Assessment of Liver Cell Apoptosis In Obese Children With Suspected Nonalcoholic Fatty Liver Disease(NAFLD)

Thesis

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of Master degree ***in Pediatrics***

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وأنزل الله عليك
الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن
تَعْلَمُ وكَانَ فَضْلُ اللَّهِ
عَلَيْكَ عَظِيماً
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Magda Elsherbiny Sarhan

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LIST OF ABBREVIATIONS

Abbrev.		Meaning
11βHSD1	:	11 Beta hydroxysteroid dehydrogenase 1
ALT	:	Alanine aminotransferase
ASH	:	Alcoholic steatohepatitis
AST	:	Aspartate aminotransferase
AUROC	:	Area under the receiver operating characteristic
BP	:	Blood pressure
BMI	:	Body mass index
CF	:	Cystic fibrosis
CHC	:	Chronic hepatitis C
CK-18	:	Cytokeratin 18
CRN	:	Clinical research network
CRP	:	C-reactive protein
CT	:	Computed tomography
DBP	:	Diastolic blood pressure
DM	:	Diabetes melliatus
DNL	:	De novo lipogenesis
ELISA	:	enzyme linked sandwich immunoassay
ER Stress	:	Endoplasmic reticulum stress
FA	:	Fatty liver
FFA	:	Free fatty acids
GGT	:	Gamma glutamyl transferase
G/I Ratio	:	Glucose/ insulin ratio
GSH-Px	:	Glutathione peroxidase
HBV	:	Hepatitis B virus
HCC	:	Hepatocellular carcinoma
HCV	:	Hepatitis C virus
HMG COA	:	3-Hydroxy-3 methyglutaryl coenzyme A

LIST OF ABBREVIATIONS (CONT…)

Abbrev.		Meaning
HOMA-IR	:	Homeostasis model assessment of insulin resistance
HSCs	:	Hepatic stellate cells
IKKβ	:	Inhibitor of nuclear factor kappa-b kinase subunit beta.
IL-6	:	Interleukin-6
IL-8	:	Interleukin-8
INR	:	International normalizing ratio
IR	:	Insulin resistance
IRS	:	Insulin receptors
ISAK	:	International Society for the Advancement of Kinanthropometry
LDL	:	Low density lipoprotein
LFTS	:	Liver function tests
mg/dl	:	Milligram per deciliter
mm	:	Millimeter
mm.Hg	:	Millimeter mercury
MRI	:	Magnetic resonance imaging
MRS	:	Magnetic resonance spectroscopy
NAFLD	:	Non alcoholic fatty liver disease
NAS	:	NAFLD activity score
NASH	:	Nonalcoholic steatohepatitis
NF-KB	:	Nuclear factor kappa B
NHANES	:	National Health and Nutrition Examination Survey
NHBPEP	:	National High Blood Pressure Education Program
NHMRC	:	National Health and Medical Research Council
PPAR	:	Peroxisome proliferative activated receptor
ROC	:	receiver Operating Characteristic

LIST OF ABBREVIATIONS (CONT…)

Abbrev.		Meaning
ROS	:	Reactive oxygen species
SBP	:	systolic blood pressure
SD	:	Standard deviation
SREBP	:	Sterol regulatory element binding protein
TG	:	Triglycerides
TGF-β	:	Tissue growth factor-beta
THV	:	Terminal hepatic venule
TNF-α	:	Tumor necrosis factor alpha
TPS	:	Tissue polypeptide specific antigen
U/L	:	Unit/liter
U/S	:	Ultrasonography
UDCA	:	Urosdeoxy cholic acid
VLDL	:	Very low density lipoproteins
W/H	:	Waist to hip ratio
Wt.	:	Weight

Introduction

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is now the most common cause of chronic liver disease in children and adolescents in the United States ***(Shneider et al., 2006).***

NAFLD is a clinico-pathologic entity defined as presence of hepatic steatosis in individuals who drink little or no alcohol and represents a spectrum of liver disease ranging from blandsteatosis to nonalcoholic steatohepatitis (NASH) ***(Kleiner et al., 2005).***

The development of NAFLD in children requires the coexistence of multiple factors. Among the numerous risk factors, many are similar to risk factors that have been identified in the adult population, including obesity, visceral adiposity, insulin resistance, and presence of other features of the metabolic syndrome. Other risk factors, such as race, ethnicity, sex, and distribution and progression of pubertal development, are exclusive to pediatric NAFLD ***(Alisi, 2009).***

Most patients with NAFLD have no or few symptoms. Infrequently, patients may complain of fatigue, malaise and dull right upper quadrant abdominal discomfort ***(Adams et al., 2005).***

NAFLD is most often diagnosed in asymptomatic people after the detection of raised aminotransferases during routine

screening or abnormal hepatic imaging performed for another purpose. Radiographic evidence of fatty infiltration of the liver, combined with an elevation of aminotransferases as a marker of hepatic inflammatory change, can be used to make a presumed diagnosis of NASH in the absence of liver biopsy ***(Stephen et al., 2002).***

Liver biopsy remains the only reliable way of diagnosing NASH, however, it's an invasive procedure, therefore, there's an urgent need to develop and validate a simple, non invasive test that distinguish NASH from NAFLD and determines stage and grade of the disease ***(Campos et al., 2008).***

Cytokeratin 18 (CK18) is an intracellular protein released into the blood by both necrosis and apoptosis of hepatocytes ***(Schutte et al., 2004).***

Plasma CK18 levels are elevated in children with a clinical diagnosis of NAFLD relative to normal-weight children and overweight children without NAFLD. This suggests that plasma CK18 may have potential as a serologic marker of NAFLD in children. That, by itself, may have some value in clinical medicine because it could help to identify children with obesity-related liver disease among those with obesity ***(Vos et al., 2008).***

Aim of the Work