Relation Between NAFLD, Carotid Intimal Thickness And Metabolic Syndrome

Thesis

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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ABSTRACT

Introduction: NAFLD is a term used to define a large spectrum of conditions, ranging from simple non-symptomatic steatosis to non-alcoholic steatohepatitis, and cirrhosis. Cardiovascular disorders constitute major health threats in NAFLD .Thus, prediction of NAFLD at earlier stage is important in prevention of the inherent process of NAFLD and the associated fatal cardiovascular disorders. NAFLD frequently associated with the metabolic syndrome (MS), which has led many authors to suggest that NAFLD represents the hepatic component of this syndrome.

Aim of work: To assess the relation between NAFLD, carotid intimal thickness and metabolic syndrome.

Material and methods: This study was conducted on 30 patients in Gastroenterology clinic Ain Shams University Hospital. Patients were divided into 2 groups:

Group1: 15 Patients with NAFLD and metabolic syndrome.

Group2: 15 Patients with NAFLD without metabolic syndrome.

Result: Our study revealed a significant increase in carotid IMT in patients of NAFLD in both groups with mean value in group 1 (1.011 $\pm$ 0.126 cm) and in group 2(1.012 $\pm$ 0.139cm)**.**

Conclusion: Patients with NAFLD have significantly higher mean values of intima-media thickness and prevalence of plaques resulting in an increased risk of atherosclerosis in subjects with or without metabolic syndrome and patients with fatty liver should be investigated for other factors for ischemic strokes (cerebrovascular and cardiovascular) and guarded against it.

Introduction

INTODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent state which is characterized by fatty infiltration of liver cells and occurring in patients who do not abuse alcohol **(Brea et al., 2005),** in absence of co-existing causes for chronic liver disease and exclusion of competing etiologies for hepatic steatosis **(Chalasani et al., 2012).**

The worldwide prevalence of NAFLD ranges from 6.3% to 33% with a median of 20% in the general population, based on a variety of assessment methods **(Vernon et al., 2011).**

Fatty liver can develop as the result of various metabolic conditions that promote fat accumulation in the liver and may cause liver damage **(Marchesini et al., 2003).**

NAFLD is histologically categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) which may progress to liver cirrhosis **(Chalasani et al., 2012).** Progression of NASH to hepatocellular carcinoma, in the absence of cirrhosis has been reported **(Ekstedt et al., 2006),**

NAFLD is commonly associated with obesity, metabolic syndrome, and type 2 diabetes **(Kim et al., 2009).** The presence of metabolic syndrome is a strong predictor for the presence of steatohepatitis in patients with NAFLD **(Chalasani et al., 2012).**

Several studies suggest that NAFLD is independently associated with an increased risk of cardiovascular disease in nondiabetic subjects **(Sookoian and Pirola, 2008) (Targher et al., 2006) (Targher et al., 2008).** Also, it has been reported to be associated with carotid artery atherosclerosis, which is evaluated using the intima-media thickness (IMT) **(Brea, et al. 2005)**.

However, whether NAFLD has a direct impact on atherosclerosis independent of other metabolic risk factors is unclear.

Aim of the work

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The aim of this study is to assess the relation between NAFLD, carotid intimal thickness and metabolic syndrome, and detect the value of these relation as a risk factor for ischemic strokes (cardiovascular and cerebrovascular).

Review of Literature

CHAPTER (1)

NON ALCHOLIC FATTY LIVER DISEASE (NAFLD)

Definition of NAFLD: Nonalcoholic fatty liver disease (NAFLD) has evolved as the world's epidemic and is one of the most common chronic diseases in the United States **(Milic. et al., 2012 and Nassir. et al., 2013).** NAFLD involves a spectrum of hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) that occurs in the absence of significant alcohol intake and absence of other viral, genetic and autoimmune components. Hepatic steatosis is defined as liver content exceeding 5% of liver weight **(Cohen. et al., 2011, Fabbrini. et al., 2010, Grattagliano. et al., 2011and Szczepaniak. et al., 2005).** NAFL is non progressive whereas NASH can advance to cirrhosis and hepatocellular carcinoma **(VernoG. et al., 2011).** NAFLD is a part of the metabolic syndrome, particularly in obesity, hyperlipidemia, and diabetes **(Bril F. et al., 2014).**

Table 1: **Terminology of nonalcoholic fatty liver disease (NAFLD) (Zhang X. et al., 2014).**

NAFLD: Predominantly macro vesicular steatosis.
Simple steatosis: Benign form of NAFLD.
NASH: The progressive form of NAFLD that includes necroinflammation, ballooning of hepatocytes, and variable degrees of fibrosis.
NAFLD-associated cirrhosis: Loss of one of the histological hallmark features of NAFLD (fat).
NAFLD-associated HCC.

Table2: **Histopathologic abnormalities in nonalcoholic steatohepatitis (NASH) (Miyake T. et al., 2014).**

Steatosis
Inflammation
Hepatocytes ballooning
Fibrosis.

Prevalence of NAFLD:

The prevalence of NAFLD is rapidly increasing worldwide in parallel with the increase in obesity and type 2 diabetes **(Björnsson et al., 2007).** It is important to note that this prevalence is partly dependent upon the method used to diagnose fatty liver (FL) , the method used to assess alcohol intake and the cut-off point used to exclude relevant alcohol intake **(Radu C et al., 2008).** NAFLD affects about 30% of the general population in western society, and is recognized as the most common cause of liver dysfunction worldwide **(Chalasani et al., 2012),** 15% in Asian countries and in Saudi Arabia, the prevalence of NAFLD as evaluated by computed tomography is about 10 % **(Ong JPet al., 2007and Browning JD et al., 2007).** The prevalence of NASH related cirrhosis and HCC is also high among patients with diabetes, as in obesity **(Browning JD et al., 2004).** Liver ultrasonography is known to underestimate the prevalence of fatty liver although it is the only technique that can be used in the general population for ethical and logistic reasons **(Ong JP et al., 2007).** The prevalence of NAFLD varies according to age, gender and weight status. NAFLD and the NASH have been reported in subjects of all ages, including children, where the prevalence of steatosis is smaller than in adults (13–15%), but increases in presence of obesity (30 –80%) **(Rashid M, et al., 2000).** NAFLD increases with obesity and type 2 diabetes; it is present in up to 90% of obese individuals **(Alisi et al., 2009).** It was estimated that 10%-20% of patients with NAFL would develop NASH, and 10%-29% of patients with NASH would progress to cirrhosis within 10 years **(Argo CK and Caldwell SH2009).** NASH-induced cirrhosis is the third leading cause of liver transplantation in the United States **(Charlton MR et al., 2011)** and is associated with high liver-related morbidity and mortality **(Vernon,G et al., 2011).**

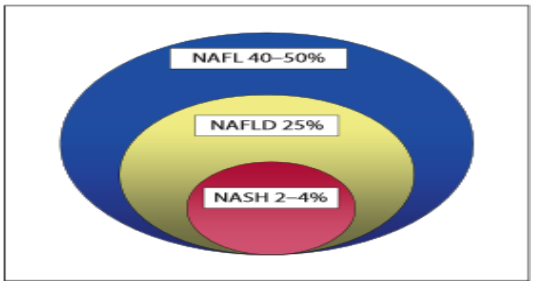

Figure (1): Estimated prevalence of NAFL, NAFLD and NASH **(Charlton MR et al., 2011)**.

PATHOGENESIS OF NAFLD:

Insulin resistance, oxidative stress, and inflammatory cascades are believed to play a central role in the pathogenesis of NAFLD **(Lewis et al., 2010).** The pathogenesis of NAFLD is based on the disrupted uptake, synthesis, oxidation and export of fatty acids. This imbalance leads to excessive fat accumulation in the liver **(Podrini C. et al., 2013 and Ucar F. et al., 2013),** the main element of NAFLD is the accumulation of triglycerideides (TG) as fat droplets within the cytoplasm of hepatocytes due to, which is a predispose for subsequent events of NASH, as more than 5%-10% of hepatocytes have fat droplets as evident on liver biopsy **(Miyake T. et al., 2014).** According to the original hypothesis (the "two hit") hypothesis, NAFLD is a progressive disease in which insulin resistance ("the first hit") leads to increased free fatty acids (FFA) flux to the liver. If FFAs are not oxidized or secreted, hepato-steatosis develops **(Day et al., 1998).** Hepatic steatosis predisposes the liver to "second hits" such as mitochondrial dysfunction, cytokines, adipokines and bacterial endotoxins. This original hypothesis has been modified to suggest that NAFLD may be a consequence of parallel"multi-hits" **(Tilg et al., 2010).** In this model, insulin resistance leads to increased lipogenesis and increased uptake of FFAs into the liver. Lipotoxicity sensitizes the liver to injury by "multiple parallel hits" (oxidative damage, activation of fibrogenic pathways, activation of hepatic stellate cells, altered expression of adipokines) leading to NASH and fibrosis. More recently a new theory, the "distinct-hit", has been proposed to suggest distinct pathogenic pathways for hepatic steatosis and NASH**(Vernon, G. et al., 2010, Lonardo, A. et al., 2011 and Yilmaz, Y. 2012).**

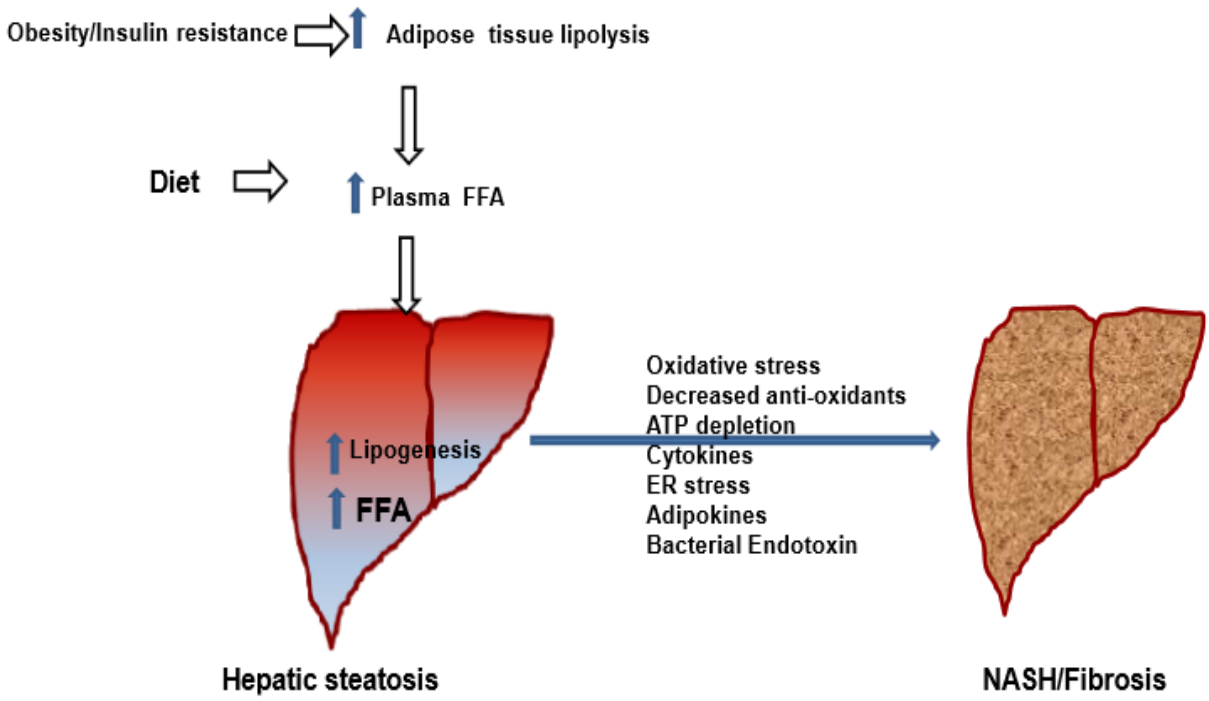

Figure (2): The "multiple parallel-hits" hypothesis of NAFLD **(Tilg, H. et al., 2010).**

Mechanisms Leading to NAFLD:

A-Source of Fatty Acids (FAs) in the Live: Hepatic lipid accumulation can be caused by different metabolic abnormalities: increased FA delivery to hepatocytes from lipolyzed adipose TAG, dietary lipids, or hepatic de novo lipogenesis (DNL); increased TAG synthesis; decreased hepatic FA oxidation; and inadequate TAG secretion in very low density lipoproteins (VLDL) **(Ruhl et al., 2004).**

1- Diet: Dietary fatty acids are absorbed from the small intestine, assembled into lipoprotein rich particles (chylomicrons) and secreted in to the blood about 59% of liver FFAs in NAFLD patients are derived from the circulation, 26% from de novo lipogenesis and 15% from the diet**(Donnelly et al., 2005).**

2- Adipose Tissue Lipolysis: Lipolysis is the process by which stored triglycerides (TGs) are released as FFAs, this process is regulated by insulin, Increasing calorie intake such as in obesity causes insulin resistance leading to increased adipose tissue Lipolysis, release of FFAs in the circulation and ectopic lipid accumulation **(Lafontan, M. et al., 2009).**

3-De Novo Lipogenesis: De novo lipogenesis is a process by which the cell converts excess carbohydrates into FAs. Hepatic lipogenesis is activated primarily by insulin secreted from the pancreas after a high-carbohydrate meal; de novo lipogenesis is now considered an important contributing factor to NAFLD development **(Donnelly et al., 2005).**

B- Fatty Acid Uptake by the Liver: FFAs generated by adipose tissue lipolysis under fasting conditions circulate in the plasma bound to albumin **(Kazantzis, M et al., 2012).** CD36 plays an important role in facilitating FFAs uptake and cellular lipid metabolism; CD36 upregulation in the liver is associated with insulin resistance, hyperinsulinaemia and increased steatosis in nonalcoholic steatohepatitis **(Miquilena-Colin et al., 2011).** Depending on the physiological conditions, FFAs have multiple destinations in the liver: FFAs are converted into complex lipid species, packaged into very low density lipoproteins (VLDL) and released into the circulation; oxidized by β-oxidation; or esterified into TG and stored as lipid droplets surrounded by lipid droplet proteins within the hepatocytes**(Wolins, N.E. et al., 2005).**

C-Disposal of Hepatic FFAs:

D-Secretion of Hepatic TG: The liver secretes TG in the form of very low density lipoprotein (VLD L) **(Sen, D. et al., 2007);** insulin plays an important role in the regulation of VLDL assembly and secretion **(Welty, F.K. 2014 and Ginsberg, H.N. et al., 2009).** Insulin resistance results in increased TG secretion and hypertriglyceridemia; the hepatic steatosis associated with insulin resistance results from increased TG synthesis exceeding liver capacity to secrete TG. Both hypertriglycedemia and hepatic steatosis are observed in NAFLD patients **(Choi, S.H. et al., 2011).** However, advanced NASH is associated with reduced or complete loss of fat. The mechanisms for fat loss are not understood but may implicate adiponectin **(Van der Poorten, D. et al., 2013).**