994)*** in addition to the hyperfibrinolytic state which contribute to the bleeding tendency causing a premature removal of hemostatic plug ***(Piscaglia et al.2001).***

Plasma levels of fragment D-dimer represent an accurate marker of fibrinolytic activity ***(Agarwal et al., 2000)***.

The finding of high D-dimer plasma concentration in patients with liver cirrhosis decompansated by ascites suggest a major role of ascites in pathogenesis of hyperfibrinolytic state associated with liver failure ***(Agarwal et al., 2000)***.

Also high D-dimer levels found in patient with hepatocellular carcinoma without ascites ***(Kim et al., 2003)***.

Aim of the work

To evaluate the relationship between the presence of ascites and/or hepatocellular carcinoma (HCC) with hyperfibrinolytic state in liver cirrhosis measuring the circulating levels of D-dimer in patients with and without ascites and HCC , and to assess the effect of ascites aspiration in the plasma concentration of D-dimers.

LIVER CIRRHOSIS

Cirrhosis is a pathologic condition characterized by fibrosis of the liver parenchyma and evidence of regenerative activity ***(Podolsky & Isselbacher, 1998).*** It is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules with a disturbed intrahepatic circulation ***(Wolf, 2004).***

The most common and important causes are chronic infection with the hepatitis viruses B and C, and prolonged alcohol abuse ***(Weather et al, 2003).***

Viral Hepatitis:

Hepatitis is seen in many viral diseases usually as part of generalized infection: These include Yellow fever, Cytomegalovirus, Epstein-Barr virus and congenital rubella However, some viruses primarily target the liver to cause the disease of viral hepatitis as hepatitis C virus, hepatitis B virus and hepatitis Delta virus ***(Morag, 1997).***

A) Chronic hepatitis "C"

In Egypt, prevalence ratio of antibodies to HCV ranges from 10% to 30*%* ***(El Sayed et al., 1996),*** while ***(Abdel Aziz et al. 2000)*** found that the prevalence of HCV in Nile Delta of Egypt was 24% with marked raise of HCV infection in the third decade reaching a peak over 60% in the fifth decade, and they explained the rise in anti-HCV positivity with age as it may be due to continuous exposure.

Cirrhosis may develop in as many as 15% to 20% of infected patients at 20 years after exposure ***(National Institutes of Health, 2002).***

B) Chronic hepatitis "B"

Hepatitis B virus (HBV) infection is a serious global health problem, with 2 billion people infected worldwide, and 350 million suffering from chronic HBV infection. The 10th leading cause of death worldwide, HBV infections result in 500 000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma; the last accounts for 320 000 deaths per year ***(Lavanchy, 2004).***

C) Hepatitis "D" virus.

HDV is an incomplete virus that has HBV infection as a prerequisite. Superinfection by HDV leads to acute hepatitis and causes progression to liver cirrhosis in a significant proportion of HBsAg carriers. ***(Bean, 2002).***

D) Cytomegalovirus (CMV) infection

Cytomegalovirus (CMV) infection is more widespread in developing countries and in areas of lower socioeconomic conditions. CMV infection generally causes an asymptomatic or mildly symptomatic acute illness and no long-term health consequences in immunocompetent adults ***(Taylor, 2003).***

Pathology and Classification:

Macroscopic picture:

Cirrhotic livers are firm and may be large, of normal size, or small and shrunken. Their lower edge is blunted, and there may be considerable distortion of the normal shape. The surface is nodular, but the size of the nodules is very variable ***(Podolsky & Isselbacher 1998).***