Ain Shams University
Faculty of Medicine
Internal Medicine department

Association of Non-Alcoholic Fatty Liver Disease with Chronic Obstructive Lung Disease Patients: An Egyptian Study

A thesis

For fulfillment of Master Degree in Internal Medicine

Submitted by

Mina Mofreh Ramzy Faheem
M.B.B.CH

Supervised by

Prof. Dr. Engy Yousry El Sayed Ashour
Professor of Internal Medicine, Gastroenterology and Hepatology Unit
Faculty of Medicine, Ain Shams University

Prof. Dr. Amir Helmy Samy Beshay
Professor of Internal Medicine, Gastroenterology and Hepatology Unit
Faculty of Medicine, Ain Shams University

Dr. Tari Magdy Aziz George
Lecturer of Internal Medicine, Gastroenterology and Hepatology Unit
Faculty of Medicine, Ain Shams University

Dr. Noha Osman Ahmed Salah eldin
Lecturer of Chest Disease Department
Faculty of Medicine, Ain Shams University

Ain Shams University
Faculty of Medicine
2022

Acknowledgement

My thanks first to "Allah" who give me the ability and strength to complete this work.

I would like to express my indebtedness and deepest gratitude to ***Prof. Dr. Engy Yousry El Sayed Ashour,*** *Professor of Internal Medicine, Faculty of Medicine, Ain Shams University for her valuable advice, guidance and constructive criticism, also for the invaluable assistance and efforts she devoted in the supervision of this study.*

I'll never forget, how co-operative was ***Prof. Dr. Amir Helmy Samy Beshay,*** *Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, also he was encouraging all the time. It is honorable to be supervised by him.*

I would like also, to express my great thanks to ***Dr. Tari Magdy Aziz George,*** *Lecturer of Internal Medicine, Faculty of Medicine – Ain Shams University. His valuable advises and continuous support facilitated completing this work.*

I would like also, to express my great thanks to ***Dr. Noha Osman Ahmed Salah eldin,*** *Lecturer of Chest Disease Department, and Faculty of Medicine – Ain Shams University. Her valuable advises and continuous support facilitated completing this work.*

I'd like to give my wormiest appreciation to my family and my friends who always give me a great support.

I would like to thank my colleagues and everyone who made this work possible and enjoyable.

Mina Mofreh Ramzy Faheem

2021

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abb	Full Term
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
NAFLD	Non-alcoholic fatty liver disease
Mets	metabolic syndrome
HCC	hepatocellular carcinoma
NAFL	Non-alcoholic fatty liver
NASH	non-alcoholic steatohepatitis
T2DM	type 2 diabetes mellitus
PCOS	Polycystic ovarian syndrome
BMI	body mass index
OSA	Obstructive sleep apnea
HTAG	hepatic triacylglycerol
USG	ultrasonographies
CAP	controlled attenuation parameter
CT	Computed tomography
MRI	Magnetic resonance imaging
ALD	alcoholic liver disease
FEV_1	forced expiratory volume in 1 second
AAt	alpha-1-antitrypsin
LVRS	Lung volume reduction surgery
GOLD	Global initiative for chronic Obstructive Lung Disease
TNF-α	tumor necrosis factor-alpha
TGF-β1	transforming growth factor-beta 1
MCP-1	monocyte chemoattractant protein 1
CBC	Complete blood count
HB	Hemoglopin
wbcs	White blood cells
ALT	Alanine amino transferase
AST	Aspartate amino transferase
P.T	Prothrombin time
VLDL	very low density lipoproteins
LDL	low-density lipoprotein
HDL	High-density lipoprotein
SPSS	Statistical Package of Social Science
OLD	Obstructive lung disease
PVD	peripheral vascular disease

SBP	systolic blood pressure
DBP	diastolic blood pressure
AHI	apnea-hypopnea index

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is independently linked to cardio-metabolic morbidity and mortality. Low-grade inflammation, oxidative stress and ectopic fat, common features of chronic obstructive pulmonary disease (COPD), might contribute to the development of NAFLD.

Aim and objectives: The aim of the study was to determine the possible association between Chronic Obstructive Lung Disease and Non-Alcoholic Fatty Liver Disease.

Subjects and methods: This was a cross sectional study, which was carried out at Outpatient Clinics at Ain Shams Hospital, 60 Egyptian Patients divided into two groups: Group 1:40 Patients diagnosed with COPD (Patients diagnosed by history of disease, smoking history and A ration of post bronchodilator FEV1 10 FVC of less than 70% of the predicted value) and Group 2: 20 Normal Healthy People (Control Group).

Results: there was a statistical significant difference with p-value <0.05 between study groups as regards spirometry with low mean FEV1, FVC , and FEV1/ FVC ratio among cases.

Conclusion: NAFLD is associated with COPD. Physicians should be aware of possible liver comorbidities in COPD patients and that extra-hepatic disease in NAFLD patients may vary more than previously thought.

Keywords: obstructive lung disease, non-alcoholic fatty liver disease, spirometry, comorbidities.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a growing public health concern, causing considerable health-related costs and increased premature mortality. Although diagnosis is mainly based on chronic airflow limitation, as assessed by post-bronchodilator spirometry, COPD is nowadays considered a complex, heterogeneous and multi-organ condition. It is increasingly recognized that the presence of comorbidities such as obesity and/or cardiovascular (CV) and metabolic diseases substantially contribute to the recurrence of hospitalization for exacerbation and significantly impacts prognosis and the incidence of late CV events **(Viglino, 2018)**.

Non-alcoholic fatty liver disease (NAFLD) represents a unique "challenge" for the hepatologist and is defined by the presence of hepatic steatosis in the absence of other causes for hepatic fat accumulation, including alcohol use, medication, or other causes of chronic liver disease. In fact, NAFLD is often referred to as the "hepatic manifestation" of metabolic syndrome (Mets) and, recently, growing evidence has highlighted the possibility that NAFLD may be a key driver in MetS **(Rosato, 2019)**.

Clinically, NAFLD patients tend to be obese, with insulin resistance and/or type 2diabetes, dyslipidemia, hypertriglyceridemia, and hypertension, which are all risk factors for cardiovascular diseases **(Vernon, 2011).**

As a result of the changes in dietary habits and the increased sedentary lifestyle, its incidence has definitely increased worldwide over the last few years, consequently, NAFLD can now be considered the most frequent liver alteration in the world. In the general population, a

prevalence of NAFLD ranging between 17% and 33% was estimated, whereas, in obese and/or diabetic individuals, this prevalence reached 75% (**Federico, 2016).**

Based on their high prevalence and dangerous outcomes, COPD and NAFLD claim a high health and economic toll. COPD and NAFLD are increasingly recognised as multisystem diseases with high comorbidity rate, mainly clustered in the metabolic, cardiovascular and neoplastic area. Both COPD and NAFLD are complex non-communicable diseases determined by environmental factors (unhealthy lifestyle habits) and genetic predisposition. Principles of treatment of COPD and NAFLD include lifestyle changes (smoking cessation, diet and physical activity) as a first step **(Lonardo, 2017).**

NAFLD has been poorly studied in COPD patients, although there is a strong mechanistic rationale supporting the hypothesis of increased NAFLD prevalence in COPD patients. There is still debate over the "spill-over" theory: that oxidative stress and systemic inflammation reported in some COPD subtypes might participate in the production of reactive oxygen the liver. Patients with COPD have increased visceral fat, a known inflammatory and lipolitic fat deposit. Thus, the subsequent increase in free fatty acids accumulating in the liver might lead to NAFLD development in COPD. Nocturnal hypoxia subsequent to COPD per se, or related to the obstructive sleep apnoea (OSA) that is frequently associated with it, might also trigger the development of NAFLD **(Viglino, 2017)**.

AIM OF THE WORK

The aim of the study is to determine the possible association between Chronic Obstructive Lung Disease and Non-Alcoholic Fatty Liver Disease

Chapter **(1)**

Non-Alcoholic Fatty Liver Disease

I. Definition

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term and encompasses the simple deposition of adipose tissue in the liver to more progressive steatosis with associated hepatitis, fibrosis, cirrhosis, and in some cases hepatocellular carcinoma (HCC). For the sake of terminology, NAFLD is comprised of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is characterized by steatosis of the liver, involving greater than 5% of parenchyma, with no evidence of hepatocyte injury. Whereas, NASH is defined by histologic terms, that is a necroinflammatory process whereby the liver cells become injured in a background of steatosis. Although the natural history of NAFLD remains incompletely characterized, what is clear from the published data is a risk of progression to cirrhosis and HCC (**Lebeaupin et al., 2018).**

However, whether there is a clear progression of NAFL to NASH is under active investigation, but early evidence suggests this could be the case. In terms of epidemiology, several studies have tried to quantify the true worldwide incidence of NAFL/NASH; however, due to extreme variations in study parameters and available testing, a clear and reliable occurrence rate is not currently available. With that being said, estimates have been posited suggesting the incidence of NAFLD to be 20%-30% in Western countries and 5%-18% in Asia. It is no surprise that the prevalence of NAFLD is increasing worldwide with each passing year,

given the current trends in dietary irresponsibility and preponderance of a sedentary lifestyle (**Bellentani, 2017).**

Additionally, there has been a linear rise of NAFLD with that of diabetes and metabolic syndrome. In one study from the United States, it was shown that the incidence of NAFLD was 10% higher in overweight individuals compared to lean persons. In fact, NAFLD has been projected, within the next 20 years, to become the major cause of liver related morbidity and mortality as well as a leading indication for liver transplantation. As it currently stands, NAFLD represents the second most common reason to be listed for a liver transplant Additionally, not only does NAFLD place a strain on the medical system and its resources, it also is associated with a 34%-69% chance of dying over the next 15 years when compared with the general population. The pathogenetic processes that underscore NAFLD typically lead to death by cardiovascular disease with liver related mortality only accounting for 5% in these individuals (**Buzzetti et al., 2016).**

In three types of epidemiological studies that included prevalence, risk factors and management/complications of NAFLD, there was noticeable variation in the prevalence of NAFLD among different countries, based on the variation in the prevalence of risk factors (type 2 diabetes, obesity, metabolic syndrome and dyslipidemia) and the diagnostic tool used in the study.(**Ahmed et al., 2017)**

The highest prevalence rate was reported in some Middle East countries. In Africa, there were few studies about NAFLD and most reported variable prevalence rates. There is an increasing prevalence of NAFLD as a result of the increasing risk factors, particularly in the

Middle East, while in Africa, the situation is still unclear (**Calzadilla et al., 2016)**

In this **chapter**, we will provide context for how and why NAFLD develops, current genetic proposals, histologic criteria, differential diagnoses, and prognosis of this very important disease affecting not only the United States but much of the world.

II. RISK FACTORS AND ETIOLOGY

1. Metabolic syndrome and type 2 diabetes mellitus

Metabolic Syndrome (MetSyn) is an asymptomatic, pathophysiological state characterised by obesity, insulin resistance, hypertension, dysglycaemia, and dyslipidaemia. While several criteria and definitions have been used to identify MetSyn; it is generally agreed that a combination of three or more of the following components must be present: large waist circumference, elevated triglycerides, low HDL-cholesterol, raised blood pressure, and elevated fasting blood glucose (**Nolan et al., 2017)**

In fact it has been stated that the incidence of NAFLD increases with increasing number of metabolic syndrome criteria met. When compared to non-diabetic patients (matched for age, sex, and body weight), type 2 diabetes mellitus (T_2DM) patients have liver fat contents that are 80% higher. Interestingly, it has been shown that T_2DM patients with NAFLD can have normal liver function tests, which may lead one to believe that the prevalence of NAFLD in T_2DM patients is much higher than reported in this patient population. Additionally, T_2DM patients display a very high risk of developing NASH as well as a two-to-four-