ASSOCIATIONS BETWEEN NON ALCOHOLIC FATTY LIVER DISEASE AND CAROTID INTIMA-MEDIA THICKNESS

THESIS

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ABSTRACT

The aim of the present work was to compare carotid intima-media thickness in patients with NAFLD and normal control persons and to correlate it with the different risk factors of atherosclerosis namely lipid pattern, blood glucose levels, C- reactive protein, body mass index, and hypertension.

KEY WORDS

Between

Disease

carotid

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List of Abbreviations

ALK Ph.	Alkaline phosphates
ALT	Alanine transferase
AMPK	AMP- Activated Protein Kinase
Apo B	Apolipoprotein B
AST	Aspartate transferase
ATP	Adenosine Triphosphate
BMI	Body Mass Index
CCA	Common Carotid Artery
CHD	Coronary Heart Disease
CIMT	Carotid Intima Media Thickness
CRP	C-Reactive Protein
CT	Computed Tomographic scanning
CVD	Cardio Vascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
ECA	External Carotid Artery
FBS	Fasting Blood Sugar
FFA	Free Fatty Acid
GGT	Gamma Glutamic Transpeptidase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCVab	Hepatitis C virus antibody
HNE	4-Hydroxynonenal
HS	Highly Significant
HTN	Systemic Hypertension
ICA	Internal Carotid Artery
IGT	Impaired Glucose Tolerance
IL	Interleukin
IMT	Intima Media Thickness
IRS	Insulin Resistance Syndrome
MDA	Malondialdehyde
MTP	Microsomal Triglyceride Transfer Protein

NAFLD	Non Alcoholic Fatty Liver Disease
NASH	Non Alcoholic Steatohepatitis
NS	Non Significant
P value	Probability value
PPAR-γ	Peroxisome Proliferators-activated Receptor gamma
PT	Prothrombin Time
S	Significant
SBP	Systolic Blood Pressure
SPSS	statistical program for social science version 12
SREBP-1	Sterol Regulatory Element Binding Protein 1
TG	Triglyceride
TNF	Tumour Necrotic Factor
UDCA	Ursodeoxycholic acid
US	Ultrasound
VLDL	Very Low Density Lipoprotein

CONTENTS

Introduction

Non alcoholic fatty liver disease is a clinicopathological syndrome that is closely associated with visceral obesity, dyslipidemia, insulin resistance and type II diabetes, thus suggesting that NAFLD is another feature of the metabolic syndrome **(Angulo P. et al., 2002)**.

Recent cross-sectional studies **(Targher G. et al., 2004 ; Bera A. et al., 2005 and Volzke H. et al., 2005)** have shown that NAFLD is associated with increased carotid intima-media thickness (IMT) as a reliable marker of early atherosclerosis **(O'Leary DH. et al., 2002)**.

Clarification of this aspect may help to explain the underlying mechanism and may be of clinical importance in planning prevention and therapeutic strategies **(Volzke H. et al., 2005)**.

Aim of the work

The aim of the present work is to compare carotid intima-media thickness in patients with NAFLD and normal control persons and to correlate it with the different risk factors of atherosclerosis namely lipid pattern , blood glucose levels , C- reactive protein , body mass index , and hypertension.

Nonalcoholic Fatty Liver Disease

Introduction:

Non alcoholic fatty liver disease is an increasingly recognized condition that may progress to end-stage liver disease. The pathological picture resembles that of alcohol-induced liver injury, but it occurs in patients who do not abuse alcohol. Variety of terms have been used to describe this entity, including fatty-liver hepatitis, nonalcoholic Laënnec's disease, diabetes hepatitis, alcohol-like liver disease, and nonalcoholic steatohepatitis **(Ludwig et al., 1980)**.

The spectrum of NAFLD:

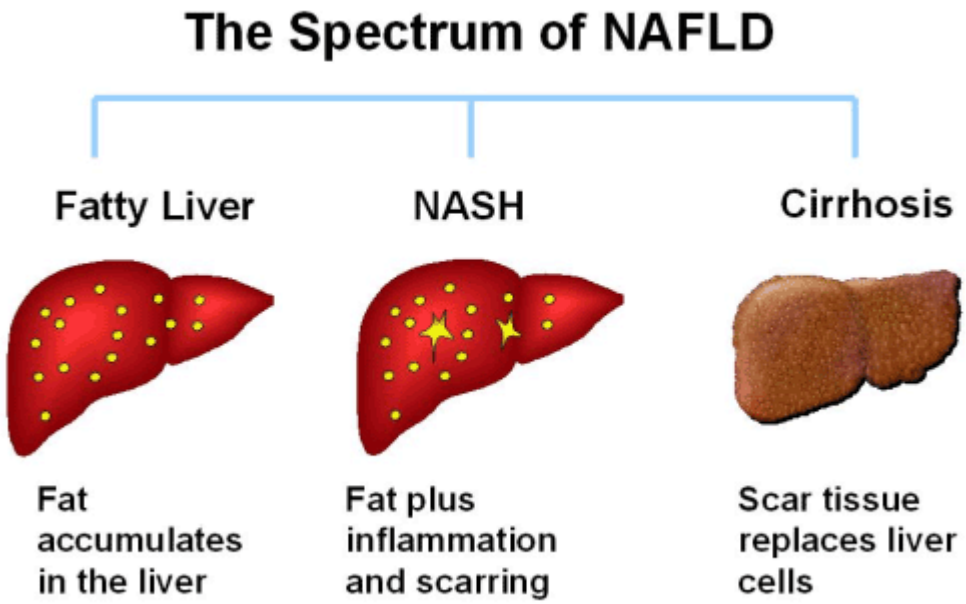
The NAFLD spectrum is thought to begin with and progress from its simplest stage called simple fatty liver to more advanced stage steatohepatitis. Simple fatty liver involves just the accumulation of fat in the liver cell with no inflammation or scarring. The fat is actually composed of a particular type of fat (triglyceride) that accumulates in tiny sacs within the liver cells (adipocytes) that constitute our body fat. Fatty liver is a harmless, benign condition, which means that it by itself does not cause any significant liver damage **(Schaffner and Thaler, 1986)**.

The next stage and degree of severity in the NAFLD spectrum is Non Alcoholic Steatohepatitis (NASH). Fortunately, only a fraction of patients with simple fatty liver will develop NASH. NASH involves the accumulation of fat in the liver cells as well as inflammation of the liver, The inflammatory cells can destroy the liver cells (hepatocellular necrosis). In the terms (steatohepatitis) and (steatonecrosis), steato refers to fatty infiltration, hepatitis refers to inflammation in the liver and necrosis refers to destroyed liver cells.

Strong evidence suggests that NASH, in contrast to simple fatty liver is not a harmless condition.
This means that NASH can ultimately lead to scarring of the liver (fibrosis) and then irreversible advanced scarring (cirrhosis). Cirrhosis that is caused by NASH is the last and most severe stage in the NAFLD spectrum **(Schaffner and Thaler, 1986)**.

Much is not yet known about NASH and NAFLD. For examples, the progression from each of the different stages of NAFLD is not well understood. Moreover, even liver specialists still do not agree on the exact microscopic definition of NASH. Nevertheless, individuals who develop any of the three stages of NAFLD (fatty liver, NASH, or cirrhosis) share common risk factors **(Figure 1)**. Nonalcoholic fatty liver disease is becoming the preferred term and it refers to a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis. Steatohepatitis (nonalcoholic steatohepatitis) represents only a stage within the spectrum of nonalcoholic fatty liver disease **(Bacon et al., 1994)**.

The clinical implication of NAFLD are derived mostly from its common occurrence in the general population and its potential to progress to cirrhosis and liver failure. NAFLD should be differentiated from steatosis, with or without hepatitis, resulting from secondary causes of fatty liver disease because these conditions have distinctly different pathogenesis and outcomes **(Schaffner and Thaler, 1986)**.



(Figure 1): The spectrum of NAFLD

Secondary causes of fatty liver disease:

1-Nutritional:
1. Protein calorie malnutrition.
2. Starvation.
3. Total parentral nutrition.
4. Rapid weight loss.

2-Drugs:
1. Glucocorticoids, Aspirin, Amiodarone.
2. Calcium channel blockers.
3. Tamoxifen, Valproic acid.
4. Methotrexate,Tetracycline.
5. Antiviral drugs (didanosine, zedavidine).

3-Metabolic and genetic:
1. Lipodystrophy.
2. Dysbetalipoproteinemia.
3. Cholesterol ester storage syndrome.

4-Others:
1. Inflammatory Bowel Disease.
2. HIV.
3. Enviromental hepatotoxins (phosphates, petrochemicals, organic solvents and toxic mushrooms).

Epidemiological Factors:

**Risk Factors:*

Obesity, type 2 (non-insulin-dependent) diabetes mellitus, and hyperlipidemia are coexisting conditions frequently associated with nonalcoholic fatty liver disease. The reported prevalence of obesity in several series of patients with nonalcoholic fatty liver disease varied between 30 and 100 percent, the prevalence of type 2 diabetes varied between 10 and 75 percent **(Adler and Schaffner, 1979)**. And the prevalence of hyperlipidemia varied between 20 and 92 percent. Some children with nonalcoholic fatty liver disease have type 1 diabetes mellitus **(Rashid and Roberts, 2000)**.