ADIPOKINE LEVELS AS A PREDICTOR OF LVER INJURY IN NON-ALCOHOLIC FATTY LIVER DISEASE

Thesis

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بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ
الْحَكِيمُ

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List Abbreviations

ACC	**Acetyl Coenzyme A carboxylase**
ACE	**Angiotensin-converting enzyme**
ACOX	**Acyl-CoA oxidase**
ACP	**Acylation stimulating protein**
ADP	**Adenosine diphosphate**
AGRP	**Agouti-related peptide**
ALP	**Alkaline phosphatase**
ALT	**Alanine aminotransferase**
AMPK	**5' AMP-activated protein kinase**
AOX1	**Aldehyde oxidase 1**
ARB	**Angiotensin II type 1 receptor blocker**
AST	**Aspartate aminotransferase**
AT-I	**Angiotensin II type 1**
ATP	**Adenosine triphosphate**
BBB	**Blood brain barrier**
BMI	**Body mass index**
CAMP	**Cyclic adenosine monophosphate**
CK-18	**Cytokeratin-18**
CPT-1	**Carnitine palmitoyl transferase 1**
CRP	**C-reactive protein**
CT	***Computed Tomography***
CTGF	**Connective tissue growth factor**
DNL	**De novo lipogenesis**
DPI	**Doppler perfusion index**
ECM	**Extracellular matrix (ECM)**
EGP	**Endogenous glucose production**
ER	**Endoplasmic reticulum**
ET-1	**Endothelin-1**
FAS	**Fatty acid synthase**
FFA	**Free fatty acids**
GGT	**Gamma-glutamyltransferase**
GLP-1	**Glucagon-like peptide 1**
GLUT4	**Glucose transporter 4**
GNG	**Gluconeogenesis**
GPAT	**Glycerol-3-phosphate acyltransferase (GPAT)**
GSH-Px	**Glutathione peroxidase**
GSK3	**Glycogen synthase kinase 3**
H2O2	**Hydrogen peroxide**
HCC	**Hepatocellular carcinoma**

HMG CoA	Hepatic 3-hydroxyl-3-methylglutaryl coenzyme A
HMW	High-molecular weight
HNE	4-hydroxynonenal
HOMA	Homeostasis model assessment
HSCs	Hepatic stellate cells
HTGC	Hepatic triglyceride content
Hus	Hounsfield units
ICV	Intracerebroventricular
IGFBP2	IGF binding protein-2
IL-1	Interleukin -1
L-6	Interleukin-6
IR	Insulin resistance
IRS	Insulin receptor substrates
JAK2	Janus kinase 2
KATP	ATP-sensitive potassium channels
KCs	Kupffer cells
LCAS	Long chain acyl-CoA synthetase .
LDL-C	Low-density lipoprotein cholesterol
LHA	Lateral hypothalamic area
MAPK	Mitogen activated protein kinase
MCH	Melanin-concentrating hormone
MDA	malondialdehyde
MRI	Magnetic Resonance Imaging
MRS	Proton Magnetic Resonance Spectroscopy
NAFL	nonalcoholic fatty liver
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Non-alcoholic steatohepatitis
NFκB	Nuclear factor-kappaB
NPC1L1	Niemann-Pick type C protein
NPY	Neuropeptide Y
PAI-1	Plasminogen activator -1
PDGF	Platelet-derived growth factor
PGC-1 α	PPARγ coactivator-1 α
PI3K	Phosphoinositide 3-kinase
PKC	Protein kinase C
PPAR-γ	Peroxisome proliferator activator receptor gamma
PTP1B	Protein tyrosine phosphatase 1B
PTX3	Plasma pentraxin 3
PVN	Paraventricular nucleus.
ROS	Reactive oxygen species

SAMe	**S-adenosylmethionine**
SAT	**Subcutaneous adipose tissue**
SECs	**Sinusoidal endothelial cells**
SNPs	**Single nucleotide polymorphisms**
SNS	**sympathetic nervous system**
SOCS-3	**Suppressor of cytokine signaling-3**
SPEA	**Serum prolidase enzyme activity**
SREBP-1c	**transcription factor sterol regulatory element binding protein-1c**
STAT3	**Signal transducer and activator of transcription 3**
T2DM	**Type 2 diabetes mellitus**
TGFb-1	**Transforming growth factor beta-1**
TGF-β	**Transforming growth factor beta**
TNF α	**Tumour necrosis factor α**
TRX	**Thioredoxin**
TZDs	**Thiazolidinediones**
UDCA	**Ursodeoxycholic acid**
VAT	**Visceral adipose tissue**
VEGF	**Vascular endothelial growth factor**
VLDL	**Very low density lipoprotein**
WAT	**White adipose tissue**
α-MSH	**α-melanocyte stimulating hormone**
11b-HSD1	**11b-hydroxysteroid dehydrogenase type 1**
5αR	**5-α reductase**

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome and covers a wide spectrum of liver pathology-from steatosis alone, through the necroinflammatory disorder of non-alcoholic steatohepatitis (NASH) to cirrhosis and liver cancer (***Raszega-Wyszoirska et al., 2008***). The pathogenesis of NASH is currently thought to involve a multiple-hit process with the first hit being the accumulation of liver fat which is followed by the development of necroinflammation and fibrosis. There is mounting evidence that cytokines secreted from adipose tissue, namely, adipokines, are implicated in the pathogenesis and progression of NAFLD (***Emmanuel et al., 2009***).

Adipose tissue is a massive source of bioactive substances known as adipocytokines, including tumor necrosis factor (TNF)-alpha, resistin, leptin, and adiponectin. Recent advances in medical research view obesity as a chronic low-grade inflammatory state. Hypertrophied adipocytes in obesity release chemokines that induce macrophage accumulation in adipose tissue. Accumulated macrophnges in obese adipose tissue produce proinflammatory cytokines and nitric oxide, and these inflammatory changes induce adipocytokine dysregulation. The latter is characterized by a decrease in insulin sensitizing and anti-inflammatory adipocytokines, and an increase in proinflammatory adipocytokines. Adipocytokine dysregulation induces obesity-related metabolic disorders, the so-called metabolic syndrome, which is a cluster of metabolic abnormalities, including diabetes mellitus, hypertension, hyperlipidemia, and NASH (***Kamada el al., 2008***).

Adiponectin is exclusively secreted by adipocytes and is considered as an anti-inflammatory adipokine. It reduces body fat, improves hepatic and peripheral insulin sensitivity, and is inversely associated with body mass index and insulin resistance. In the liver, it prevents lipid accumulation by increasing B oxidation of free fatty acid and/ or by decreasing de novo free fatty acid within hepatocytes (***Emmanuel et al., 2009***).

Leptin is a circulating 16 kDa peptide hormone secreted mainly by adipocytes of white fat tissue. It regulates food intake, body fat, insulin action, thermogenesis, induction of angiogenesis, and modulation of the immune system. Leptin synthesis in adipocytes is regulated by several hormones. Although it is considered as an anorexigenic hormone, its levels are elevated in obesity as a result of resistance to its actions. Leptin is thought to participate in both hits of NASH development. Initially, it contributes to the development of insulin resistance and subsequently steatosis. Furthermore, in the context of liver insult, leptin has a proinflammatory role and is considered to be an essential mediator of liver fibrosis (***Tsochatzis, 2006***).

THE AIM OF THIS WORK

The aim of this work is to determine whether serum levels of adipokines, including the ratio of serum adiponectin to leptin (A/L) levels could predict the severity of liver injury in patients with non-alcoholic fatty liver disease (NAFLD).