Association between Fatty Liver Disease and Hyperinsulinemia

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

”وَمَا أُوتِيتُم مِّنَ الْعِلْمِ إِلَّا قَلِيلًا“

صدَقَ اللهُ العَظِيم

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List of Abbreviations

AACE	American college of endocrinology
ACEI	Angiotensin-converting enzyme inhibitors
ALD	Alcoholic liver disease
ALT	Alanine Aminotransferase
AMA	Antimitochondrial Antibody
ANA	Antinuclear Antibody
ARBs	Angiotensin-receptor blockers
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
BMI	Body mass index
Ca2+	Calcium
C AMP	Cyclic adenosine monophosphate
CK 18	Cytokeratin 18
C-peptide	Connecting peptide
CT	Computed Tomography
CVD	cardiovascular disease
DAG	Diacylglycerol
DM	Diabetes mellitus
DNL	De novo lipogenesis
FFA	Free fatty acid
FSIVGTT	Frequently sampled intravenous glucose tolerance test
g/dL	gram/deciliter
g/L	gram/liter
G6P	Glucose 6 Phosphate
GIP	Gastric inhibitory polypeptide

GGT	Gamma Glutamyltransferase
GLUT-1	Glucose transporter 1
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HMG-CoA	3-Hydroxy-3-Methylglutaryl-coenzyme A
HOMA-IR	Homeostatic model assessment of Insulin resistance
IAPP	Islet cell amyloid polypeptide
IDF	International Dairy Federation
IGFBP-1	Insulin-like growth factor-binding protein 1
IL-6	Interleukin-6
IM	Intestinal microbiota
IP-3-kinase	Inositol 1,4,5-trisphosphate 3-kinases
IR	Insulin Resistance
IRS-1	Insulin receptor substrate 1
K	Potassium
kPa	Kilopascals
LDL	Low Density Lipoprotein
LFTs	Liver function tests
LSM	liver stiffness measurement
MetS	Metabolic Syndrome
mmol/l	millimoles/liter
mu/ml	milliunits/ milliliter
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Non-alcoholic steatohepatitis

NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NEFA	Non-esterified fatty acids
NF-κB	Nuclear Fasctor kappa -light-chain-enhancer of activated B cells
ng/mL	nanogram/milliliter
NPY	Neuropeptide Y
PACAP	Pituitary Adenylate Cyclase-Activating Polypeptide
PCOS	polycystic ovary syndrome
PI	phosphatidylinositol
PKCϵ	protein kinase Cϵ
PO4	Phosphate
PPAR-G	peroxisome proliferator-activated receptor gamma
RAAS	Renin-angiotensin-aldosterone system
RER	Rough endoplasmic reticulum
SREBP1c	Sterol Regulatory Element Binding Protein 1c
TGF-β	Transforming growth factor β
TNF-α	Tumor necrosis factor alpha
Trp	Tryptophan
UDCA	Ursodeoxycholic Acid
UPS	Ubiquitin proteasome system
U/S	Ultrasonography
VIP	vasoactive intestinal peptide
VLDL	Very low density lipoprotein
Wk	Week

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Introduction

The liver is the primary site of insulin clearance.The majority (80%) of endogenously secreted insulin is cleared by the liver, 15% by the kidney, and 5% by muscle ***(Kotronen et al., 2007a).***

In advanced liver disease, insulin clearance is decreased, which is considered to be one of the main causes of hyperinsulinemia in liver cirrhosis ***(Kotronen et al., 2007b).***

Fatty Liver Disease is associated with impaired insulin action to suppress hepatic glucose production when measured directly in both nondiabetic subjects ***(Seppala-Lindroos et al., 2002)*** and type 2 diabetic patients ***(Ryysy et al., 2000)*** & Fatty Liver Disease is closely correlated with fasting serum insulin concentrations but the extent to which impaired insulin clearance due to hepatic fat accumulation contributes to hyperinsulinemia has not previously been determined ***(Westerbacka et al., 2004).***

Previous studies have shown that insulin clearance is decreased in obesity. It has also been suggested that intra-abdominal rather than subcutaneous fat influences splanchnic insulin clearance ***(Chan et al., 2006).***

Insulin resistance (IR) is the principal indication for development of metabolic syndrome and type 2 diabetes ***(Grundy, 2008 and Eckel et al., 2010).*** It appears as a consequence of the inability of insulin to induce the appropriate effect on glucose metabolism. Inordinately large

amounts of insulin are required to achieve a normal response in a state of IR. A hyperinsulinemic state causes several clinical abnormalities to appear in the blood vessels, kidneys, and liver, and these represent the major features of metabolic syndrome ***(Lorenzo et al., 2003).***

Metabolic syndrome generally refers to a combination of metabolic diseases such as abdominal obesity, high blood pressure, dyslipidemia and elevated blood glucose, that appear together in an individual patient ***(Eckel et al., 2010).***

Because metabolic syndrome is recognized as a serious risk factor for cardiovascular disease, prevention and comprehensive management are important in treating this condition ***(Isomaa et al., 2001).***

Aim of the Work

The aim of this work is to study the relationship between fatty liver disease and insulin resistance.