a Association Between Non Alcoholic Fatty liver Disease and Early Carotid Atherosclerosis

Thesis

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Dedication

All appreciation to my parents and my wife for their support and Patience to complete this work .

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Khaled Marzouk Sadek
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Abbreviations

AASLD :American Association for the Study of Liver Diseases
ACA :anterior cerebral artery
ACA :anterior communicating artery
ACC:acetyl-CoA carboxylase
ACRP30:adipocyte complement related protein of 30 kDa
ALP :Serum alkaline phosphatase
ALT:Alanine Aminotransferase
AMPK:AMP-activated protein kinase
Anti MDA : Anti Malondialdehyde
apM1 gene :adipose tissue-specific transcript-1
ARIC : Atherosclerosis Risk in Communities
AST :aspartate aminotransferase
bHLH/LZ :basic/helix–loop–helix/leucine zipper
BMI :body-mass index
CAD:coronary artery disease
Carotid-IMT$_{max}$: Carotid - intima-media thickness- maximum
CCA :the common carotid artery
CHD :coronary heart disease
ChoRE :carbohydrate responsive element
ChREBP :Charbohydrate regulatory element binding protein
CRP:C-reactive protein
CT: computed tomographic scanning
CTGF :_connective tissue growth factor
CVD : coronary vascular disease
CW :continuous wave
CYP :cytochrome P450
DS : Diameter stenosis
ECA :external carotid artery
ECM :extracellular matrix
ECU : external carotid ultrasound
ELF :European Liver Fibrosis
FAS:fatty acid synthase
FFA : free fatty acid
FFAs : free fatty acids
FHBL:familial hypobetalipoproteinemia

FL :fatty liver
GGT: γ-glutamyltransferase
GK:glucose kinase
GLUT 4:glucose trasporter-4
GPAT:glyceraldehydes 3-phosphate acyltransferase
G6Pase :glucose 6 phosphodehydrogenase
HA : Hyaluronic acid
HCV :hepatitis C virus
HFE: hemochromatosis gene
HNE:.4-hydroxynonenal
HOMA –IR : Homeostasis Model Assessment- estimated insulin resistance
HSC **:** hepatic stellatecell
ICA :the internal carotid artery
IL-8: interleukin-8
IMT : intima-media thickness
INSIG-1: Insulin-induced gene
IR: insulin resistence
IRS2 :insulin resistence substance2
IVUS : intravascular ultrasound
LDL: low density lipoprotein.
L-PK:liver-type pyruvate kinase
LXR :liver x receptor
MCA :middle cerebral artery
MDA: malondialdehyde
MMP :matrix metalloproteinase
MRA :magnetic resonance angiography
MRI :magnetic resonance imaging
MS: metabolic syndrome
NADPH :Nicotinamide adenine dinucleotide phosphate
NAFLD : non-alcoholic fatty liver disease
NASH :non-alcoholic steatohepatitis
NEFA: Non-esterified fatty acid
NLS: nuclear localization signal
Ox-LDL: oxidized low density lipoprotein
PAV **:** percent **a**therom**a** volume
PC-1: A membrane glycoprotein that has a role in insulin resistance

PDGF: platelet-derived growth factor
PEPCK :phosphoenol pyruvate carboxykinase
PPARgamma :peroxisome proliferators activated receptor gamma
PRF : pulse recurrence frequency
QCA : quantitative coronary angiography
Rad : ras associated with diabetes
ROS: reactive oxygen species
SCD-1:stearoyl-CoA desaturase 1
SREBP-1 : sterol regulatoryelement-binding protein-1
TA**V :** Tot**a**l **a**therom**a** volume
TBARS :thiobarbituric acid-reacting substances
TG: triglecrides
TGF-β: tissue growth factor-beta
TIA : transient ischemic attack
TIMPs: tissue inhibitors of metalloproteinases
TNF∞ : tumor necrosis factor-alpha
t-PAI :tissue plasminogen activator inhibitor
TZDs: thiozolidindiones
T2DM :type 2 diabetes mellitus
VLDL: very lowdensity lipoprotein
protein kinase B (Akt),

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ABSTRACT

A) Title :

- **Association between Non Alcoholic Fatty Liver Disease and Early Carotid Atherosclerosis**

B) Summary:

- **Background**:
  - **Non Alcoholic Fatty Liver Disease is a common cause of elevated liver enzyme and it may increase incidence of increased intima-media thickness of carotid artery as a marker of early-generalized atherosclerosis due to visceral obesity and dyslipidemia or as apart of metabolic syndrome.**
- **Objectives :**
  - **To compare between patients with NAFLD known to have negative serology for hepatitis B or C with no history of alcohol or drugs intake with normal level of LDL and control persons with normal Abdominal Ultrasound and normal Liver enzymes to detect the incidence of early carotid atherosclerosis in patient with NAFLD**
- **Methods : 70 patients and 30 controls will have**
  1- **Full history intake**
  2- **Clinical examination for**
     - **Blood pressure**
     - **Body mass index**
     - **Waist circumference**
  3- **Abdominal ultrasound**
  4- **Hepatitis B and C**
  5- **Liver enzymes**
  6- **Carotid ultrasound**

*** Keywords : Non Alcoholic Fatty Liver Disease (NAFLD)**
Body Mass Index (BMI)
Low Density Lipoprotien (LDL)

Introduction

Nonalcoholic fatty liver disease (NAFLD), the most common cause of abnormal liver function tests in hepatology practice, is frequently associated with visceral obesity, dyslipidemia , insulin resistance, and type 2 diabetes and may represent another component of the metabolic syndrome . **(Ludwig et al.,1980)**

Recent cross-sectional studies have shown that NAFLD is associated with increased carotid artery intima-media thickness (IMT), a marker of early generalized atherosclerosis**.**However, in these studies the NAFLD diagnosis was exclusively based on ultrasound imaging but was not confirmed by liver biopsy, which is the best diagnostic tool for confirming NAFLD . **(Powell et al., 1990)**

Thus, currently it is uncertain whether there is a significant association between early carotid atherosclerosis and the severity of liver histology among NAFLD patients. Clarification of this aspect may help to explain the underlying mechanisms and may be of clinical importance in planning preventive and therapeutic strategies. **(Volzke et al ., 2005)**

We have, therefore, assessed whether patients with NAFLD have a greater carotid IMT than control subjects and whether there is a significant association between liver histology and carotid IMT among NAFLD patients.

Aim Of Work :

In this study we hope to identify:

1-Whether the severity of NAFLD is strongly associated with early carotid atherosclerosis, independent of classical risk factors, insulin resistance, and the presence of metabolic syndrome.

2-What are the possible mechanisms by which NAFLD can cause early carotid atherosclerosis.

3- Whether improving NAFLD will ultimately prevent the development of Cardiovascular disease (CVD).

Chapter 1

Non Alcoholic Fatty Liver Disease

Introduction:

Nonalcoholic fatty liver disease (NAFLD) 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 .A 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, steatosis. That is, fatty liver is the initial abnormality in the spectrum of NAFLD. Simple fatty liver involves just the accumulation of fat in the liver cells 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. This accumulation of fat in liver cells is not the same as the fat 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. As mentioned, 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.