

# HEPATIC IMPAIRMENT IN TYPE 1 DIABETES MELLITUS

Thesis  
Submitted in partial fulfillment of MD  
Degree in Pediatrics

Investigator  
**Hanan Mina Fouad**  
(M.B.B.ch – M.S.)  
Cairo University

*Supervised by*

**Prof. Dr. Hanaa Mustafa El-Karaksy**  
Prof. of Pediatrics  
Faculty of Medicine-Cairo University

**Prof. Dr. Ghada Mohamed Anwar**  
Assistant Prof. of Pediatrics  
Faculty of Medicine – Cairo University

**Prof. Dr. Gamal El-Deen Esmat**  
Prof. of Tropical Medicine  
Faculty of Medicine – Cairo University

**Prof. Dr. Magda Abd El-Fattah Sabry**  
Head of Pediatrics Department  
National Hepatology & Tropical  
Medicine Research Institute

Pediatrics Department  
Faculty of Medicine  
Cairo University

2007

## *Acknowledgement*

*I would like to express my deepest gratitude to Prof. Dr. Hanaa Mustafa El-Karakasy, Prof. of Pediatrics, Faculty of Medicine, Cairo University for her instructive guidance, precious advices and kind supervision.*

*Endless thanks go to Prof. Dr. Ghada Mohamed Anwar, Assistant Prof. of Pediatrics, Faculty of Medicine, Cairo University for her continuous support and great help.*

*Also I would like to express my gratitude to Prof. Dr. Gamal El-Deen Esmat, Prof. of Tropical Medicine, Faculty of Medicine, Cairo University for his support and encouragement.*

*Special thanks go to Prof. Dr. Magda Abd El-Fattah Sabry, Head of Pediatrics Department, National Hepatology and Tropical Medicine Research Institute for her continuous encouragement.*

*Special thanks for Prof. Dr. Samah Mansour Assad for her patience in performing the ultrasonographic examination required for the children.*

*I would like also to extend my gratitude to all staff members of the hepatology and endocrinology units at Pediatric hospital for their great help that enable this work to be completed.*

*Very special thanks for my mother, husband and my two lovely daughters for their support.*

## *Abstract*

**Key words:** Children – type 1 diabetes mellitus - hepatic affection

The aim of this study was to determine the prevalence of hepatic impairment in children with type-1 diabetes and to investigate the underlying etiology. The study was carried out on 692 children with type-1 diabetes. Their mean age was  $9.65 \pm 4.2$ . They were 333 (48.1%) males and 359 (51.9%) females. Sixty (8.7%) children showed liver affection. Clinical hepatomegaly was present in 12 (1.7%) children, elevated ALT in 25 (3.6%) children, positive HCV in 25 (3.6%) children and abnormal hepatic ultrasound in 31 (4.5%) children.

## *Table of contents*

<b>Title</b>	<b>Page</b>
List of abbreviations	i
List of tables	iv
List of figures	v
Introduction and aim of the work	1
Diabetes mellitus	4
Viral hepatitis	25
Fatty liver diseases	46
Autoimmune hepatitis	66
Liver diseases & type 1 diabetes	87
Patients and Methods	95
Results	102
Discussion	123
Summary	136
Conclusion	138
Recommendations	139
References	142
Appendix (patients data)	
Arabic summary	

## *List of abbreviations*

A1C: glycosylated hemoglobin  
AAP: American Academy of Pediatrics  
ACE: angiotensin converting enzyme  
ADA: American Diabetes Association  
AFP: alpha-fetoprotein  
AGEs: Advanced glycation end products  
AIC: autoimmune cholangitis  
AIH: autoimmune hepatitis  
AIRE: autoimmune regulator gene  
ALP: alkaline phosphatase  
ALT: alanine aminotransferase  
AMA: antimitochondrial antibodies  
ANA: antinuclear antibody  
anti-ASGPR: asialoglycoprotein receptor  
anti-LC-1: anti-cytosol antibodies type 1  
APCs: antigen-presenting cells  
APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy  
Apo: apolipoprotein  
APS-1: autoimmune polyglandular syndrome type 1  
AST: aspartate aminotransferase  
BCG: bacillus Calmette Guerin  
BMI: body mass index  
CDC: Centers for Disease Control and Prevention  
CHB: chronic hepatitis B  
CMV: Cytomegalovirus  
Co: cut-off  
CRP: C-reactive protein  
CT: computed tomography  
CYPs: cytochrome P450  
DEMPU: Diabetes Endocrine Metabolic Pediatric Unit  
DKA: diabetic ketoacidosis  
DM: Diabetes Mellitus  
DNA: deoxyribonucleic acid  
EBV: Epstein-Barr Virus  
e.g.: for example  
ELISA: enzyme-linked immunosorbent assay  
FDA: Food and Drug Administration  
FFA = free fatty acids  
FPG: Fasting plasma glucose

GAD65: autoantibodies to glutamic acid decarboxylase  
GDM: Gestational Diabetes Mellitus  
GGT: Gamma glutamyl transpeptidase  
gm/kg: gram /kilogram body weight  
HAI: histological activity index  
HAV: hepatitis A virus  
HBc Ag: hepatitis B core antigen  
HBe Ab: hepatitis B e antibody  
HBe Ag: hepatitis B e antigen  
HBIG: hepatitis B virus immunoglobulin  
HBs Ab: hepatitis B surface antibody  
HBs Ag: hepatitis B surface antigen  
HBV: hepatitis B virus  
HCC: hepatocellular carcinoma  
HCV: hepatitis C virus  
HCV Abs: HCV antibodies  
HDL: high density lipoprotein  
HDV: hepatitis D virus  
HDV Ag: hepatitis D virus antigen  
HEV: hepatitis E virus  
HIV: human immunodeficiency virus  
HLA: human leukocyte antigen  
HSV: Herpes Simplex Virus  
IA-2 & IA-2  $\beta$ : autoantibodies to the tyrosine phosphatases  
IAAs: autoantibodies to insulin  
ICAs: islet cell autoantibodies  
i.e.: that is to say  
IFG: impaired fasting glucose  
IFN $\alpha$ : interferon alpha  
IGT: impaired glucose tolerance  
Ig A: immunoglobulin A  
Ig G: immunoglobulin G  
Ig M: immunoglobulin M  
IL: interleukin  
ISPAD: International society for pediatric and adolescents diabetes  
KICA: ketoisocaproic acid  
LDL: low density lipoprotein  
LKM: liver kidney microsomal antibodies  
mg/dl: milligram /deciliter  
MHC: major histocompatibility complex  
mmHg: millimeter mercury  
MMR: measles, mumps and rubella vaccine  
MODY: maturity onset diabetes of the young

MRI: magnetic resonance imaging  
n: number  
NAFLD: nonalcoholic fatty liver disease  
NASH: nonalcoholic steatohepatitis  
ng/mL: nanogram /milliliter  
OGTT: oral glucose tolerance test  
pANCA: perinuclear antineutrophil cytoplasmic antibodies  
PAS: periodic acid-Schiff  
PBC: primary biliary cirrhosis  
PC: prothrombin concentration  
PCR: polymerase chain reaction  
PEG IFN: pegylated interferon  
PNL: polymorph nuclear leucocytes  
PT: prothrombin time  
PSC: primary sclerosing cholangitis  
RIBA: recombinant immunoblot assay  
RNA: ribonucleic acid  
RT-PCR: reverse transcriptase- polymerase chain reaction  
S/Co: sample optical density / cut-off value  
SD: standard deviation  
SLA/LP: soluble liver antigen/liver-pancreas antibody  
SMA: smooth muscle antibodies  
SVR: sustained viral response  
Tc: technetium  
TGs: triglycerides  
TNF- $\alpha$ : tumor necrosis factor alpha  
t-RNA: transfer ribonucleic acid  
tTG: tissue transglutaminase  
UDCA = ursodeoxycholic acid  
UDP: uridine diphosphate  
UGTs: uridine diphosphate glucuronosyltransferases  
U/mL: unit/milliliter  
U.S.: United States  
VDR: vitamin D receptor  
VLDL = very low-density lipoproteins  
VZV: Varicella-Zoster Virus  
 $\mu$ g/min: microgram/minute  
+ve: positive

## *List of Tables*

Number	Title	Page
	Review	
Table I	Etiologic classification of Diabetes Mellitus	5
Table II	Criteria for the diagnosis of Diabetes	9
Table III	Plasma blood glucose and A1C goals for type-1 diabetes by age group	22
Table IV	Adverse Effects of Interferon and Ribavirin	44
Table V	Nomenclature of Macrovesicular Fatty Liver	47
Table VI	Conditions Associated With NAFLD	49
Table VII	Utility of Imaging Studies for the Diagnosis of Fatty Liver	61
Table VIII	Histological Findings in NAFLD (adults)	61
Table IX	Grading and Staging of NAFLD	62
Table X	Diagnostic Score for Autoimmune Hepatitis	76
Table XI	Clinical, Biochemical, Histologic, and Cholangiographic Criteria of Autoimmune Liver Diseases	77
	Results	
Table 1	Hepatic abnormalities in the 692 studied children	102
Table 2	Single & combined hepatic abnormalities among the studied group	103
Table 3	Results of hepatic ultrasonographic examination among the studied group	104
Table 4	Comparison between HCV Abs positive and negative diabetic children	105
Table 5	Comparison between risk factors for HCV in children with positive HCV Abs and the control group	107
Table 6	Symptoms of the studied group	108
Table 7	Weight for age & Height for age and body mass index percentiles of the 60 studied children	109

Table 8	Examination data of the 60 studied children	110
Table 9	Laboratory data of the 60 studied children	111
Table 10	Comparison between cases with normal and raised ALT	112
Table 11	Comparison between cases with negative and positive HCV Abs	116
Table 12	Relation between ALT levels & HCV RNA in HCV Abs positive children	117
Table 13	Comparison between cases with normal and abnormal hepatic ultrasonography	120

## *List of Figures*

<b>Number</b>	<b>Title</b>	<b>Page</b>
<i>Review</i>		
Figure I	Disorders of glycemia: etiologic types and stages	8
Figure II	Natural course of chronic hepatitis B	28
Figure III	Clinical sequelae of HCV	38
Figure IV	Patterns of hepatic steatosis	46
Figure V	A picture of NASH	47
Figure VI	The relationship between NAFLD and metabolic syndrome	48
Figure VII	The regulation of lipid metabolism in the adipocytes	51
Figure VIII	Fatty acids in the liver	52
Figure IX	Diagnostic algorithm for assessment of NAFLD	56
Figure X	A sonogram of Fatty liver	60
Figure XI	Autoantigen targets in autoimmune liver diseases are not tissue specific.	70
Figure XII	Autoantibodies play a diagnostic role in the discrimination of overlap syndromes (AIH-PBC)	78
<i>Results</i>		
Figure 1	Sex distribution in the studied group	102
Figure 2	Prevalence of HCV antibodies in the studied group	103
Figure 3	Relation between positive HCV Abs & hepatomegaly, elevated ALT and abnormal ultrasonography in the 692 studied children	105
Figure 4	Histological examination of liver biopsy of the case number (9) stained by hematoxylin and eosin	114
Figure 5	Histological examination of the same specimen by periodic acid-Schiff	114

stains (PAS)

Figure 6	Relation between ALT levels & HCV RNA in HCV Abs positive group	117
Figure 7	Comparison between cases with normal and abnormal hepatic ultrasound as regards duration of diabetes	119
Figure 8	Comparison between hepatic ultrasonography and lipid profile	119

## *INTRODUCTION*

Patients with underlying diabetes mellitus (DM) can present with abnormal liver chemistries, which can represent findings as benign as hepatic steatosis or as severe as cirrhosis of the liver (*Baig et al., 2001*).

Insulin-reversible hepatic glycogenosis is the most common cause of hepatomegaly and raised serum liver transaminase concentrations in children and adolescents with type 1 diabetes (*Munns et al., 2000*).

Hepatic glycogenosis can occur at any stage of type 1 DM and may even be one of its earliest manifestations. Since long-standing hyperglycaemia and overinsulinisation are metabolic pre-requisites for hepatic glycogen storage, liver glycogenosis should be expected to be not uncommon during the first phases of type 1 DM, especially in the cases who are initially treated with supraphysiological insulin doses (*Carcione et al., 2003*).

Epidemiologically there seems to be a correlation between DM, the most common endocrinologic disease, and hepatitis C infection (*Baig et al., 2001*). Chronic hepatitis C patients have specific host factors that can modulate their fibrogenic response. Obesity, because of its prevalence and diabetes, which seems to occur more frequently in patients infected by the hepatitis C virus (HCV), are often present in patients with chronic hepatitis C. Both conditions result in fatty liver, which in turn is associated with more severe liver damage, especially fibrosis or inflammation. Steatosis can originate either from associated metabolic

alterations or from a direct cytopathic effect of the virus (*Ratziu et al., 2004, B*).

Autoimmune polyglandular syndrome type-1 (APS-1) is caused by a single gene mutation in autoimmune regulator gene (AIRE). Its onset occurs in childhood with development of organ-specific autoantibodies and the evolution of multiple autoimmune manifestations including type 1 DM and hepatitis (*Obermayer-Straub and Manns, 1998*).

The term "nonalcoholic fatty liver disease" (NAFLD) is a clinicopathologic syndrome which includes a wide spectrum of liver injury ranging from simple steatosis to steatohepatitis, fibrosis and cirrhosis. Whereas simple steatosis without inflammation has a benign clinical course (which may not lead to progressive liver injury), nonalcoholic steatohepatitis (NASH) may progress to cirrhosis and liver-related death in 25% and 10% of patients respectively. Liver biopsy is required for definitive diagnosis (*Mehta et al., 2002; McCullough, 2002*). The progression from simple fatty liver to more severe forms of NAFLD (nonalcoholic steatohepatitis and cirrhosis) is much less clear but evidence suggests that oxidative stress may preferentially enhance proinflammatory cytokines, which leads to cellular adaptations and dysfunction followed by development of inflammation, necrosis and fibrosis (*Harrison and Di Bisceglie, 2003*).

Diabetes is a risk factor for the development of NASH. Most of the patients are clinically asymptomatic. This means, that a diagnosis of NASH is a diagnosis of exclusion. Viral induced, autoimmune, metabolic and toxic liver diseases have to be excluded (*Maier, 2002*).

## *AIM OF THE WORK*

The aim of the present work is to determine the prevalence of hepatic impairment in children and adolescents with type 1 diabetes mellitus and to investigate the underlying etiology whether infectious, autoimmune or metabolic (glycogenosis or fatty infiltration).

# *DIABETES MELLITUS (DM)*

## *Definition*

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. The basis of the abnormalities in carbohydrate, fat and protein metabolism in DM is deficient action of insulin on target tissues (*The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003*).

## *Epidemiology*

The prevalence of type 1 DM in Egypt is 0.13: 0.4% according to the International Diabetes Federation while the prevalence of type 2 DM is about 9% (*Elbache, 2003*).

Diabetes mellitus affects 1.7 out of 1,000 people under the age of 20 (*Caughron and Smith, 2002*).

In Latin America, the prevalence of type 1 diabetes among students was 0.042% and 0.125% among those aged 3-13 years and 13-20 years, respectively, with incidence rates around 6.5/100,000 children/year from 1985-1990 (*de Sereday et al., 2003*).

## *Classification*

Classification of diabetes according to American Diabetes Association (ADA) (2007) is shown in table I.