The Diagnostic Significance of Human Patatin Like Phospholipase Domain Containing Protein 3, PNPLA3 versus Fibro scan in Nonalcoholic fatty liver disease (NAFLD)

Thesis

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Dedication

*Special thanks to my **Mother** and **Father** for their supports and love. Without their help I wouldn't be here. And also, my lovely **Sister** and **Brother***

بسم الله الرحمن الرحيم

﴿وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا﴾

صدق الله العظيم
سورة النساء آية (١١٣)

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List of Abbreviations

Abb.	Full term
AASLD	*American association for the study of liver diseases*
ACEI	*Angiotensin converting enzyme inhibitor*
ALD	*Alcoholic liver disease*
ALT	*Alanine amino transferase*
ANA	*Antinuclear antibody*
ARB	*angiotensin receptor blockers*
ASMA	*Anti smooth muscle antibody*
AST	*Aspartate amino transferase*
BASH	*Both alcoholic and nonalcoholic steatohepatitis*
BMI	*Body mass index*
CAP	*controlled attenuation parameter*
CASH	*chemotherapy-associated steatohepatitis*
CHB	*Chronic hepatitis B virus*
CHC	*Chronic hepatitis C virus*
CHOL	*Cholesterol*
CKD	*Chronic kidney disease*
CT	*computed tomography*
CVD	*Cardiovascular disease*
DASH	*Drug -associated steatohepatitis*
EASD–	*European association for study of diabetes*
EASL	*European association for study of liver*
EASO	*European association for study of obesity*
e-GFR	*Estimated – glomerular filtration rate*
ELF	*European Liver Fibrosis*
FBG	*Fasting blood glucose*
FDA	*Food and drug administration*
FFA	*Free fatty acids*

List of Abbreviations cont…

Abb.	Full term
GGT	*Gamma glutamyl transferase*
GWAS	*Genome-wide association studies*
HA	*Hyaluronic acid*
HBV	*Hepatitis B virus*
HCV	*Hepatitis C virus*
HDL	*Low high-density lipoprotein*
Hh	*Hedgehog*
HIF	*Hypoxia inducible factors*
HSCs	*Hepatic stellate cells*
IFG	*Impaired fasting glucose*
IH	*Intermittent hypoxia*
IH	*Intermittent hypoxia*
IL	*Interleukin*
IR	*Insulin resistance*
LDL	*Low-density lipoprotein*
LSM	*Liver stiffness measurement*
MetS	*Metabolic syndrome*
MRI	*Magnetic resonance imaging*
MRI	*Magnetic resonance imaging*
mRNA	*Messenger ribonucleic acid*
NAFLD	*Nonalcoholic fatty liver disease*
NAS	*NAFLDActivity Score*
NASH	*Nonalcoholic steatohepatitis*
NFS	*NAFLD fibrosis score*
NPV	*Negative predictive value*
OSA	*Obstructive sleep apnea*
P3NP	*Peptide of pro-collagen III*
PASH	*PNPLA3-associated steatohepatitis*

List of Abbreviations cont…

Abb.	Full term
PNPLA	*Patatin-like phospholipase domain-containing protein*
PPV	*Positive predictive value*
RAAS	*Renin-Angiotensin-Aldosterone System*
RCTs	*Randomized controlled trials*
SOS	*Swedish obese subjects*
SS	*Simple steatosis*
TE	*Transient elastography*
TG	*Triglycerides*
TIMP	*Tissue inhibitor of metalloproteinase*
TNF	*Tumor necrosis factor*
TNF	*Tumour necrosis factor-alpha*
TZD	*Thiazolidinediones*
UDCA	*Ursodeoxycholic acid*
US	*Ultrasonography*
VEGF	*Vascular endothelial growth factor*
WGO	*World Gastroenterology Organisation*
WHO	*World Health Organization*

INTRODUCTION

Non alcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver function test results in both adults and children ***(Angulo, 2002; Wieckowska and Feldstein, 2005)***.

The prevalence of NAFLD in obese patients is approximately 70% and has become the most common liver disorder in Western countries ***(Lazo and Clark, 2008).***

Accompanying an increase in the prevalence of obesity, the disease burden of NAFLD is also increasing in Eastern countries ***(Hsiao et al., 2007; Hsieh et al., 2009).***

NAFLD in fact covers a histological spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis ***(Angulo, 2002; Argo and Caldwell, 2009).***

Simple steatosis without fibrosis or inflammation has a benign clinical course in most but not in all cases without excess mortality ***(Ekstedt et al., 2006).***

NASH, on the other hand, may have a more progressive course that can lead to cirrhosis in 10-15% of patients ***(Xie et al., 2012).***

Survival is lower in patients with NASH based on the findings from long-term longitudinal studies ***(Ekstedt et al., 2006; Soderberg et al., 2010).***

It is therefore imperative to distinguish simple steatosis from NASH in order to provide risk stratification and intervention slowing down disease progression for patients with the latter condition ***(Wieckowska et al., 2007)***.

Liver biopsy remains the gold standard for making the diagnosis of NASH. However, this procedure is invasive, costly, and is associated with rare but potential complications and sampling errors. Hence it is not suitable as a screening tool for a condition that affects one-third of the American population ***(Wieckowska et al., 2007)***.

Imaging studies such as ultrasonography, computed tomography (CT), and magnetic resonance imaging have been used to diagnose NAFLD ***(Rotman et al., 2010).***

These modalities have the advantages of being noninvasive and can be repetitively performed over a period of time ***(Rotman et al., 2010).***

Nevertheless, none of them have sufficient sensitivity and specificity for staging the disease and cannot distinguish between simple steatosis and NASH with or without fibrosis ***(Wieckowska et al., 2007)***.

Transient elastography (FibroscanR) is a new technique that allows rapid, non-invasive measurement of mean tissue stiffness, which has been shown to be useful for accurate estimation of hepatic fibrosis ***(Moreno-Otero et al., 2006).***

Guidelines from the national institute of health and care excellence, the European Association of the study of liver, and the Asian Pacific Association for the study of liver recommend using fibroscan technology for the initial evaluation of liver diseases ***(Afdhal, 2012).***

Several biomarkers that are associated with inflammation, ECM, and apoptosis have been individually studied for their performances in distinguishing NASH from simple steatosis, and Through the use of genome wide association studies, several genetic factors have recently been shown to be associated with NAFLD ***(Pearce et al., 2013).***

Romeo et al demonstrated that an allele of patatin-like phospholipase domain-containing protein3 (PNPLA3, rs738409 C/G, encoding I148M) is associated with an increased liver fat content ***(Romeo et al., 2008)***

The PNPLA3 rs738409variant has also been found to be associated with histologic disease severity of NAFLD, including steatosis, NASH, and fibrosis ***(Sookoian et al., 2009; Valenti et al., 2010; Rotman et al., 2010; Sookoian and Pirola, 2011; Hotta et al., 2010).***