

**NONALCOHOLIC FATTY LIVER DISEASE IN
OBESE EGYPTIAN CHILDREN**

Thesis

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Abstract

Obesity has emerged as a significant global health problem in the children. Nonalcoholic fatty liver disease (NAFLD) is a serious complication of childhood obesity and characterized by macrovesicular steatosis that occur in the absence of consumption of harmful amounts of alcohol. NAFLD ranges from: simple steatosis, steatosis with nonspecific inflammation, steatohepatitis, cirrhosis and hepatocellular carcinoma.

It is already evident that children with NASH risk progressive liver damage, including liver cirrhosis. The aim of this study is to determine the prevalence of asymptomatic hepatic steatosis and presumed nonalcoholic steatohepatitis, in our local population of obese Egyptian children referred for medical assessment, and to assess the correlation between severity of ultrasonographic hepatic steatosis and degree of obesity, insulin resistance and serum biochemical abnormalities.

Seventy six patients with simple obesity: 37 were overweight (17 male and 20 females) and 39 were obese (21 males and 18 females) (mean age 7.7 ± 3.5 years) were included in the study. They were subjected to: 1- Assessment of biochemical tests of liver functions, lipid profile (TG, total cholesterol, HDL-c and LDL-c), post suppression cortisol and ACTH., fasting insulin, C-peptide, serum ferritin and HBV&HCV markers in selected cases. 2-Full abdominal ultrasonography 3- Liver biopsy for selected cases(those had clinical hepatomegaly $\pm$ elevated liver enzymes $\pm$ echogenic liver). The prevalence of NAFLD in our study was 19.7% (simple steatosis 10.5% and NASH 9.2%). BMI, W/H ratio, grade III echogenicity of the lever and dyslipidemia were highly predicting factors for NASH.

Key words: Childhood obesity, NAFLD , insulin resistance, predicting factors for NASH, liver biopsy, BMI, echogenicity.

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List of Abbreviations

Abbreviations	Full word
<	Less than
>	More than
%	percent
1 st	first
2 nd	second
3 rd	Third
4 th	Fourth
AB	Abstract
ACE	Angiotensin converting enzyme
ALP	Alkaline phosphatase.
ASH	alcoholic steatohepatitis
AMP	Adenosine monophosphate
ALT	Alanine aminotransferase
ANS	Autonomic nervous system
AOX	Acyl CoA oxidase
Apo B	Apolipoprotein B
ASH	Alcoholic steatohepatitis
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
β	Beta
BMI	Body mass index
CBC	Complete blood count
CBD	Common bile duct
cm	Centi meter
CT	Computerized tomography
CPT-1	carnitine palmitoyl transferase-1
CV	central vein
dl	Deci meter
DEMPU	Diabetes Endocrine Metabolic Pediatric Unit
DM	Diabetes mellitus
DNL	De Novo Lipogenesis

Continued:

Abbreviations	Full word
ESR	Erythrocyte sedimentation rate
FA	Fatty acid
FF	Fat fraction
FFA	free Fatty acid
fl	Fento liter
Fig	Figure
FNA	Fine needle aspiration
g	gram
GB	Gall bladder
GGT	Gamma glutamile transpeptidase
GLP-1	Glucagon-like peptide-1
h	Hour
HBcAb	Hepatitis B virus core antibody
HBsAg	Hepatitis B virus surface antigen
HCVAb	Hepatitis C virus antibody
HDL	High density lipoprotein
HSL	Hormone-sensitive lipase
IDF	International Diabetes Federation
IR	Insulin resistance
IL-6	Interleukin-6
LPL	Lipoprotein lipase
MRI	Magnetic resonance imaging
MSSH	Metabolic syndrome steatohepatitis
MTP	Microsomal triglyceride transfer protein
NAFL	Non alcoholic fatty liver
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic Steatohepatitis.
NHANES III	National Health and Examination Survey, cycle III
O ₂	Oxygen
OH	Oxygen-hydrogen
PTX	Pentoxifylline
PPAR γ	peroxisome proliferator-activated receptor gamma
PPAR α	peroxisome proliferators-activated receptor α

Continued:

Abbreviations	Full word
RAS	Renin-angiotensin system
RBP4	Retinol binding protein
ROS	Reactive oxygen species
RxR α	Retinoid receptor α
SREBP-1c	Sterol regulatory element binding protein-1c
TNF- α	Tumor necrosis factor-alpha
TG	Triglycerides
TPN	Total parenteral nutrition
UDCA	Ursodeoxycolic acid
US	Ultrasound
VLDL	Very-low-density lipoproteins

Introduction and aim of the work

The rising pandemic of obesity and type 2 diabetes, both manifestations of insulin resistance, has heralded a rise in associated liver injury in the form of non-alcoholic fatty liver disease (NAFLD) (**Jimba et al., 2005**).

Non-alcoholic steatohepatitis (NASH) is an entity in the spectrum of NAFLD ranges from fat in the liver (simple steatosis), NASH/ steatohepatitis (fat with inflammation) and/or fibrosis to advanced fibrosis and cirrhosis when fat may no longer be present. NASH is associated with obesity, type 2 diabetes, insulin resistance (IR), and hypertriglyceridemia. NAFLD is likely to become the most common cause of chronic liver disease (**Browning et al., 2004**).

NAFLD is a chronic liver disease that affects a high proportion of the world's population. Insulin resistance and oxidative stress play a critical role in the pathogenesis of NAFLD (**Diehl et al., 2005**).

Although much remains to be learned about pediatric NAFLD, it is already evident that children with NASH risk progressive liver damage, including cirrhosis. Clinical, biochemical and imaging studies are of value in the diagnostic evaluation of patients with NAFLD, but liver biopsy remains the most sensitive and specific means of providing important diagnostic and prognostic information. Insulin resistance and oxidative stress play a critical role in the pathogenesis (**Raman and Allard, 2006**).

No effective medical therapy is currently available for patients with NAFLD. Weight reduction, when achieved and sustained, may improve the liver disease. In patients with diabetes mellitus and hyperlipidemia, appropriate metabolic control is always recommended, but rarely effective in resolving the liver disease (**Clark et al., 2002**).

The aim of this study is to determine the prevalence of asymptomatic hepatic steatosis and presumed nonalcoholic steatohepatitis, in our local population of obese Egyptian children referred for medical assessment, and to assess the correlation between severity of ultrasonographic hepatic steatosis and degree of obesity, insulin resistance and serum biochemical abnormalities.

Nonalcoholic Steatohepatitis (NASH)

1-Definition and Historical Background

Definition:

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders characterized by macrovesicular steatosis that occur in the absence of consumption of harmful amounts of alcohol.

This spectrum ranges from:

- Simple steatosis (fat accumulation within liver cells).
- Steatosis with nonspecific inflammation.
- Steatohepatitis (fat accumulation and liver cell injury).
- Cirrhosis (fibrosis, scarring, and nodule formation).
- Hepatocellular carcinoma.

(Duseja et al., 2006).

History of discovery of NASH:

The association of macrovesicular steatosis of the liver with inflammatory changes and fibrosis in obese subjects has been known for several decades **(Zelman, 1958).**

However, it was largely ignored as a clinical entity until several reports documented the development of liver failure in some patients following surgical jejunoileal bypass for morbid obesity **(Catlin, 1963).**

The hepatic histology in such patients was indistinguishable from that seen in alcoholic hepatitis and included macrovesicular steatosis, Mallory bodies, ballooning degeneration, hepatocyte necrosis, and fibrosis **(Peters et al., 1975).**



Similar hepatic lesions subsequently were described in obese patients who had neither abused alcohol nor undergone weight-loss surgery and in diabetic individuals (**Adler & Schaffner, 1979**).

NASH was described twenty seven years ago, lesions of alcoholic steatohepatitis (ASH) were found in patients who had no history of regular alcohol consumption and did not suffer from other liver diseases (**Ludwig et al., 1980**).

Many names have been used synonymously with NASH including :

- Fatty liver hepatitis (**Adler & Schaffner, 1979**).
- Non-alcoholic steatonecrosis (**Baker, 1985**).
- Alcohol-like liver disease in non-alcoholics (**Scaffner & Thaler, 1986**).
- Non-alcoholic fatty hepatitis, steatonecrosis and diabetic hepatitis (**French et al., 1989**).
- Non-alcoholic fatty liver disease (**Bacon et al., 1994**).
- Metabolic syndrome steatohepatitis (MSSH) (**Dixon et al., 2002**).

2-Epidemiology of NAFLD

1-Incidence and prevalence:

The prevalence of NAFLD in the US population is estimated at 3% to 24%. Prevalence is higher for special populations particularly the obese and/or those with the metabolic syndrome characterized by type II diabetes mellitus, hypertension, and hypertriglyceridemia (**Clark, 2006**).

There have been several attempts to estimate the frequency of NAFLD in population-based studies. **Ruhl and Everhart (2003)** used the NHANES (National Health and Nutrition Examination Survey) database and estimated that as many as 2.8% of the general population have NAFLD, as based on increased serum aminotransferase activities and the absence of serologic markers of viral hepatitis.



2-Demographics:

Both steatosis and NASH have been reported worldwide and in all age groups, even in children. Although it was initially suggested that women were more frequently affected than men, more recent studies have demonstrated that men and women are probably equally affected. The true prevalence of non alcoholic fatty liver (NAFL) and NASH in the general population remains unknown, but despite limitations of published data, it is agreed that NAFLD is probably the most common form of liver disease (Sanyal, 2002).

3-Familial clustering of NAFLD:

The genesis of NAFLD is dependent on a complex interplay between host genetic factors and environmental insults. Familial clustering of insulin resistance and liver disease supports the postulate of a genetic predisposition to NAFLD (Abdelmalek et al., 2005).

3-Causes & Risk Factors Associated With NAFLD

The major causes of NAFLD, as recently published by Adams et al (2005) are:

1-Primary NAFLD:

Primary NAFLD is related to insulin resistance and thus frequently occurs as part of the metabolic syndrome–related conditions, such as obesity, type 2 diabetes, hypertriglyceridaemia, low high density lipoprotein (HDL) cholesterol, hypertension and insulin resistance. In most cases there is a combination of two or more of these factors, although insulin resistance and hyperinsulinaemia is the most consistent association.

