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The pattern of Liver Disease In non-B, non-C Egyptian patients With Type2 Diabetes

Thesis

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Contents

List of tables

List of figures

List of Abbreviations

4-HN	4-Hydroxynonenal
ACC	Acetyl-coenzyme a carborxylase
ACTH	Adrenocorticotrophic hormone
ADMA	Asymmetric dimethyl arginine
ADP	Adiponectin
AGEs	Advanced glycation end products
ALT	Alanine transaminase
AMPK	Amp-activated protein kinase
APC	Asia pacific criteria
ASH	Alcoholic steatohepatitis
AST	Aspartate transaminase
ATP	Adenosine tri-phosphate
BMI	Body mass index
BAAT	BMI, age at liver biopsy, alt and serum triglycerides
cAMP	Cyclic adenosine monophosphate
ChREBP	Carbohydrate response element binding protein
CPT-1	Carnitine palmitoyl transferase-1
CRP	C-reactive protein
CT	Computed tomography
CTGF	Connective tissue growth factor
CVD	Cardiovascular disease
CYP2E1	Cytochrome p450 2e1

DM	Diabetes millets
DNA	Deoxyribo nucleic acid
DNL	de Novo lipogenesis
EGlR	European group for the study of insulin resistance
ELISA	Enzyme linked immunosorbant assay
eNOS	Endothelial nitric oxide (no) synthase
FFAs	Free fatty acids
HbsAg	Hepatitis b surface antigen
HCC	Hepatoceliular carcinoma
HCV	Hepatitis c virus
HDL	High density lipoprotein
HFE	Hyperferritinemia
HIC	Hepatic iron concentration
HOMA	Homeostasis model assessment
HSCs	Hepatic stellate cells
HSL	Hormone sensitive lipase
IDF	International diabetes federation
IR	Insulin resistance
IRS	Insulin-receptor syndrome
KCs	Kupffer cells
LDL	Low-density lipoprotein
lL	Interleukin
LPL	Lipoprotein lipase
MDA	Malondialdehyde

MnSOD	Manganese superoxide dismutase
MR	Magnetic resonance
mRNA	Messenger ribonucleic acid
MTP	Microsomal triglyceride transfer protein
NAFLD	Nonalcoholic fatty liver disease
NAS	Nafld activity score
NASH	Nonalcoholic steatohepatitis
NCEP	National cholesterol educational program
NHANES	National health and nutritional examination survey
NIDDM	Non-insulin dependent diabetes millets
NIH	National institutes of health
NO	Nitric oxide
NPV	Negative predictive value
OGTT	Oral glucose tolerance test
PI3K	Phosphatidy inositol 3 kinase
PPARs	Peroxisome proliferator-activated receptors
PPV	Positive predictive value
ROS	Reactive oxygen species
PUFAs	Poly unsaturated fatty acids
RXR	Retinoid x receptor
SREBP-1c	Sterol regulatory element-binding protein-1c
TGF- α1	Tumor growth factor- α1
TGFbl	Transforming growth factor beta-1

TNF-α	Tumor necrotizing factor-α
TPN	Total parentral nutrition
TZDs	Thiazolidinediones
UCP-2	Uncoupling protein-2
UDCA	Ursodeoxycholic acid
US	Ultrasound
VLDL	Very low density lipoproteins
WHO	World health organization
WHR	Waist-to-hip ratio
γGT	Gamma glutamile transferase

Introduction

There is an association between diabetes, the liver, and liver disease. Hepatitis C infection is more prevalent in type 2 but not type 1 diabetes. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis are associated with obesity, insulin resistance, and diabetes. Lowering of insulin resistance may modify the progress of these conditions. Liver dysfunction associated with advanced liver disease is associated with insulin resistance, pancreatic beta cell dysfunction, and diabetes, which are reversible in most cases with hepatic transplantation ***(Eric and Albright, 2003).***

Nonalcoholic fatty liver disease (NAFLD) is an increasing recognized clinical pathologic condition that may progress to end stage liver disease; the pathological picture resembles that of alcohol-induced liver injury, but occurs in patients who deny alcohol abuse. Nonalcoholic fatty liver disease refers to a wide spectrum of liver damage ranging from simple steatosis, steatohepatitis, advanced fibrosis up to cirrhosis ***(Angulo et al, 2002).*** Steatosis referres to the accumulation of droplets of triglycerides in hepatocytes ***(Daniel et al, 1999).***

While nonalcoholic steatohepatitis (NASH) is a chronic liver disease that occurs in patients with no significant alcohol consumption, characterized by macro vesicular steatosis, hepatocellular necrosis, mixed inflammatory infiltrate and various grades of fibrosis and in some cases Mallory bodies ***(Alvarez-Martinez et al, 2004).***

Steatosis alone is associated with good prognosis, whereas NASH can progress to fibrosis and cirrhosis in up to 30% of cases, potentially leading to liver failure and hepatocellular carcinoma ***(Ruhl and* Everhart, *2003).*** NAFLD is now present in 17% to 33% of Americans ***(Farrellet al, 2006).*** The prevalence of NASH is unknown. However, recent studies showed that it is about 3% ***(Alvarez-Martinez et al, 2004).*** NASH could be present in one third of NAFLD.

Age activity of steatohepatitis and established fibrosis predispose to cirrhosis, which has a 7 to 10 years related mortality of 12% to 25%. Many cases of cryptogenic cirrhosis are likely end stage NASH. While end stage NAFLD currently account for 4% to 10% of liver transplant ***(Farrell et al, 2006).***

There is no specific cause for fatty liver. NAFLD can be primary or secondary depending on the cause, primary NASH is

associated with metabolic syndrome-related condition, such as obesity , diabetes mellitus type 2 , hyperlipeamia and hypertension, and secondary NASH associated with obesity-related intestinal surgery, drugs such as amiodarone or preexilian maleate, lipodystrophy, or Wilson's Disease ***(Medina et al, 2004).***

The pathogenesis of NAFLD is involved in two steps. The first step involves insulin resistance and obesity and cause development of steatosis, the second step is oxidative stress, activating an inflammatory response and causing NASH ***(Day et al, 2002).***

The diagnosis of NAFLD is suggested by increase echogenicity (bright liver) in ultrasound and increase radiolucency in computerized tomography (Steatosis) with sensitivity of both investigations up to 75% to 85% ***(Saadeh et al, 2002).*** But liver biopsy is the only confirmative diagnosis for NASH ***(Farrell, 2005).***

Aim of the work

The aim of the present work is to study the pattern of hepatic changes whether morphologic or histopathologic in long-standing type 2 diabetic patients on oral hypoglycemic medications with characterization of the clinical presentation of the liver affection, including NAFLD and NASH.

Epidemiology

NAFLD\NASH has a very high prevalence in North and South America, much of Asia Pacific (including Australia and New Zeeland), the Middle East and Europe. It is now the leading cause of referral to Hepatology clinics in most regions but accurate estimation of it is incidence, prevalence and nature history are lacking ***(McCullough, 2002)***.

According to The Third National Health and Nutritional Examination Survey (NHANES) between 3% and 23% of the adult population may have NAFLD, NASH ***(Ruhl and* Everhart, *2003)***.

A recent study using proton magnetic resonance spectrometry found that approximately 30% of the United State population had increased triglyceride content in the liver ***(Browning et al, 2004)***. Another recent study based on Ultrasonography found an apparent prevalence of NAFLD of 29% among healthy Japanese adult ***(Jimba et al, 2005)***.

Type 2 DM, hyperglycemia and glucose intolerance have been described in 20–75% of adult patients with NASH. Some authors have reported that a history of type 2 DM was associated with a 2.6-fold increase in the prevalence of NASH ***(Browning et***

al, 2004). The prevalence of type 2 diabetes has doubled tripled or increased 10- to 20-fold during the last decade (as in Japanese youth), rates reaching 40% or more of the adult population in some communities ***(Omagari et al, 2002)***.

NASH may be even more prevalent among asymptomatic patients with elevated liver function test results, negative viral marker, and negligible alcohol intake because many of these patients do not undergo liver biopsy ***(Zatloukal et al, 2004)***.

The wide range in the prevalence most likely reflects difference in the definitions used and patient population studied. Lower prevalence occurred in studies including patients only with steatohepatitis. A higher prevalence occurred in studies including steatosis as apart of definition, patients with diabetes mellitus 50% and obesity 76%. it is almost universal among diabetic people who are morbidly obese ***(Gupte et al, 2004)***.