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Study Of Serum Dipeptidyle Peptidase IV (DPP IV, CD26) Activity In Patients With Non – Alcoholic Fatty Liver Disease And Its Role In Development Of Non – Alcoholic Steatohepatitis

Protocol of Thesis

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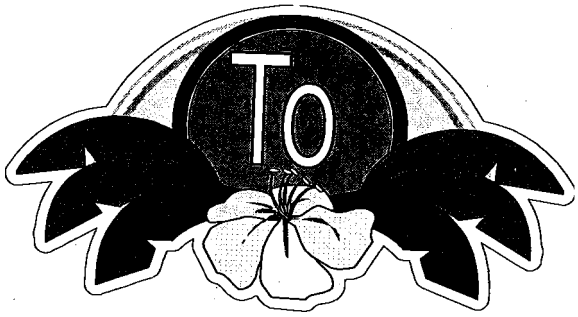
بسم الله الرحمن الرحيم

وَمَا تَوْفِيقِي إِلَّا بِاللَّهِ عَلَيْهِ
تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ

صدق الله العظيم
(هود: من الآية٨٨)

Dedication



My **family**

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Contents

List of abbreviations

lH MRS	proton magnetic resonance spectroscopy with lH
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AdipoR	adiponectin receptor
ADSF	adipose tissue-specific secretory factor
AFP	Alpha-Feto Protein
AST	aspartate aminotransferase
BMI	body mass index
C3aR	C3a anaphylatoxin receptor
CAP	controlled attenuation parameter
CB	Cannabinoid
CCL2	CC-chemokine ligand-2
CD26	cluster of differentiation 26
CEUS	contrast-enhanced US
CHB	chronic hepatitis B
CK18	Cytokeratin 18
CRP	C-reactive protein
CT	Computed Tomography
CXCL12/SDF-1	chemokine ligand 12/stromal-derived factor-I
DPP4	Dipeptidyl peptidase-4
ECM	extracellular matrix

GALT	Gut-Associated Lymphoid Tissue
GGT	gamma-glutamyltranspeptidase
GLP	glucagon-like peptide
GLUT-4	Glucose Transporter-4
GPCRs	G protein -coupled receptors
HbAlc	glycosylated hemoglobin
HIF-la	Hypoxia-inducible factor-1 alpha
HMW	High Molecular Weight
ITAM	immunoreceptor tyrosine-based activation motif
ITIM	immunoreceptor tyrosine-based inhibition motif
J chain	Joinint chain
kPa	Kilopascal
LDL	low-density lipoprotein
LESTR	leukocyte-expressed seven-transmembrane domain receptor
LMW	Low Molecular Weight
LMWP	Low Molecular Weight Protein
MCP-1	monocyte chemoattractant protein-I
MRI	magnetic resonance imaging
NAFLD	Nonalcoholic fatty liver disease
NF-"b	nuclear factor-"b
NPV	negative predictive value

plgA	produce polymeric IgA
plgR	polymeric lg Receptor
PPV	Positive Predictive Value
PUFAs	polyunsaturated fatty acids
RBP	Retinal-Binding Protein
RCT	randomized controlled trial
RELMp	resistin-like molecule
RGS	regulators of G-protein signaling
SAP	serum amyloid P component
SDF-1	stromal cell-derived factor **1**
SFAs	saturated fatty adds
SPEA	serum prolidase enzyme activity
sRAGE	soluble receptor for advanced glycation end products
T2DM	type II diabetes mellitus
TE	Transient elastography
TNF	tumor necrosis factor
TTR	Transthyretin
VCTE	vibration-controlled transient elastography

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the abnormal accumulation of lipids, primarily in the form of triglycerides in individuals who do not consume significant amounts of alcohol (≤ 20 g ethanol/d)**.** It is characterized by a spectrum of disease varying from simple steatosis through to steatohepatitis with fibrosis and scarring, which can lead to cirrhosis **(Hazlehurst and Tomlinson, 2013).**

Dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing protein 2 or CD26 (cluster of differentiation 26) is a protein that, in humans, is encoded by the DPP4 gene **(Kameoka et al., 1993)**.

Although various factors are responsible for the development of NAFLD, a high glucose load is known to induce DPP-4 expression in HepG2 cells and hepatic DPP-4 mRNA expression level in the livers is significantly higher in patients with NAFLD, compared to healthy subjects **(Eguchi et al., 2012)**.

Itou et al. (2012) also experienced a case of refractory NAFLD that was successfully treated with sitagliptin, a DDP-4 inhibitor. Moreover, it is reported that sitagliptin ameliorates liver enzymes and hepatocyte ballooning in patients with nonalcoholic steatohepatitis. So, DPP-4 inhibitors ameliorate hepatic injury and glucose impairment in patients with NAFLD.

Aim of the work

The aim of this work is to study the role of serum dipeptidyle peptidase IV activity in development and progression of simple steatosis to non-alcoholic steatohepatitis in patients with non-alcoholic fatty liver disease and its role in follow up the progression to chronic liver disease.

Non-alcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is defined as the abnormal accumulation of lipids, primarily in the form of triglycerides in individuals who do not consume significant amounts of alcohol (≤ 20 g ethanol/d)**.** It is characterized by a spectrum of disease varying from simple steatosis through to steatohepatitis with fibrosis and scarring, which can lead to cirrhosis **(Hazlehurst and Tomlinson, 2013).**

The prevalence of individuals diagnosed with NAFLD varies from 10-39% of the world population. The disease can be associated with other co-morbidities and affects 50% of diabetics, 57 to 74% of obese people, and 90% of morbidly obese people. In the pediatric population, NAFLD affects 2.6% of eutrophic children and up to 60% of obese children and adolescents **(Cotrim et al., 2011).** NAFLD is currently recognized as a clinically emergent problem among obese patients **(Lam and Younossi, 2010).**

Because of the inordinately high prevalence of NAFLD, it is important to identify those patients with NASH, particularly those at risk for advanced disease. Liver biopsy traditionally has been the gold standard used to make the diagnosis of NASH. However, without adequate biopsy tissue, there is a high degree of sampling variability **(Harrison and Neuschwander-Tetri, 2004)**.

Additional problems include the small but inherent risk of complications, potential patient discomfort, and cost. Subsequently, noninvasive tools to correctly identify NAFLD patients who have

histopathologic evidence of NASH with or without advanced fibrosis are in development and include a variety of techniques that vary from composite laboratory and biomarker data to tests that measure hepatic tissue elasticity such as the Fibroscan **(Harrison and Neuschwander-Tetri, 2004)**.

Natural history:

The natural history of patients with NAFLD has a mixed picture. In a large cohort study, it was demonstrated that liver related illness was the third leading cause of death in liver patients, and the hazard ratio for general mortality and liver related mortality was 1.038 and 9.32, respectively**.** As in the general population, the leading cause of death in patients with NAFLD is cardiovascular disease **(Ong et al., 2008).**

This highlights the need for patients with NAFLD to have extensive risk management therapy for the prevention of cardiovascular disease; however, no concrete guidelines have been made for the prevention of adverse cardiac events in these patients **(Monsour et al., 2012).**

Wilfred de Alwis and Day (2008) have estimated the overall risk of a patient with simple steatosis advancing to clinically significant cirrhosis at approximately 1%-2%**.** However, patients who have progressed to or presented with NASH are at increased risk of developing hepatic decompensation and liver failure**.**