



# **Cytokeratin-18 Fragment Level As a Biomarker of Non-Alcoholic Fatty Liver Disease In Egyptian Patients With Type II Diabetes Mellitus**

**Thesis**

*Submitted for Partial Fulfillment of Master degree  
in Internal Medicine*

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**2017**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببناك لا علم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



*First, I feel always indebted to **ALLAH**, the Most Kind and the Most Merciful.*

*I would like also to express my deep appreciation and gratitude to **Prof. Dr./ Tarek Mohamed Youssef**, Professor of Internal Medicine, Faculty of Medicine – Ain Shams University, for his unlimited help, great efforts and time he has devoted to accomplish this work. I really have the honor to complete this work under his supervision.*

*I am deeply grateful to **Prof. Dr./ Maha Mohsen Mohamed** Assistant Professor of Internal Medicine, Faculty of Medicine – Ain Shams University, for her unlimited help and giving me the privilege to work under her supervision. Her care and support are really valuable and precious.*

*I would like also to express my deep appreciation and gratitude to **Dr./ Mohamed Osama Aly**, Lecturer of Internal Medicine, Faculty of Medicine – Ain Shams University, for his care and support, also for the efforts and time he has devoted to accomplish this work.*

*Finally, I wish to extend my thanks to my **Family**, especially my dear **Parents** and **Wife** for their care and support.*

*Ibrahim Attia*

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## *List of Abbreviations*

| <b>Abb.</b>          | <b>Full term</b>                                       |
|----------------------|--------------------------------------------------------|
| <b>4HNE</b> .....    | <i>4-hydroxy-2-nonenal</i>                             |
| <b>AASLD</b> .....   | <i>American Association of Studying Liver Diseases</i> |
| <b>ABL</b> .....     | <i>Abetalipoproteinemia</i>                            |
| <b>ApoB100</b> ..... | <i>Apo Lipoprotein B 100</i>                           |
| <b>ApoB48</b> .....  | <i>Apo Lipoprotein B 48</i>                            |
| <b>ACC</b> .....     | <i>Acetyl CO-A Carboxylase</i>                         |
| <b>ACG</b> .....     | <i>American College of Gastroenterology</i>            |
| <b>ACO</b> .....     | <i>Acetyl CO-A</i>                                     |
| <b>ADP</b> .....     | <i>Adenosine di-phosphate</i>                          |
| <b>AFLD</b> .....    | <i>Alcoholic fatty liver disease</i>                   |
| <b>AGA</b> .....     | <i>American Gastroenterological Association</i>        |
| <b>AGE</b> .....     | <i>Advanced glycosylation end-products</i>             |
| <b>AIDS</b> .....    | <i>Acquired immunodeficiency syndrome</i>              |
| <b>ALT</b> .....     | <i>Alanine Aminotransferase</i>                        |
| <b>AMPK</b> .....    | <i>AMP-Activated Kinase</i>                            |
| <b>AST</b> .....     | <i>Aspartate aminotransferase</i>                      |
| <b>ATF 6</b> .....   | <i>Activating transcription factor 6</i>               |
| <b>ATP</b> .....     | <i>Adenosine triphosphate</i>                          |
| <b>BMI</b> .....     | <i>Body mass index</i>                                 |
| <b>CBC</b> .....     | <i>Complete blood count</i>                            |
| <b>CCL2</b> .....    | <i>Chemokine Ligand-2</i>                              |
| <b>CCR</b> .....     | <i>Chemokine receptor</i>                              |
| <b>CK</b> .....      | <i>Cytokeratin</i>                                     |
| <b>CK-18</b> .....   | <i>Cytokeratin-18 fragments</i>                        |
| <b>CKD</b> .....     | <i>Chronic kidney disease</i>                          |
| <b>CRN</b> .....     | <i>Clinical Research Network</i>                       |
| <b>CRP</b> .....     | <i>C-reactive protein</i>                              |
| <b>CT</b> .....      | <i>Computed Tomography.</i>                            |
| <b>CTGF</b> .....    | <i>Connective tissue growth factor</i>                 |

## *List of Abbreviations (cont...)*

| <b>Abb.</b>                | <b>Full term</b>                                       |
|----------------------------|--------------------------------------------------------|
| <b><i>CVD</i></b> .....    | <i>Cardiovascular disease</i>                          |
| <b><i>DAG</i></b> .....    | <i>Diacylglycerol</i>                                  |
| <b><i>DGAT1</i></b> .....  | <i>Diacylglycerol O-acyl-transferase</i>               |
| <b><i>DNA</i></b> .....    | <i>Deoxyribonucleic acid</i>                           |
| <b><i>DNL</i></b> .....    | <i>De Novo Lipogenesis</i>                             |
| <b><i>DPP-IV</i></b> ..... | <i>Dipeptidyl peptidase IV</i>                         |
| <b><i>EASD</i></b> .....   | <i>European Association for the Study of Diabetes</i>  |
| <b><i>EASL</i></b> .....   | <i>European Association for the Study of the Liver</i> |
| <b><i>EASO</i></b> .....   | <i>European Association for the Study of Obesity</i>   |
| <b><i>eGFR</i></b> .....   | <i>estimated glomerular filtration rate</i>            |
| <b><i>ELF</i></b> .....    | <i>Enhanced liver fibrosis</i>                         |
| <b><i>ELISA</i></b> .....  | <i>Enzyme Linked Immuno Sorbent Assay</i>              |
| <b><i>ER</i></b> .....     | <i>Endoplasmic reticulum</i>                           |
| <b><i>ETC</i></b> .....    | <i>Electron Transport Chain</i>                        |
| <b><i>EMA</i></b> .....    | <i>European medicines agency</i>                       |
| <b><i>F</i></b> .....      | <i>Fibrosis stage</i>                                  |
| <b><i>FC</i></b> .....     | <i>Free cholesterol</i>                                |
| <b><i>FCHL</i></b> .....   | <i>Familial combined hyperlipidemia</i>                |
| <b><i>FDA</i></b> .....    | <i>Food and Drug Administration</i>                    |
| <b><i>FFA</i></b> .....    | <i>Free fatty acid</i>                                 |
| <b><i>FHBL</i></b> .....   | <i>Familial hypobetalipoproteinemia</i>                |
| <b><i>FIB-4</i></b> .....  | <i>Fibrosis 4 calculator</i>                           |
| <b><i>FLI</i></b> .....    | <i>Fatty liver index</i>                               |
| <b><i>FOXO1</i></b> .....  | <i>Forkhead box protein O1</i>                         |
| <b><i>FxR</i></b> .....    | <i>Farnesoid x receptor</i>                            |
| <b><i>G6Pase</i></b> ..... | <i>Glucose-6-phosphatase</i>                           |
| <b><i>GGT</i></b> .....    | <i>Gamma glutamyl transferase</i>                      |
| <b><i>GLP 1</i></b> .....  | <i>Glucagon like peptide 1</i>                         |
| <b><i>GLUT</i></b> .....   | <i>Glucose transporter</i>                             |
| <b><i>GS</i></b> .....     | <i>Glycogen synthase</i>                               |

## *List of Abbreviations (cont...)*

| <b>Abb.</b>                           | <b>Full term</b>                                                                  |
|---------------------------------------|-----------------------------------------------------------------------------------|
| <b>GSD</b> .....                      | <i>Glycogen storage disease</i>                                                   |
| <b>GSK3</b> .....                     | <i>Glycogen synthase kinase-3</i>                                                 |
| <b>GWAS</b> .....                     | <i>Genome-Wide association study</i>                                              |
| <b>HAART</b> .....                    | <i>Highly Active Antiretroviral Drugs</i>                                         |
| <b>HbA1c</b> .....                    | <i>Glycosylated hemoglobin</i>                                                    |
| <b>HBsAg</b> .....                    | <i>Hepatitis B Surface Antigen</i>                                                |
| <b>HCC</b> .....                      | <i>Hepatocellular carcinoma</i>                                                   |
| <b>HCV</b> .....                      | <i>Hepatitis C Virus</i>                                                          |
| <b>HDL</b> .....                      | <i>High-density lipoprotein</i>                                                   |
| <b>HFC</b> .....                      | <i>Hepatic fat content</i>                                                        |
| <b>HIV</b> .....                      | <i>Human immunodeficiency virus</i>                                               |
| <b>HMG-CoA</b> .....                  | <i>Hydroxy-3-methyl glutaryl-coenzyme A</i>                                       |
| <b>HOMA-IR</b> .....                  | <i>Homeostasis model assessment of insulin resistance</i>                         |
| <b>HR</b> .....                       | <i>Hazard ratio</i>                                                               |
| <b>HSCs</b> .....                     | <i>Hepatic stellate cells</i>                                                     |
| <b>HSI</b> .....                      | <i>Hepatic steatosis index</i>                                                    |
| <b>IFG</b> .....                      | <i>Impaired fasting glucose</i>                                                   |
| <b>IGT</b> .....                      | <i>Impaired glucose tolerance</i>                                                 |
| <b>IKK-<math>\beta</math></b> .....   | <i>Inhibitor of nuclear factor <math>\kappa</math>B kinase-<math>\beta</math></i> |
| <b>IL6</b> .....                      | <i>Interleukin 6</i>                                                              |
| <b>IR</b> .....                       | <i>Insulin resistance</i>                                                         |
| <b>IRE 1<math>\alpha</math></b> ..... | <i>Inositol-requiring protein 1 <math>\alpha</math></i>                           |
| <b>IRS</b> .....                      | <i>Insulin receptor substrates</i>                                                |
| <b>IRS2</b> .....                     | <i>Insulin receptor substrate-2</i>                                               |
| <b>IRTK</b> .....                     | <i>Insulin receptor tyrosine kinase</i>                                           |
| <b>JI</b> .....                       | <i>Jejunoileal</i>                                                                |
| <b>JNK-1</b> .....                    | <i>Jun N-Terminal Kinase -1</i>                                                   |
| <b>KCs</b> .....                      | <i>Kupffer Cells</i>                                                              |

## *List of Abbreviations (cont...)*

| <b>Abb.</b>                          | <b>Full term</b>                                              |
|--------------------------------------|---------------------------------------------------------------|
| <b>LB</b> .....                      | <i>Liver biopsy</i>                                           |
| <b>LDL-C</b> .....                   | <i>Low Density Lipoprotein-Cholesterol</i>                    |
| <b>LFTs</b> .....                    | <i>Liver function tests</i>                                   |
| <b>LOXL2</b> .....                   | <i>Anti-lysyl oxidase-like monoclonal antibodies</i>          |
| <b>MDA</b> .....                     | <i>Malondialdehyde</i>                                        |
| <b>MDF</b> .....                     | <i>Mitochondrial dysfunction</i>                              |
| <b>MetS</b> .....                    | <i>Metabolic syndrome</i>                                     |
| <b>MRI</b> .....                     | <i>Magnetic resonance imaging</i>                             |
| <b>mRNA</b> .....                    | <i>Messenger Ribonucleic Acid</i>                             |
| <b>MRS</b> .....                     | <i>Magnetic resonance spectroscopy</i>                        |
| <b>MTTP</b> .....                    | <i>Microsomal triglyceride transfer protein</i>               |
| <b>MyD88</b> .....                   | <i>Myeloid differentiation factor 88</i>                      |
| <b>NAFL</b> .....                    | <i>Non-alcoholic fatty liver</i>                              |
| <b>NAFLD</b> .....                   | <i>Non alcoholic fatty liver disease</i>                      |
| <b>NAS</b> .....                     | <i>NAFLD Activity Score</i>                                   |
| <b>NASH CRN</b> ..                   | <i>Nonalcoholic Steatohepatitis Clinical Research Network</i> |
| <b>NASH</b> .....                    | <i>Non Alcoholic Steatohepatitis</i>                          |
| <b>NFS</b> .....                     | <i>NAFLD fibrosis score</i>                                   |
| <b>NF-<math>\kappa</math>B</b> ..... | <i>Nuclear factor kappa B</i>                                 |
| <b>NNFL</b> .....                    | <i>Non-NASH fatty liver</i>                                   |
| <b>NPV</b> .....                     | <i>Negative predictive value</i>                              |
| <b>OGTT</b> .....                    | <i>Oral glucose tolerance test</i>                            |
| <b>OR</b> .....                      | <i>Odds Ratio</i>                                             |
| <b>PASH</b> .....                    | <i>PNPLA3-associated steatohepatitis</i>                      |
| <b>PC</b> .....                      | <i>Pyruvate carboxylase</i>                                   |
| <b>PDK1</b> .....                    | <i>3-phosphoinositide-dependent protein kinase 1</i>          |
| <b>PEPCK</b> .....                   | <i>Phosphoenol pyruvate carboxykinase</i>                     |

## *List of Abbreviations (cont...)*

| <b>Abb.</b>                           | <b>Full term</b>                                                      |
|---------------------------------------|-----------------------------------------------------------------------|
| <b>PEPCK</b> .....                    | <i>Phosphoenolpyruvate</i>                                            |
| <b>PERK</b> .....                     | <i>Protein kinase RNA-like ER kinase</i>                              |
| <b>PI(3)K</b> .....                   | <i>Phosphatidylinositol-3-OH kinase</i>                               |
| <b>PIP3</b> .....                     | <i>Phosphatidylinositol (3,4,5)-triphosphate</i>                      |
| <b>PKC<math>\epsilon</math></b> ..... | <i>Protein kinase C<math>\epsilon</math></i>                          |
| <b>PNPLA3</b> .....                   | <i>Patatin like phospholipase domain containing protein</i>           |
| <b>PPAR</b> .....                     | <i>Peroxisome proliferator-activated receptor</i>                     |
| <b>PPARs</b> .....                    | <i>Peroxisomal Proliferator Activated Receptors</i>                   |
| <b>PPAR-<math>\alpha</math></b> ..... | <i>Peroxisome-proliferator-activated receptor <math>\alpha</math></i> |
| <b>PPAR-<math>\gamma</math></b> ..... | <i>Peroxisome-proliferator-activated receptor <math>\gamma</math></i> |
| <b>PPAR-<math>\delta</math></b> ..... | <i>Peroxisome-proliferator-activated receptor <math>\delta</math></i> |
| <b>PPV</b> .....                      | <i>Positive predictive value</i>                                      |
| <b>PPV</b> .....                      | <i>Positive predictive value</i>                                      |
| <b>PUFA</b> .....                     | <i>Polyunsaturated fatty acids</i>                                    |
| <b>RCT</b> .....                      | <i>Randomized controlled trials</i>                                   |
| <b>REC</b> .....                      | <i>Research Ethical Committee</i>                                     |
| <b>RNA</b> .....                      | <i>Ribonucleic acid</i>                                               |
| <b>RNS</b> .....                      | <i>Reactive nitrogen species</i>                                      |
| <b>ROC</b> .....                      | <i>Receiver operating characteristic curve</i>                        |
| <b>ROS</b> .....                      | <i>Reactive Oxygen Species</i>                                        |
| <b>SAF</b> .....                      | <i>Steatosis, activity and fibrosis</i>                               |
| <b>SD</b> .....                       | <i>Standard deviation</i>                                             |
| <b>SFA</b> .....                      | <i>Saturated fatty acids</i>                                          |
| <b>SGLT2</b> .....                    | <i>Sodium glucose cotransporter2</i>                                  |
| <b>SOCS3</b> .....                    | <i>Suppressor of Cytokine Signaling</i>                               |
| <b>SREBP</b> .....                    | <i>Sterol Regulatory Element Binding Protein</i>                      |
| <b>SU</b> .....                       | <i>Sulfonylurea</i>                                                   |
| <b>T2 DM</b> .....                    | <i>Type 2 diabetes mellitus</i>                                       |

## *List of Abbreviations (cont...)*

| Abb.                       | Full term                                                         |
|----------------------------|-------------------------------------------------------------------|
| <b><i>TAG</i></b> .....    | <i>Triacylglycerol</i>                                            |
| <b><i>TGF1,β</i></b> ..... | <i>Tumor growth factor, β</i>                                     |
| <b><i>TGF-β</i></b> .....  | <i>Tissue growth factor β</i>                                     |
| <b><i>TIMP 1</i></b> ..... | <i>Tissue-Inhibited matrix Metalloproteinase<br/>Inhibitor-1</i>  |
| <b><i>TIRAP</i></b> .....  | <i>Toll / IL-1 receptor domain containing adaptor<br/>protein</i> |
| <b><i>TLR</i></b> .....    | <i>Toll-like receptor</i>                                         |
| <b><i>TLR-4</i></b> .....  | <i>Toll like receptor-4</i>                                       |
| <b><i>TM6SF2</i></b> ..... | <i>Trans-membrane 6 superfamily 2</i>                             |
| <b><i>TNF</i></b> .....    | <i>Tumor necrosis factor</i>                                      |
| <b><i>TNF-α</i></b> .....  | <i>Tumor necrosis factor-α</i>                                    |
| <b><i>TPN</i></b> .....    | <i>Total parenteral nutrition</i>                                 |
| <b><i>TZDs</i></b> .....   | <i>Thiazolidinediones</i>                                         |
| <b><i>UDCA</i></b> .....   | <i>Ursodeoxycholic acid</i>                                       |
| <b><i>UPR</i></b> .....    | <i>Unfolded protein response</i>                                  |
| <b><i>US</i></b> .....     | <i>Ultrasonography</i>                                            |
| <b><i>USA</i></b> .....    | <i>United Status of America</i>                                   |
| <b><i>VLDL</i></b> .....   | <b><i>Very low density lipoprotein</i></b>                        |

## **Abstract**

T2DM patients are insulin resistant, often obese, dyslipidemic, display increased liver enzymes and tend to accumulate hepatic fat independently of BMI. The prevalence of NAFLD is also higher in person at risk of T2DM. Furthermore, IR and T2DM are among the strongest predictors of the progression of NAFLD to advance fibrosis and cirrhosis. Also, HCC is twice more likely to develop in individuals with T2DM.

Liver biopsy is the only reliable way of diagnosis and staging NAFLD, especially NASH, but its invasive nature limits its use. Moreover, it is prone to complications, some minor, such as pain, others more severe with a recorded risk of death of 0.01%. So, the need for non-invasive diagnostic tool for NAFLD became insidious.

Plasma-caspase-generated cytokeratin – 18 fragments (CK -18) has been proposed as a non invasive alternative and highly specific for NAFLD.

**Keywords:** *Ursodeoxycholic acid, Unfolded protein response, Ultrasonography, United States of America*

## INTRODUCTION

**N**AFLD has become one of the most common forms of chronic liver disease worldwide, accounting for 20-40 % of the general population. NAFLD represent a continuum of hepatic injuries, which progress from simple fatty liver (NAFL) to steatohepatitis (NASH), liver cirrhosis or even HCC (*Eliades and Spyron, 2015*).

It is apparently more slowly progressive than other chronic liver diseases, such as alcohol or viral-induced disease (*Fassio et al., 2004*). However, because NAFLD is so common, occurring in 1 out of 3 persons in the developed world (*Bellentani et al., 2010*), it is the 3rd cause of liver transplantation in USA (*Charlton et al., 2011*). Moreover, the problem of hepatocytes being fatty, overcomes the liver itself, as it increases the risk for cardiovascular disease & death & duplicates the risk for type 2 diabetes mellitus (T2 DM), independently of the severity of liver injury (*Musso et al., 2011*).

Patients with T2 DM have a higher risk of development of non-alcoholic fatty liver disease (NAFLD) (*Leite et al., 2009*) than those without T2 DM (*Hossain et al., 2009*). The prevalence of NAFLD is increasing mostly likely due to the rise in obesity and diabetes (*Kojima et al., 2003*). It is reported that 13.3% of deaths among diabetic patients are attributable to liver diseases, representing the increasing prevalence of