

**Study of Cytokeratin 18 in Obese
Children with Suspected Nonalcoholic
Fatty Liver Disease (NAFLD)**

Thesis

Submitted for the partial fulfillment
of Master degree *in Pediatrics*

By

Marwa Atef Mohamed Ali
(M.B,B.ch) Ain Shams University (2006)

Supervised by

Asst. Prof. Amel Abd Elmagied El-Faramawy

Asst. Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Asst. Prof. Nermeen Helmy Mahmoud

Asst. Professor of Clinical Pathology
Faculty of Medicine - Ain Shams University

*Faculty of medicine
Ain Shams University*

2012



ACKNOWLEDGMENT

*First of all, I wish to express my endless thanks to **ALLAH** for giving me the help to perform this work*

*I would like to express my deepest thanks and highest appreciation to **Assist. Prof. Dr. Amel Abd Elmagied El Faramawy** Assist. Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her valuable help, precious advice, continuous encouragement and constructive guidance that were the most driving forces for the initiation, progress and completion of this work.*

*I owe special thanks and gratitude to **Assist. Prof. Dr. Nermeen Helmy Mahmoud** Assist. Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her precious help and fruitful guidance.*

Also, I would like to convey my special thanks to my family for their constant support.

Marwa Atef Mohamed Ali

LIST OF CONTENTS

Title	Page
• List of contents.....	i
• List of Tables	ii
• List of Figures	vi
• List of abbreviations.....	ix
Introduction	1
Aim of the Work.....	4
Review of Literature	5
• Chapter (1): Nonalcoholic Fatty Liver Disease	5
• Chapter (2): Cytokeratin-18	60
Subjects and Methods.....	66
Results	79
Discussion	121
Summary	137
Conclusion	139
Recommendations	140
References	141
Arabic Summary.....	--

LIST OF TABLES

Tab. No.	Title	Page No.
Table (1):	Various causes of hepatic steatosis	Error! Bookmark not defined.
Table (2):	Burnt grading system for NAS	Error! Bookmark not defined.
Table (3):	Burnt staging system for NAS	Error! Bookmark not defined.
Table (4):	NASH Clinical Research Network Scoring System for NAFLD	Error! Bookmark not defined.
Table (5):	Comparison between cases and controls as regards age	Error! Bookmark not defined.
Table (6):	Comparison between cases and controls as regards sex distribution	Error! Bookmark not defined.
Table (7):	Comparison between cases and controls as regards complications of obesity	Error! Bookmark not defined.
Table (8):	Comparison between cases and controls as regards complains related to liver	Error! Bookmark not defined.
Table (9):	Comparison between cases and controls as regards family history	Error! Bookmark not defined.
Table (10):	Comparison between cases and controls as regards systolic blood pressure (SBP) and diastolic blood pressure (DBP)	Error! Bookmark not defined.
Table (11):	Comparison between cases and controls as regards liver span by abdominal examination.....	Error! Bookmark not defined.
Table (12):	Comparison between cases and controls as regards Anthropometric measures	Error! Bookmark not defined.
Table (13):	Comparison between cases and controls as regards results of liver function tests	Error! Bookmark not defined.

LIST OF TABLES (CONT...)

Tab. No.	Title	Page No.
Table (14):	Comparison between cases and controls as regards Fasting Lipid Profile results	Error! Bookmark not defined.
Table (15):	Comparison between cases and controls as regards fasting blood glucose & blood insulin levels	Error! Bookmark not defined.
Table (16):	Comparison between cases and controls as regards liver size by U/S	Error! Bookmark not defined.
Table (17):	Comparison between cases and controls as regards U/S findings	Error! Bookmark not defined.
Table (18):	Comparison between cases and controls as regards CK18	Error! Bookmark not defined.
Table (19):	Correlation between CK 18 and blood pressure.....	Error! Bookmark not defined.
Table (20):	Correlation between CK 18 and liver span by abdominal examination	Error! Bookmark not defined.
Table (21):	Correlation between CK 18 and Anthropometric measurements	Error! Bookmark not defined.
Table (22):	Correlation between CK 18 and Metabolic Profile.....	Error! Bookmark not defined.
Table (23):	Correlation between CK 18 and liver functions	Error! Bookmark not defined.
Table (24):	Correlation between CK 18 and US finding	Error! Bookmark not defined.
Table (25):	Comparison between cases with fatty liver proven by U/S and without as regards Anthropometric measures	Error! Bookmark not defined.

LIST OF TABLES (CONT...)

Tab. No.	Title	Page No.
Table (26):	Comparison between cases with fatty liver proven by U/S and without as regards liver functions	Error! Bookmark not defined.
Table (27):	Comparison between cases with fatty liver proven by U/S and without as regards Fasting Lipid profile	Error! Bookmark not defined.
Table (28):	Comparison between cases with fatty liver proven by U/S and without as regards fasting blood glucose & blood insulin levels.....	Error! Bookmark not defined.
Table (29):	Comparison between controls, fatty liver and no fatty liver as regards CK18	Error! Bookmark not defined.
Table (30):	Comparison between CK 18, mild, moderate and severe cases with fatty liver proven by U/S.....	Error! Bookmark not defined.
Table (31):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards BP.....	Error! Bookmark not defined.
Table (32):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards anthropometric measurements	Error! Bookmark not defined.
Table (33):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards liver span	Error! Bookmark not defined.
Table (34):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards liver size by U/S	Error! Bookmark not defined.

LIST OF TABLES (CONT...)

Tab. No.	Title	Page No.
Table (35):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards fasting lipid profile	Error! Bookmark not defined.
Table (36):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards fasting blood glucose & blood insulin levels	Error! Bookmark not defined.
Table (37):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards CK18	Error! Bookmark not defined.
Table (38):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards U/S fatty liver grade	Error! Bookmark not defined.
Table (39):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards presence of fibrosis by U/S	Error! Bookmark not defined.

LIST OF FIGURES

Fig. No.	Title	Page No.
Figure (1):	Proposed pathogenesis of NASH.	Error! Bookmark not defined.
Figure(2):	Non alcoholic fatty liver disease (macrovesicular steatosis)	Error! Bookmark not defined.
Figure(3):	Non alcoholic fatty liver disease (microvesicular steatosis)	Error! Bookmark not defined.
Figure(4):	Non alcoholic fatty liver disease: macrovesicular steatosis, mixed lobular inflammation and ballooned hepatocytes	Error! Bookmark not defined.
Figure (5):	Non alcoholic steatohepatitis.	Error! Bookmark not defined.
Figure(6):	Non alcoholic steatohepatitis: immunohistochemistry for keratin 18	Error! Bookmark not defined.
Figure(7):	Nonalcoholic steatohepatitis: perisinusoidal/ pericellular fibrosis in zone 3	Error! Bookmark not defined.
Figure (8):	Top; Typical type 1 (adult) NASH pattern.	Error! Bookmark not defined.
Figure(9):	High-power photomicrographs show the histological features of each stage of fatty liver disease.....	Error! Bookmark not defined.
Figure(10):	Diagnostic flow chart for children with suspected NAFLD or NASH	Error! Bookmark not defined.
Figure (11):	The ROC curve comparing obese cases and controls	Error! Bookmark not defined.
Figure (12):	Correlation between CK18 and SBP	Error! Bookmark not defined.
Figure (13):	Correlation between CK18 and DBP	Error! Bookmark not defined.
Figure (14):	Correlation between CK18 and liver span	Error! Bookmark not defined.

LIST OF FIGURES (CONT...)

Fig. No.	Title	Page No.
Figure (15):	Correlation between CK18 and weight	Error! Bookmark not defined.
Figure (16):	Correlation between CK18 and weight SDS	Error! Bookmark not defined.
Figure (17):	Correlation between CK18 and BMI	Error! Bookmark not defined.
Figure(18):	Correlation between CK18 and waist circumference.....	Error! Bookmark not defined.
Figure(19):	Correlation between CK18 and hip circumference.....	Error! Bookmark not defined.
Figure(20):	Correlation between CK18 and waist/hip ratio.....	Error! Bookmark not defined.
Figure (21):	Correlation between CK18 and abdominal fat thickness	Error! Bookmark not defined.
Figure (22):	Correlation between CK18 and Cholesterol	Error! Bookmark not defined.
Figure (23):	Correlation between CK18 and triglycerides	Error! Bookmark not defined.
Figure (24):	Correlation between CK18 and HDL	Error! Bookmark not defined.
Figure (25):	Correlation between CK18 and LDL	Error! Bookmark not defined.
Figure (26):	Correlation between CK18 and ALT	Error! Bookmark not defined.
Figure (27):	Correlation between CK18 and AST	Error! Bookmark not defined.
Figure (28):	Correlation between CK18 and liver size by ultrasound.....	Error! Bookmark not defined.
Figure (29):	The ROC curve comparing cases with fatty liver proved by U/S (40) and cases without fatty liver (10)	Error! Bookmark not defined.

LIST OF FIGURES (CONT...)

Fig. No.	Title	Page No.
Figure (30):	Comparison between CK 18, mild, moderate and severe cases with fatty liver proven by U/S.....	Error! Bookmark not defined.
Figure (31):	Mean SBP, DBP in cases of fatty liver with and without elevated liver enzymes	Error! Bookmark not defined.
Figure (32):	Liver span in cases of fatty liver with and without elevated liver enzymes	Error! Bookmark not defined.
Figure (33):	Liver size by U/S in cases of fatty liver with and without elevated liver enzymes	Error! Bookmark not defined.
Figure (34):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards CK18	Error! Bookmark not defined.
Figure (35):	The ROC curve comparing the cases with fatty liver proved by U/S with elevated liver enzymes (7) and without elevated liver enzymes(33)..	Error! Bookmark not defined.
Figure (36):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards U/S fatty liver grade	Error! Bookmark not defined.
Figure (37):	Comparison between cases of fatty liver with and without elevated liver enzymes as regards presence of fibrosis by U/S.	Error! Bookmark not defined.

LIST OF ABBREVIATIONS

Abbrev.	Meaning
11 β HSD1	: 11 Beta hydroxysteroid dehydrogenase 1
ALT	: Alanine aminotransaminase
ASH	: Alcoholic steatohepatitis
AST	: Aspartate aminotransaminase
AUROC	: Area under the receiver operating characteristic
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
DNL	: De novo lipogenesis
ER Stress	: Endoplasmic reticulum stress
FFA	: Free fatty acids
GGT	: Gamma glutamyl transferase
GSH-Px	: Glutathione peroxidase
HBV	: Hepatitis B virus
HCC	: Hepatocellular carcinoma
HCV	: Hepatitis C virus
HMG COA	: 3-Hydroxy-3 methylglutaryl coenzyme A
HOMA-IR	: Homeostasis model assessment of insulin resistance
HSCs	: Hepatic stellate cells
IKK β	: Inhibitor of nuclear factor kappa-b kinase subunit beta.
IL-6	: Interleukin-6

LIST OF ABBREVIATIONS (CONT...)

Abbrev.	Meaning
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
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
ROS	: Reactive oxygen species
SBP	: systolic blood pressure
SREBP	: Sterol regulatory element binding protein
TG	: Triglycerides
TGF- β	: Tissue growth factor-beta
TNF- α	: Tumor necrosis factor alpha
TPS	: Tissue polypeptide specific antigen
U/S	: Ultrasonography
UDCA	: Urosdeoxy cholic acid
VLDL	: Very low density lipoproteins



Introduction



Chapter 1

Nonalcoholic Fatty Liver Disease
