The Role Of MR Imaging Techniques In the Detection and Quantification of Liver Steatosis

Essay

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Chapter 1
INTRODUCTION

Fatty liver disease is considered one of the commonest causes of chronic liver disease. This term is applied to a wide spectrum of conditions characterized histologically by triglyceride accumulation within the cytoplasm of hepatocytes affecting the liver in a diffuse pattern or less commonly focal pattern . The two most common conditions associated with fatty liver are alcoholic liver disease and nonalcoholic fatty liver disease

Alcoholic **liver** disease is caused by excess alcohol consumption, whereas the nonalcoholic variant is related to insulin resistance and the metabolic syndrome. Other relatively common conditions associated with fat accumulation in the **liver** include viral hepatitis and the use or overuse of certain drugs. Rarer associated conditions include dietary and nutritional abnormalities and congenital disorders

(Hamer et al., 2006)

The prevalence of **fatty liver** in the general population is about 15%, but it is higher among those who consume large quantities of alcohol (>60 g per day) as it reaches (45%), for those with hyperlipidemia it reaches (50%) or obesity (body mass index, >30 kg/m^2) it reaches (75%), and for those with both obesity and high alcohol consumption it reaches up to (95%) **(Shen et al , 2003)**

In many conditions associated with fatty liver, steatosis may progress to steatohepatitis (with inflammation, cell injury, or fibrosis accompanying steatosis) and then cirrhosis **(mendez-Sanchez et al, 2005)**

Noninvasive early detection and quantification of fat is becoming more and more important clinically, due in large part to the growing prevalence of nonalcoholic fatty liver disease

Steatosis, the accumulation of fat-containing vacuoles within hepatocytes, is a key histologic feature of fatty liver disease. Liver biopsy, the current standard of reference for the assessment of steatosis, is invasive, has sampling errors, and is not appropriate in some clinical settings

So, Several magnetic resonance (MR) imaging based techniques including, **chemical shift imaging**, **frequency-selective imaging**, and **MR spectroscopy** are currently in clinical use for the detection and quantification of fat-water admixtures, with each technique having important advantages, disadvantages, and limitations. These techniques permit the breakdown of the net MR signal into fat and water signal components, allowing the quantification of fat in liver tissue, and are increasingly being used in the diagnosis, treatment, and follow-up of fatty liver disease

(Cassidy et al, 2009)

Aim of the Work

The aim of this study is to discuss the role of recent MRI techniques in diagnosis and quantification of fatty liver disease.

Chapter 2
PATHOLOGY OF HEPATIC STEATOSIS

Hepatic steatosis or fatty liver is infiltration of fat mainly triglycerides, inside the hepatocytes, usually exceeding 5% of liver weight **(Sherlock & Dooley ,2002)**

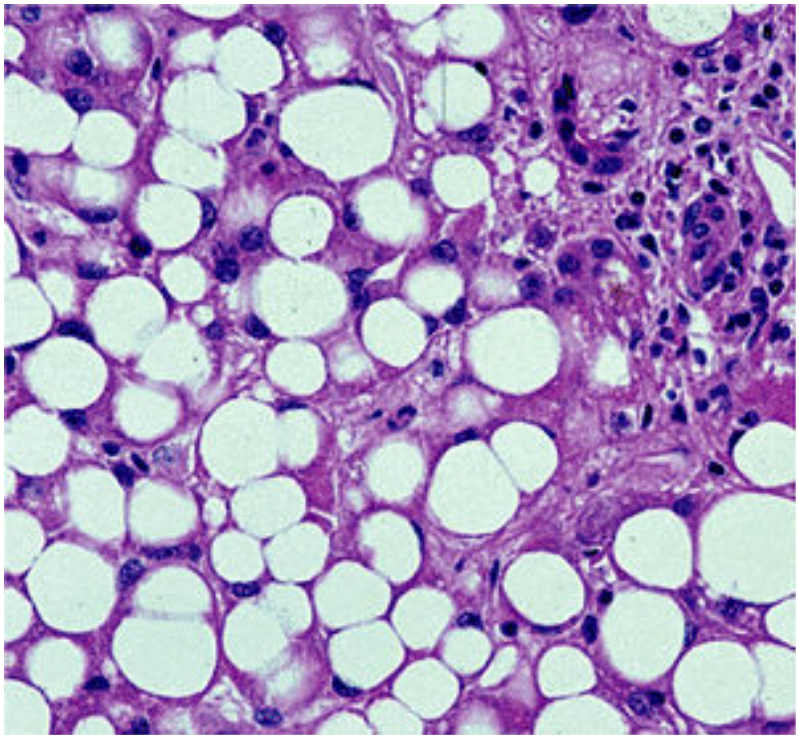
The triglyceride accumulation (Steatosis) within hepatocytes is achieved by altering the hepatocellular lipid metabolism, in particular, by causing defects in free fatty acid metabolic pathways **(Clark & Diehl ,2003)**

Hepatocytes in the center of the lobule (near the central vein) are particularly vulnerable to metabolic stress and tend to accumulate lipid earlier than those in the periphery **(Brunt& Tiniakos, 2002)**

Consequently, in many of these conditions, steatosis tends to be most pronounced histologically in the zone around the central veins and less pronounced in zones around the portal triads. In advanced cases, there is diffuse, relatively homogeneous involvement of the entire lobule **(Scheuer & Lefkowitch , 2000)**

Pathology of hepatic steatosis…

Fatty change represents the intra-cytoplasmic accumulation of triglyceride (neutral fats). At the beginning, the hepatocytes present small fat vacuoles (liposomes) around the nucleus (microvesicular fatty change). In this stage liver cells are filled with multiple fat droplets that do not displace the centrally located nucleus. In the late stages, the size of the vacuoles increase pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance (macrovesicular fatty change) (figure1). These vesicles are well delineated and optically "empty" because fats dissolve during tissue processing. Large vacuoles may coalesce and produce fatty cysts which are irreversible lesions. Macrovesicular steatosis is the most common form and is typically associated with alcohol, diabetes, obesity and corticosteroids. Acute fatty liver of pregnancy and Reye's syndrome are examples of severe liver disease caused by microvesicular fatty change **(Goldman, Lee. 2003)**



(Figure 1) Alcoholic fatty liver. A photomicrograph shows the cytoplasm of almost all the hepatocytes distended by fat that displaces the nucleus to the periphery **(quoted from Ruben E and Ruben R ,2008)**

The diagnosis of Steatosis is made when fat in the liver exceeds 5–10% body weight .

Defects in fat metabolism are responsible for pathogenesis of FLD which may be due to imbalance in energy consumption and its combustion resulting in lipid storage or can be a consequence of peripheral resistance to insulin, whereby the transport of fatty acids from adipose tissue to the liver is increased.

(Reddy et al., 2006)

A severe fatty liver is sometimes accompanied by inflammation, a situation that is referred to steatohepatitis. Progression to alcoholic steatohepatitis (ASH) or non alcoholic steatohepatitis (NASH) depends on persistence or severity of inciting cause. Pathological lesions in both conditions are similar. However, the extent of the inflammatory response varies widely and does not always correlate with the degree of fat accumulation. Steatosis and steatohepatitis may represent successive stages in fatty liver disease (FLD) progression (**Day &James, 1998)**

Liver with extensive inflammation and high degree of Steatosis often progresses to more severe forms of the disease (**Gramlich et al., 2004)**

Hepatocyte ballooning and hepatocyte necrosis of varying degree are often present at this stage (figure 2) .liver cell death and inflammatory response lead to activation of stellate cells which play a pivotal role in hepatic fibrosis. The extent of fibrosis varies widely. Perisinusoidal fibrosis is most common, especially in adults and predominates in zone 3 around the terminal hepatic vein **(Zafrani, 2004)**

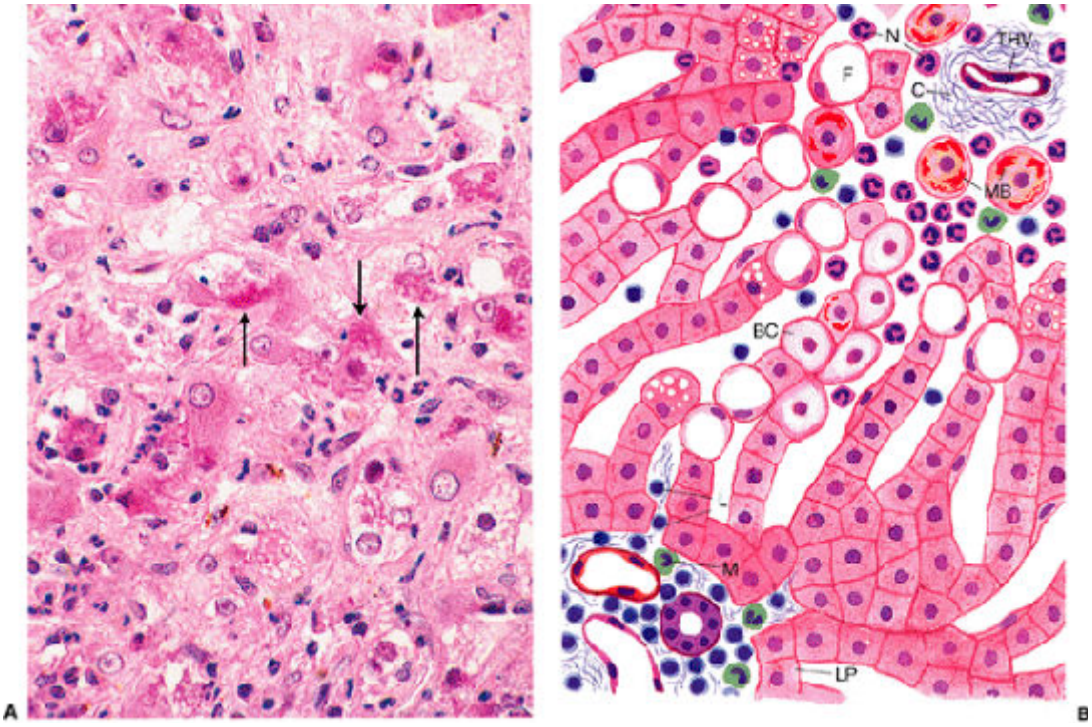


FIGURE 2. **A**. photomicrograph shows necrosis and degeneration of hepatocytes; Mallory bodies (eosinophilic inclusions) in the cytoplasm of injured hepatocytes (arrows); and infiltration by neutrophils. **B**. Schematic representation of the major pathologic features of alcoholic hepatitis. The lesions are predominantly centrilobular and include necrosis and loss of hepatocytes, ballooned cells (BC), and Mallory bodies (MB) in the cytoplasm of damaged hepatocytes. The inflammatory infiltrate consists predominantly of neutrophils (N), although a few lymphocytes (L) and macrophages (M) are also present. The central vein, or terminal hepatic venule (THV), is encased in connective tissue (C) (central sclerosis). Fat-laden hepatocytes (F) are evident in the lobule. The portal tract displays moderate chronic inflammation, and the limiting plate (LP) I focally breached. **(quoted from Ruben E and Ruben R ,2008)**

1-ALCOHOLIC FATTY LIVER

1.1 Epidemiology ……

The prevalence of cirrhosis is high in those countries with the highest per capita consumption of alcohol this relationship is valid regardless the specific nature of the preferred beverage although a minority of chronic alcoholics develop cirrhosis a dose response relationship between the life time dose of alcohol (duration of exposure and the daily amount of alcohol consumed) **(Ruben E and Ruben R ,2008)**

1.2 Pathogenesis…

Steatosis, the earliest response of the liver to alcohol abuse, is characterized by the accumulation of fat (mainly triglycerides, phospholipids ,and cholesterol esters) in hepatocytes.

Early studies indicated that alcohol consumption increases the ratio of reduced nicotinamide adenine dinucleotide/oxidized nicotinamide adenine dinucleotidein hepatocytes, which disrupts mitochondrial oxidation of fatty acids and results in Steatosis.

However, the contribution of these mechanisms to the development of Steatosis after long-term alcohol consumption is not clear and requires further investigation.

(Gao and Bataller, 2011)

Alcohol intake has also been shown to augment the supply of lipids to the liver from the small intestine, increasing mobilization of fatty acids from adipose tissue and uptake of fatty acids by the liver.

Dietary fat in the form of chylomicrons and free fatty acids is transported to the liver where it is taken by the hepatocytes .Triglycerides are then hydrolized to free fatty acids ,these in turn undergo β-oxidation in the mitochondria or converted to triglycerides in the endoplasmic reticulum the newly synthesized triglycerides are secreted in the form of lipoproteins or are retained for storage.

Most of the fat deposited in the liver after chronic alcohol consumption is derived from the diet. Ethanol increases the lipolysis and thus the delivery of free fatty acids to the liver. Within the hepatocytes ; ethanol increases fatty acid synthesis , decreases mitochondrial oxidation , increases the production of triglycerides and impairs the release of lipoproteins.Collectively these metabolic consequences produce fatty liver .

(Ruben E and Ruben R ,2008)

Recent studies indicate that alcohol exposure, directly or indirectly, regulates lipid metabolism-associated transcription factors; this stimulates lipogenesis and inhibits fatty acid oxidation

Ethanol increases fatty acid synthesis in hepatocytes via up-regulation of sterol regulatory element-binding protein 1c (SREBP-1c), a transcription factor that promotes fatty acid synthesis via up-regulation of lipogenic genes

Alcohol consumption could directly increase transcription of SREBP-1c gene via its metabolite acetaldehyde or indirectly up-regulateSREBP-1c expression by activating processes and factors that stimulate SREBP-1c expression, such as the endoplasmic reticulum response to cell stress.

Alcohol consumption inhibits fatty acid oxidation in hepatocytes mainly via inactivation of the peroxisome proliferator-activated receptor (PPAR), a nuclear hormone receptor that controls transcription of a range of genes involved in free fatty acid transport and oxidation.

(Gao and Bataller, 2011)

1.3 Pathology…

In the alcoholics the liver become yellow and enlarged ,sometimes massively ,to as much as three times the normal weight .The increased weight does not reflect fat accumulation alone, since protein and water content also increase. Microscopically the extent of visible fat accumulation varies from minute droplets scattered in the cytoplasm of few hepatocytes to distension of entire cytoplasm of most cells by coalesced droplets. In the latter situations the liver cell is scarcely recognizable as such and bears resemblance to an adipocyte, the cytoplasm being represented by a distended clear area and the nucleus is flattened and displaced to the periphery of the cell .

The ultrastructural appearance of the hepatocyte in alcohol induced fatty liver reflects the cytotoxicity of the ethanol rather than the effect of fat per se .The mitochondria are enlarged with occasional bizarre giants forms. The smooth endoplasmic reticulum exhibits hyperplasia .Initially the fat accumulates as globules, which originally merge to form large large cytoplasmic bodies of variable electron density .

The ultrastructural changes in mitochondria and endoplasmic reticulum produced by chronic alcohol ingestion are paralleled by functional alterations. Hepatic mitochondria show decreased rate of substrate oxidation (e.g. fatty acids) and impaired formation of ATP .

Hyperplasia of the smooth endoplasmic reticulum is accompanied by an increase in the activity of cytochrome P450 dependent mixed function oxidases. Not only is the microsomal ethanol-oxidizing system oxidases induced, but the metabolism of wide variety of drugs is also enhanced

(Ruben E and Ruben R ,2008)

1.4 Alcoholic Steatohepatitis Pathogenesis

ASH is a syndrome characterized by infiltration of the liver by inflammatory cells and hepatocellular injury .ASH develops in patients with Steatosis and is usually associated with progressive fibrosis.

The prevalence of ASH has not been accurately determined; it is believed to occur in 10% to 35% of heavy drinkers.

ASH includes a spectrum of diseases that range from mild injury to severe life threatening injury. the histologic characteristics of ASH include centrilobular ballooning of hepatocytes, neutrophilic infiltration, Mallory–Denk hyaline inclusions, Steatosis, and a “chicken wire”–like pattern of fibrosis.

Hepatocyte apoptosis is an important pathologic feature of human ALD. Apoptosis results from multiple mechanisms, including ethanol-mediated hepatotoxicity, induction of oxidative stress, inhibition of survival genes, and induction of proapoptotic signaling molecules (TNF- and Fas ligand)

(**Gao and Bataller, 2011**)

1.5 Alcoholic Steatohepatitis Pathology

In the typical case of acute alcoholic hepatitis, the hepatic architecture is basically intact, with a normal relation of portal tracts to central venules. The hepatocytes show variable hydropic swelling, which gives them a heterogeneous appearance

Isolated necrotic liver cells or clusters of them exhibit pyknotic nuclei and karyorrhexis. Scattered hepatocytes contain Mallory bodies (alcoholic hyaline). These cytoplasmic inclusions, which are more common in visibly damaged, swollen hepatocytes, are visualized as irregular skeins of eosinophilic material or as solid eosinophilic masses, often in a perinuclear location

Ultrastructurally, they are composed of aggregates of intermediate (cytokeratin) filaments. The damaged, ballooned hepatocytes, particularly those containing Mallory bodies, are surrounded by neutrophils, although a more diffuse, intralobular inflammatory infiltrate is also present

Collagen deposition is a constant feature of alcoholic hepatitis, especially around the central vein (terminal hepatic venule). In severe cases, the venule and perivenular sinusoids are obliterated and surrounded by dense fibrous tissue, in which case the lesion has been termed central hyaline sclerosis, The appearance of the portal tracts in alcoholic hepatitis is highly variable. In some instances, they are virtually normal, whereas in others they are enlarged and contain a mononuclear infiltrate and
Proliferated bile ductules. The altered portal tracts often display spurs of fibrous tissue that penetrate the lobules

(**Ruben E and Ruben R.,2008**)

2-NON ALCOHOLIC FATTY LIVER DISEASE

2.1 Introduction

Nonalcoholic fatty liver disease (NAFLD) is so named because of its close resemblance to alcoholic liver disease. It represents a spectrum of liver injuries that initially display simple steatosis, with or without associated hepatitis (nonalcoholic steatohepatitis [NASH]), and progress to bridging fibrosis and cirrhosis.

Histologic features of NAFLD overlap with alcoholic liver disease and include steatosis, lobular and portal inflammation, hepatocyte necrosis, Mallory's hyaline, and fibrosis. As in alcoholic liver disease, centrilobular fibrosis is commonly observed. With the development of cirrhosis, steatosis often disappears. Thus, NAFLD is the likely cause of many cases of so-called cryptogenic cirrhosis

(Ruben E and Ruben R ,2008)

2.2 mechanisms of hepatic accumulation of fat

In NAFLD patients, liver fat derives from dietary free fatty acids (FFA), and from two other phenomena—both predominantly dependent on IR, namely liver FFA influx, and liver de novo lipogenesis. **(Petta et al .,2009)**

2.3 NAFLD: risk factors and mechanisms of the disease

Overweight and obesity are clearly associated with NAFLD, with the likelihood of developing NASH increasing with the degree of obesity .In addition, numerous reports have documented resolution of a fatty liver following gradual weight loss.

Hepatic IR is associated with impairment of glycogenesis, and with an increase of gluconeogenesis and glycogenolysis . In light of these data it appears clear that IR is the physiopathological hallmark of NAFLD.

In fact IR is the key factor in the promotion of liver fat accumulation not only by inducing an increase of liver FFA influx, but also, via hyperinsulinemia, by stimulating the activity of enzymes implicated in de novo hepatic lipogenesis. However, it is worth nothing that IR also seems able to promote the progression of simple steatosis to NASH and fibrosis

(Petta et al .,2009)