Reversal of Hepatic Fibrosis

Essay
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In General Surgery
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نقـض التليـف الكبـدى

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ACE-I	Angiotensin converting enzyme inhibitor
ADP	Adenosine diphosphate
ALT	Alanine aminotransferase
APRI	AST to platelet ratio index
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AT1	Angiotensin 1 receptor
AUC	Area under the curve
BM	Bone marrow
CLD	Chronic liver disease
CT	Computerized tomography
DDRs	Discoidin domain receptors
ECM	Extracellular matrix
EGF	Epidermal growth factor
ELFG	European Liver Fibrosis Group
ET- 1	Endothelin-1
ET_AR	Endothelin A receptor
G-CSF	Granulocyte colony stimulating factor
GGT	Gamma glutamyl transpeptidase
GUCI	Göteborg University Cirrhosis Index
HA	Hyaluronic acid
HAI	Histological activity index
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HSCs	Hepatic stellate cells
IFN	Interferon
IL	Interleukin

INR	International normalized ratio
MCP-1	Monocyte chemotactic protein-1
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
NASH	Non alcoholic steatohepatitis
NO	Nitric oxide
NPV	Negative predictive value
OLT	Orthotopic liver transplantation
PDGF	Platelet derived growth factor
PICP	Procollagen type I carboxyterminal peptide
PIIINP	Procollagen type III aminoterminal peptide
PLT	Platelets
PPV	Positive predictive value
PPAR	Peroxisome proliferators activated nuclear receptors
RER	Rough endoplasmic reticulum
RME	Receptor mediated endocytosis
ROC	Receiver operatot characteristic
ROS	Reactive oxygen species
RTKs	Receptor tyrosine kinases
SAMe	S-adenosyl-L- methionine
SER	Smooth endoplasmic reticulum
TGF	Transforming growth factor
TGP	Transforming growth factor
Th	T-helper cell
TIMP	Tissue inhibitor of metalloproteinases
TNF	Tumour necrosing factor
ULN	Upper limit normal
US	United States

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Introduction

Fibrosis is a wound healing response in which damaged regions are encapsulated by an extra cellular matrix or scar. It develops in almost all patients with chronic liver injury at variable rates depending in part upon the cause of liver disease and host factors ***(Poynard et al., 2003a).***

Fibrosis occurs earliest in regions where injury is most severe, particularly in chronic inflammatory liver disease due to alcohol or viral infection ***(Ismair et al., 2001).***

Hepatic fibrosis refers to the accumulation of interstitial or 'scar' extracellular matrix after either acute or chronic liver injury. Cirrhosis, the end-stage of progressive fibrosis, is characterized by septum formation and rings of scar that surround nodules of hepatocytes. Typically fibrosis requires years or decades to become clinically apparent, but notable exceptions in which cirrhosis develops over months may include pediatric liver disease (e.g. biliary atresia), drug-induced liver disease, and viral hepatitis associated with immunosuppression after liver transplantation ***(Friedman, 2000)***

There has been great progress made in our understanding of the cellular mechanisms of hepatic fibrosis. The recognition that the hepatic stellate cell, (formerly know as lipocyte, Ito, or

fat-storing cell), played a central role in the fibrotic response was key to our understanding. Stellate cells undergo a process known as activation, in response to any insult. Activation is a broad phenotypic response, characterized by distinct functional changes in proliferation, fibrogenesis, contractility, cytokine secretion, and matrix degradation. Insights gained into the molecular regulations of stellate cell activation may lead to new antifibrotic therapies, which may reduce morbidity and mortality in patients with chronic liver injury ***(Albanis and Friedman, 2001).***

Liver fibrosis was historically thought to be a passive and irreversible process due to collapse of hepatic parenchyma and its substitution with collagen-rich tissue currently , it is considered a model of wound-healing response to chronic liver injury early clinical reports in 1970s suggested that advanced liver fibrosis is potentially reversible ***(Bataller and Brenner, 2005).***

While fibrosis is reversible in its initial stages, progressive fibrosis can lead to cirrhosis. The exact point when fibrosis becomes irreversible is incompletely understood. However, increasing evidence suggests that even early stages of cirrhosis may be reversible ***(Bonis et al., 2001).***

There are two main groups of non-invasive methodologies for the evaluation of hepatic fibrosis and its progression. The first group, defined "serum markers", is aimed at predicting fibrosis

stage and, possibly, other prognostic information, using parameters measurable in serum. The second group includes methodologies derived from elaboration of parameters obtainable with the current liver imaging techniques (ultrasound, computed tomography (CT) scan, magnetic resonance) or to the innovative use of principles of physics (that is, transient elastography) ***(Pinzani, 2006).***

The accurate diagnosis of hepatitis C virus (HCV)-related fibrosis is crucial for prognostication and treatment decisions. Due to the limitations of biopsy, noninvasive alternatives including FibroTest and FibroScan have been developed ***(Shaheen et al., 2007).***

Interferon therapy seemed to reduce the progression of hepatic fibrosis and cause regression of fibrosis in patients with virologic response to treatment, and it reduced progression of hepatic fibrosis in patients with nonsustained virologic response ***(Shiratori et al., 2000).***

Recent reports have shown the capacity of mesenchymal stem cells (MSCs) to differentiate into hepatocytes in vitro and in vivo. MSCs administration could repair injured liver, lung, or heart through reducing inflammation, collagen deposition, and remodeling. These results provide a clue to treatment of liver fibrosis ***(Zhao et al., 2005).***

We are on the cusp of new era, in which significant progress in basic research is moving the field towards novel approaches for the diagnosis and therapy of hepatic fibrosis. Accelerating progress is anticipated once validated noninvasive biomarkers of fibrosis are developed, as there are ample therapeutic targets, and many compounds in the drug development pipeline will soon be available for clinical study. If successful, antifibrotic therapy could transform the management of patients with progressive liver disease, having a significant beneficial health impact ***(Friedman, 2004).***

Aim of the work

The aim of this study is to highlight the issue of hepatic fibrosis, its pathogenesis, reversibility and recent modalities in management of hepatic fibrosis.

MICROANATOMY OF THE LIVER

HEPATIC MORPHOLOGY

Kiernan (1833) introduced the concept of hepatic lobules as the basic architecture. He described circumscribed pyramidal lobules consisting of a central tributary of the hepatic vein and at the periphery, a portal tract containing bile duct, portal vein radicle and hepatic artery branch. Columns of liver cells and blood-containing sinusoids extended between these two systems.

Stereoscopic reconstructions and scanning electron microscopy have shown the human liver as columns of liver cells radiating from a central vein, and interlaced in orderly fashion by sinusoids ***(Sherlock and Dooley, 1997).***

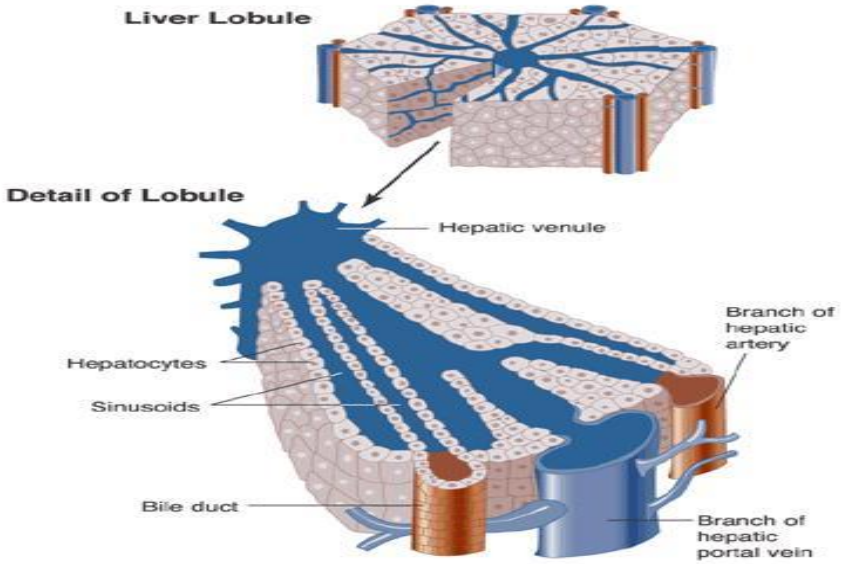

Figure (1): hepatic lobule of liver.

The liver tissue is pervaded by two systems of tunnels, the portal tracts and the hepatic central canals, which dovetail in such a way that they never touch each other. The terminal tunnels of the two systems are separated by about 0.5 mm. As far as possible the two systems of tunnels run in planes perpendicular to each other. The sinusoids are irregularly disposed, normally in a direction perpendicular to the lines connecting the central veins. The terminal branches of the portal vein discharge their blood into the sinusoids and the direction of flow is determined by the higher pressure in the portal vein than in the central vein.