Faculty of medicine

Ain-Shams university

Association between hepatic steatosis and serum liver enzyme levels with atrial fibrillation

Thesis

Submitted for partial fulfillment of Master Degree

0f Internal Medicine

By

Mahmoud Mohammed Hassan

M.B.B.Ch

Faculty of medicine-Ain Shams University

Under supervision of

Prof. Dr. Hanan Mahmoud Badawy

Professor of Internal Medicine,Gastroenterology and Hepatology

Faculty of Medicine – Ain Shams University

Dr. SherifSadekTaha

Assistant Professor of Internal Medicine,Gastroenterology and Hepatology

Faculty of Medicine – Ain Shams university

Dr. Hany Samir Rasmy

Lecturer of InternalMedicine,Gastroenterology and Hepatology

Faculty of Medicine – Ain Shams university

Faculty of Medicine

Ain Shams university

2016

Abstract

Fatty liver is the accumulation of triglycerides and the other fats in the liver cells. The amount of fatty acid in the liver depends on the balance between the processes of delivery and removal. In some patients, fatty liver may be accompanied by hepatic inflammation and liver cell death (steatohepatitis).

AF is characterized by an irregular and often rapid heart beats. The exact mechanisms by which cardiovascular risk factors predispose to AF are not understood fully but are under intense investigations. Catecholamine excess, hemodynamic stress, atrial ischemia, atrial inflammation, metabolic stress and neurohumoral cascade activation are all purported to promote AF.

In concert with obesity, dyslipidemia and type II diabetes mellitus, non-alcoholic HS is now considered as a consequence of modern lifestyle, characterized by sedentariness and high caloric food intake. Besides its association with an increased risk of all-cause mortality and liver diseases (like non-alcoholic steatohepatitis or cirrhosis), HS is also associated with multiple cardiovascular risk factors and with increased cardiovascular morbidity and mortality.

Therefore, non-alcoholic HS appears to be either an emerging causal factor for the development of overt CVD or at least a reliable marker of increased CVD risk.Similarly, elevated levels of serum liver enzymes (i.e, alanine aminotransferase [ALT], aspirate aminotransferase [AST] and

gamma glutamyl transpeptidase [GGT]) are also associated with an increased CVD risk, even in the absence of manifest liver disease, but, possibly as surrogate markers of HS.

The current study revealed that there is an association between hepatic steatosis confirmed by fibrosis index and elevated serum liver enzymes with the incidence of atrial fibrillation.

Keywords: Hepatic steatosis, elevated serum liver enzymes, Atrial fibrillati

INTRODUCTION

Non-alcoholic hepatic steatosis,the accumulation ofexcess fat in the liver in the absence of excess alcohol consumption,is one of the most common disorders in the developed and developing societies,affecting up to 35%adults in the general population***(Targher et al., 2013).***

Beside its association with an increased risk of all-cause mortality and liver diseases(like non-alcoholicsteatohepatitis or cirrhosis),hepatic steatosis is also associated with multiple cardiovascular risk factors **(Fan et *al., 2007),***and with increased cardiovascular morbidity and mortality ***(Day et al., 2010).***

Specially, increasing evidence suggeststhat individuals with non-alcoholic hepatic steatosis are at increased risk of cardiavascular disease, aortic valve sclerosis, cardiac remodeling and changes in cardiac function and rhythm***(Ballestri et al., 2014).***

Two prior community-based studies reported that elevated liver enzyme levels were associated with an increased risk of incidentatrial fibrillation ***(Alonso et al., 2014),*** as the hepatic release of increased levels of serum liver enzymes might be

accompanied by higher levels of pro-inflammatroy,pro-coagulant and pro-fibronogenic mediators that might lead to structural and electrical remodeling of the atrium resulting in the development and persistance of atrial fibrillation.

Furthermore, two small clinical studies reported that non-alcoholic HS was independently associated with both prevalent ***(Targher et al., 2013),***and incident **(Valbusa *et al., 2013),*** cases of atrial fibrillation in patients with type II diabetes mellitus.

AIM OF THE STUDY

To study the association between hepatic steatosis and serum liver enzyme levels with atrial fibrillation.

HEPATIC STEATOSIS

Fatty liver is the accumulation of triglycerides and the other fats in the liver cells. The amount of fatty acid in the liver depends on the balance between the processes of delivery and removal. In some patients, fatty liver may be accompanied by hepatic inflammation and liver cell death (steatohepatitis). **(Larter et al., 2008)**

Potential pathophysiological mechanisms for fatty liver include the following:-

- Decreased mitochondrial fatty acid beta-oxidation.
- Increased endogenous fatty acid synthesis or enhanced delivery of fatty acids to the liver.
- Deficient incorporation or export of triglycerides as very low-density lipoprotein (VLDL).

No single pathway of cause and effect has been found. However, some studies show higher levels of activation of Hedgehog pathways in patients with the most advanced fatty liver disease. **(Guy et al., 2012)**

The authors reported that in non-alcoholic fatty liver disease (NAFLD), a pro-coagulant imbalance processes from

steatosis to metabolic cirrhosis, which may be caused by an increase in factor VIII and a reduction in protein C. The investigators speculated that this imbalance could play a role in the risk for cardiovascular disease and liver fibrosis, conditions commonly associated with NAFLD. **(Tripodi et al., 2014)**

Pathological changes observed in patients with alcoholic liver disease (ALD) can be divided in the following 3 groups:

- Alcoholic fatty liver (simple steatosis).
- Alcoholic hepatitis.
- Alcohol-related cirrhosis. **(Memon et al., 2000)**

Alcoholic fatty liver is an early and reversible consequence of excessive alcohol consumption. Fatty liver develops in every individual who consumes more than 60 g of alcohol per day. Many mechanisms of ethanol-induced fatty liver have been proposed. **(Memon et al., 2000)**

Increased hepatic levels of glycerol 3-phosphate (3-GP) after ethanol ingestion are related to an increase of the ratio of the reduced form of nicotinamide adenine dinucleotide (NAD+) to the reduced form (NADH) in the liver. A higher concentration of 3-GP results in enhanced esterification of fatty acids. An increase in free fatty acids has also been incriminated

in the pathogenesis. Large amount of alcohol enhance lipolysis through direct stimulation of adrenal pituitary axis. In addition, chronic ethanol ingestion inhibits oxidation of fatty acids in the liver and release of VLDL into the blood. All of these mechanisms favor steatosis. **(Memon et al., 2000)**

Centrilobular localization of steatosis results from decreased energy stores caused by relative hypoxia and shift in lipid metabolism, along with a shift in the redox reaction as a result of preferential oxidation of alcohol in the central zone. Advances in the understanding of the pathogenesis of alcoholic steatosis have provided some useful insights, including the role of peroxisome proliferator-activated receptor alpha (PPARA), which is crucial for the regulation of hepatic fatty acid metabolism. PPARA blockade in animal models along with ethanol consumption, contributes to the development of alcoholic fatty liver. In addition, induction of liponectin, a hormone secreted by adipocytes, has been implicated in the protective effect of saturated fat against the development of alcoholic fatty liver in mice. **(Pagano et al., 2005)**

The role of early growth response-1 (Egr-1) transcription factor is thought to be essential for ethanol-induced fatty liver injury in mice. Hepatocyte death by apoptosis occurs in

alcoholic fatty liver and has been demonstrated in rats and mice after ethanol feeding. This may be related to mitochondrial proteins that regulate apoptosis and necrosis and that are shown to be induced in mouse fatty liver models. Serum leptin, a cytokine-type peptide hormone mainly produced by adipocytes may play an important role in the pathogenesis of steatosis. Steatosis occurs with decreased leptin action, whether due to leptin deficiency or resistance. **(Friedman 1998)**

In patients with alcoholic liver disease, the serum leptin level appears to be independently correlated with the grade of steatosis. Data from both animal studies and clinical studies support the role of pro-inflammatory cytokine tumor necrosis factor alpha (TNF-alpha) in the early stages of fatty liver, as well as in alcoholic steatohepatitis. **(Li et al., 2003)**

Etiology

The condition most commonly associated with fatty liver disease is metabolic syndrome. This includes conditions such as type II diabetes, obesity and hypertriglyceridemia. Other factors such as drugs (eg, amidarone, tamoxifen and methotrexate), alcohol, metabolic abnormalities (eg, galactosemia, glycogen storage diseases, homocystinuria and tyrosinemia), nutritional status (eg, over-nutrition, severe malnutrition, total parentral

nutrition [TPN], or starvation diet), or other health problems (eg, celiac sprue and wilson disease) may contribute to fatty liver disease. **(Qureshi, Abrams 2007)**

Several risk factors may influence the development of advanced ALD, including the following:-

- Minimum amounts of alcohol intake associated with an increased of ALD range from 40 to 80 g\day for 10-12 years.
- Genetics play a role in alcohol consumption and alcoholism; early data suggested a genetic predisposition to the development of ALD, mostly related to the differences in major hepatic enzymes involved in the metabolism of alcohol (eg, alcohol dehydrogenase [ADH], acetaldehyde dehydrogenase [ALDH] and the cytochrome P-450 system (CYP4502E1).
- Several studies demonstrate a high prevalence of hepatitis C virus (HCV) antibody in patients with ALD, as well as iron overload.
- Obesity and dietary habits have been implicated in individual susceptibility to ALD. **(Schattenberg et al., 2005)**

Epidemiology

- Age-related demographics:-

Fatty liver occurs in all age groups. With respect to alcoholic steatosis, the liver handles alcohol differently as the body ages and alcohol toxicity increases with age because of increased organ susceptibility. These phenomena are thought to be related to a mitochondrial transport defect developing with age, as well as to decreased function of the smooth endoplasmic reticulum and metabolism of CYP2E1-dependent microsomal ethanol oxidation. NAFLD is the most common liver disease among adolescents in the united state. Older age often is predictive of more sever grading of fibrosis. NASH is the third most common cause of chronic liver disease in adults in the United States (after hepatitis C and alcohol). It is now probably the leading reason for mild elevations of transaminases. NASH has recurred within 6 months after pediatric or adult liver transplantation. **(Jankowska 2007, Seo 2007)**

- Sex-related demographics:-

Women develop more sever ALD more quickly and at lower doses of alcohol than men do. The increased susceptibility of females may be related to sex-dependent

differences in the hepatic metabolism of alcohol, cytokine production and the gastric metabolism of alcohol. In initial studies of NAFLD, the percentage of female patients was reported to be as high as 75%; however, in subsequent studies, the percentage fell to roughly 50%. **(Bedogni et al., 2007)**

- Race-related demographics:-

Studies have shown a higher rate of cirrhosis among black persons. Fatty liver has been found across all races, but NAFLD is most common in white persons and it is in this population that most of the research has been done. In general, hispanics do not have higher rates of NASH than white patients unless diabetes is also present. **(Lomonaco et al., 2011)**

Clinical presentation

History

Fatty liver occurs commonly after the ingestion of a moderate or large amount of alcohol, even for a short period of time. Alcohol-induced steatosis usually is asymptomatic. A thorough clinical history, especially with regard to the amount of alcohol consumption, is essential for determining the role of alcohol in the etiology of abnormal liver test results. History

obtained from family members may reveal past alcohol-related problems. **(Sundaram et al., 2009)**

Sever fatty infiltration of the liver can result in symptoms of malaise, weakness, anorexia, nausea and abdominal discomfort. Jaundice is present in 15% of patients admitted to the hospital. No specific test is available to rule out drug-related toxicity, but a good review of all concurrent and recent medications, including over-the-counter medications and alternative treatments, is valuable in evaluating the possible causes of abnormal liver test results. **(Sundaram et al., 2009)**

The 2010 American association for the study of liver diseases (AASLD) practice guideline for ALD recommends the following for diagnosis:-

- If alcohol abuse or excess is suspected from discussion of alcohol use with the patient, screen the patient for alcohol abuse using a structured questionnaire such as the alcohol use disorders identification test (AUDIT).
- If the patient history or a screening test indicates alcohol abuse, use laboratory testing to verify the diagnosis of ALD and rule out other considerations.