

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

**THESIS**

Submitted for partial fulfillment of the degree of M.Sc. in  
Internal Medicine

**By**

**ASHRAF HASSAN MAHMOUD AYAD**

M.B., B.CH., Cairo University

**Supervised By**

**PROF. DR. NOUMAN M. H. EL-GAREM**

Professor of Internal Medicine, Cairo University

**PROF. DR. MONA AHMED AMIN**

Professor of Internal Medicine, Cairo University

Faculty of Medicine

Cairo University

2010

## **ACKNOWLEDGEMENT**

*First and foremost, I feel always indebted to ALLAH the most kind and the merciful.*

*Words do fail me to express sincerest appreciation and deepest gratitude to Professor Dr. NOUMAN M. H. EL-GAREM Professor of Internal Medicine. Faculty of medicine. Cairo University. Without his great support and continuous help this work would have never come to light.*

*I am deeply grateful to Dr. MONA AHMED AMIN professor of Internal Medicine. Faculty of medicine. Cairo University. For her guidance and supervision of this work.*

*I am indebted to all my dear professors and teaching staff members of Internal Medicine. Faculty of medicine. Cairo University for their cooperation and continuous advice to finish this work.*

# 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

## **List of Tables**

	<b>Page</b>
<b>(Table 1)</b> Grading and staging of the Histopathological lesions of Non Alcoholic Fatty Liver Disease	<b>15</b>
<b>(Table 2)</b> Indications for carotid ultrasound	<b>68</b>
<b>(Table 3)</b> Basic steps in Doppler examination	<b>69</b>
<b>(Table 4)</b> Identification of external and internal carotid arteries	<b>72</b>
<b>(Table 5)</b> Laboratory data of group I cases	<b>86</b>
<b>(Table 6)</b> Laboratory data of the control group	<b>87</b>
<b>(Table 7)</b> Comparison between both groups as regard demographic data	<b>88</b>
<b>(Table 8)</b> Comparison between both groups as regard blood pressure	<b>89</b>
<b>(Table 9)</b> Comparison between group I cases and controls as regard the laboratory variables	<b>90</b>
<b>(Table 10)</b> Comparison between group I cases and controls as regard sonographic liver size	<b>91</b>
<b>(Table 11)</b> Comparison between group I cases and controls as regard intima media thickness	<b>91</b>
<b>(Table 12)</b> Correlation between intima media thickness and demographic data among the group I cases	<b>92</b>
<b>(Table 13)</b> Correlation between intima media thickness and laboratory data among the group I cases	<b>93</b>
<b>(Table 14)</b> Correlation between intima media thickness and demographic data among the studied controls	<b>94</b>
<b>(Table 15)</b> Correlation between intima media thickness and laboratory data among the studied controls	<b>95</b>
<b>(Table 16)</b> Correlation between intima media thickness and liver size among both groups	<b>96</b>

## **List of Figures**

	<b>Page</b>
<b>(Figure 1)</b> The spectrum of NAFLD	<b>5</b>
<b>(Figure 2)</b> Histological findings of NAFLD	<b>13</b>
<b>(Figure 3)</b> Lipid metabolism within the hepatocytes	<b>17</b>
<b>(Figure 4)</b> Effects of insulin resistance on lipid metabolism	<b>19</b>
<b>(Figure 5)</b> Superficial dissection of the right side of the neck, showing the carotid and subclavian arteries	<b>54</b>
<b>(Figure 6)</b> The right-carotid bifurcation on transverse scanning	<b>70</b>
<b>(Figure 7)</b> Comparison between cases and controls as regard liver function tests	<b>97</b>
<b>(Figure 8)</b> Comparison between cases and controls as regard lipid profile, fasting blood sugar and CRP	<b>98</b>
<b>(Figure 9)</b> Comparison between cases and controls as regard sonographic liver size	<b>99</b>
<b>(Figure 10)</b> Comparison between cases and controls as regard intima media thickness	<b>100</b>
<b>(Figure 11)</b> Correlation between intima media thickness versus BMI among cases	<b>101</b>
<b>(Figure 12)</b> Correlation between intima media thickness versus systolic blood pressure among cases	<b>102</b>
<b>(Figure 13)</b> Correlation between intima media thickness versus diastolic blood pressure among cases	<b>103</b>
<b>(Figure 14)</b> Correlation between intima media thickness versus cholesterol among cases	<b>104</b>
<b>(Figure 15)</b> Correlation between intima media thickness versus HDL among cases	<b>105</b>
<b>(Figure 16)</b> Correlation between intima media thickness versus LDL among cases	<b>106</b>
<b>(Figure 17)</b> Correlation between intima media thickness versus Triglyceride among cases	<b>107</b>
<b>(Figure 18)</b> Correlation between intima media thickness versus fasting blood sugar among cases	<b>108</b>
<b>(Figure 19)</b> Correlation between intima media thickness versus liver size among cases	<b>109</b>

<b>(Figure 20)</b> Sonography scan from patient in group I (Study group) shows fatty liver (Liver size: 19.5cm)	<b>110</b>
<b>(Figure 21)</b> Sonography scan from patient in group II (Control group) shows normal liver (Liver size: 12.35cm)	<b>111</b>
<b>(Figure 22)</b> Arterial carotid Duplex from patient in group I (Study group) shows 0.8cm carotid intima media thickness	<b>112</b>
<b>(Figure 23)</b> Arterial carotid Duplex from patient in group II (Control group) shows 0.5cm carotid intima media thickness	<b>113</b>

### **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- $\gamma$	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**

● <b>Introduction</b> .....	1
● <b>Aim of work</b> .....	2
● <b>Review of Literature:</b> .....	3
● <b>Non Alcoholic Fatty Liver Disease</b> .....	3
◦ Introduction .....	3
◦ The spectrum of NAFLD .....	3
◦ Secondary causes of fatty liver disease .....	6
◦ Epidemiological Factors .....	6
◦ Natural History .....	9
◦ Clinical Manifestations .....	10
◦ Pathogenesis of NAFLD .....	16
◦ Management of NAFLD .....	24
◦ NAFLD & Increased risk of cardiovascular disease .....	33
● <b>Metabolic Syndrome</b> .....	42
◦ Definition and History .....	42
◦ Etiology and Risk Factors .....	43
◦ Pathophysiology .....	46
◦ Diagnosis .....	46
◦ Prevention .....	50
◦ Therapy .....	50
◦ Controversy .....	51
● <b>Carotid Intima-media Thickness</b> .....	52
◦ Anatomy of carotid artery .....	52
◦ Histology of carotid artery .....	56
◦ Possible symptoms of carotid and vertebral arteries disease .....	57
◦ Factors affecting carotid intima-media thickness .....	59
◦ Duplex Ultrasound and evaluation of extracranial carotid artery disease .....	64
● <b>Patients and Methods</b> .....	77
● <b>Results</b> .....	81
● <b>Discussion</b> .....	114
● <b>Summary and Conclusion</b> .....	121
● <b>References</b> .....	124
● <b>Arabic Summary</b>	

## **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**).

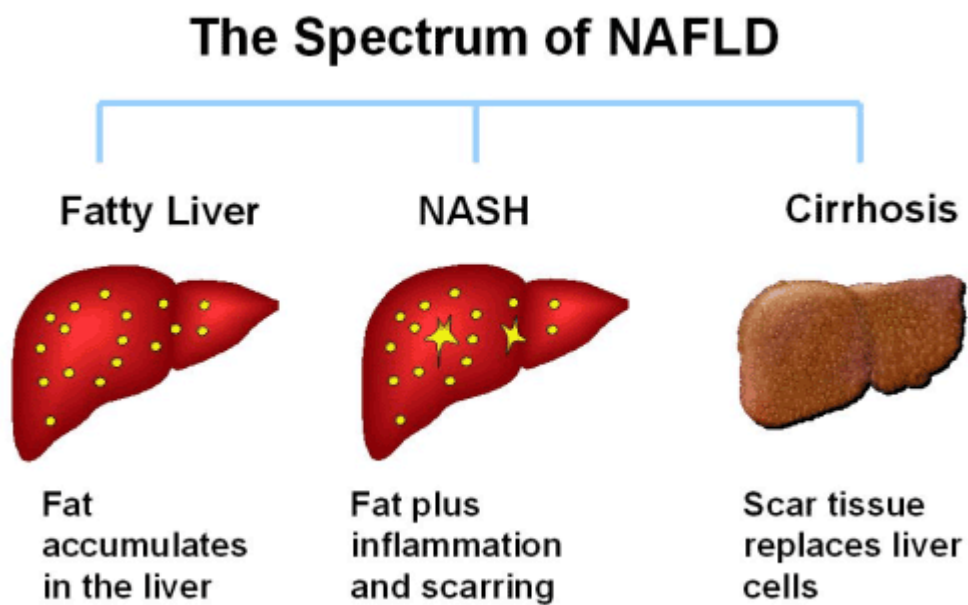
The next stage and degree of severity in the NAFLD spectrum is Non Alcoholic Steatohepatitis (NASH). Fortunately, only a fraction of patients with simple fatty liver will develop NASH. NASH involves the accumulation of fat in the liver cells as well as inflammation of the liver, The inflammatory cells 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 parenteral 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. Environmental 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**).