



Assessment of Growth and Nutritional Status in Children with Chronic Liver Diseases and Their Relation to Serum Level of Insulin-Like Growth Factor -I

Thesis submitted for the fulfillment of the Ph.D. degree
in Department of Medical Studies for Children
(Child Health and Nutrition)

By

Hany Fathy Ahmed Mohamed

M.Sc. (Cairo University)

Researcher Assistant, National Research centre

Supervised by

Dr. Ehab Mohamed Eid

Professor of Public Health

Medical Department

Institute of Postgraduate Childhood Studies

Ain shams University

Dr. Moushira Erfan Zaki

Professor of Human Genetics

Biological Anthropology Department

National Research Centre

Dr. Rokaya Mohamed El-Sayed

Professor of Pediatrics

Faculty of Medicine

Cairo University

Dr. Mona Anwar Mohamed

Professor of Medical Biochemistry

National Research Centre

Institute of Postgraduate Childhood Studies

Ain Shams University

2014

Acknowledgement

First and foremost, I thank Allah who have granted me the ability to accomplish this work.

I would like to express my profound gratitude and heavy thanks to **Dr. Ehab Mohamed Eid**, Professor of Public Health, Medical Department, Institute of Postgraduate Childhood Studies, Ain shams University for his generous supervision, valuable advice, and constant support throughout the whole work.

Words can never express my sincere appreciation to **Dr. Moushira Erfan Zaki**, Professor of Human Genetics, National Research Centre for her keen supervision, expert guidance, generous cooperation, great help. and precious time she offered me throughout the study.

I would like also to express my deepest thanks and gratitude to **Dr. Rokaya Mohamed El-Sayed Mohsen**, Professor of Pediatric Hepatology, Faculty of Medicine, Cairo University for her valuable guidance, constant advice, and great help throughout the whole work.

I am also extremely grateful to **Dr. Mona Anwar Mohamed**, Professor of Medical Biochemistry, National Research Centre for her great help, close supervision and meticulous laboratory work.

I would like also to express my sincere thanks and gratitude to **Dr. Muhammad Al-Tohamy Soliman**, Assistant professor of Biological Anthropology Department, National Research Centre for his kind supervision, generous advice and continuous help to put this work in the present form.

My deepest gratitude and thanks to the patients and their parents for their cooperation and participation in the study

I am also thankful to my family for their encouragement and support.

Contents

Title	Page
List of abbreviations	I
List of figures	II
List of tables	III
Introduction	1
Aim of the study	4
Review of literature <ul style="list-style-type: none">• Chapter (1): Chronic liver disease in children• Chapter (2): Growth & nutritional status in children with chronic liver disease• Chapter (3): Insulin like growth factor-1	5 30 56
Subjects and methods	69
Results	79
Discussion	97
Summary and conclusion	107
Recommendations	108
References	109
Arabic summary	129

List of abbreviations

AAA	Aromatic amino acids
AFI	Arm fat index
ALP	Alkaline phosphatase
ALS	Acid labile subunit
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AS	Alagille syndrome
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BCAAs	Branched chain amino acids
BP	Binding protein
Ca	Calcium
CF	Cystic fibrosis
CHF	Congenital hepatic fibrosis
CDC	Centers for Disease Control and Prevention
CIC	Conjunctival impression cytology
CLD	Chronic liver disease
CMV	Cytomegalovirus
DEXA	Dual-energy X ray absorptiometry
DNA	Double stranded nucleic acid
EBV	Epstein–Barr virus
ECM	Extracellular matrix

EEG	Electroencephalography
EFAs	Essential fatty acids
EHBA	Extrahepatic biliary atresia
ELISA	Enzyme-Linked Immuno-Sorbent Assay
FFAs	Free fatty acids
FIHC	Familial intrahepatic cholestasis
GGT	Gama glutamyltransferase
GH	Growth hormone
GHRH	Growth hormone releasing hormone
GSD	Glycogen storage disease
Hb	Haemoglobin
HBV	Hepatitis B virus
HC	Head circumference
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HPS	Hepatopulmonary syndrome
HRS	Hepatorenal syndrome
Ht	Height
IGF-1	Insulin-like growth factor -1
IGFBP	Insulin growth factor binding protein
IGF-IIR	Insulin-like growth factor –II receptor
IGFIR	Insulin-like growth factor -1 receptor
IL-6	Interleukin 6
IM	Intramuscular
INR	International normalized ratio

IQ	Intelligence Quotient
IV	Intravenous
LCTs	Long-chain triglycerides
M6P	Mannose-6-phosphate
MCT	Medium-chain triglyceride
mRNA	Messenger ribonucleic acid
MUAC	Mid upper arm circumference
MUAFA	Mid upper arm fat area
MUAMA	Mid upper arm muscle area
MUAMC	Mid upper arm muscle circumference
NH	Neonatal hepatitis
OH D	Hydroxy vitamin D
P	Phosphorus
PELD	Pediatric end-stage liver disease
PHD	Pediatric hepatology dependency
PIHBD	Paucity of intrahepatic bile duct
PIVKAI	Protein induced in vitamin K absence
PT	Prothrombin time
PTH	Parathyroid hormone
PTT	Partial thromboplastin time
PUFAs	Polyunsaturated fatty acids
RBP	Retinol-binding protein
RDA	Recommended daily allowance
RDR	Relative dose response
RhIGF-I	Recombinant human IGF-1

SBP	Spontaneous bacterial peritonitis
SD	Standard deviation
SDS	Standard deviation score
SFT	Skin-fold thickness
SPSS	Statistical package for social science
SSFT	Subscapular skinfold thickness
SST	Somatostatin
TIBC	Total iron-binding capacity
TIPS	Transjugular intrahepatic portosystemic shunt
TIPSS	Transjugular intrahepatic portosystemic stent shunt
TMB	Tetramethylbenzidine
TNF	Tumor necrosis factor
TPGS	Tocopherol polyethylene glycol-1000 succinate
TPN	Total parenteral nutrition
TSFT	Triceps skin-fold thickness
TUAA	Total upper arm area
WBCs	White blood cells
Wt	Weight
Wt/ht	Weight for height

List of figures

Figure	Title	Page
Figure (1):	Algorithm for the management of bleeding varices	25
Figure (2):	Amino acid sequence of insulin-like growth factor-I (IGF-I) and human insulin using a standard single letter code.	57
Figure (3):	Schematic illustration of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis.	64
Figure (4):	Weight measurement using an electronic digital scale	71
Figure (5):	Weight measurement using digital platform scale	71
Figure (6):	length measurement using an infantometer	72
Figure (7):	Height measurement using a standiometer	72
Figure (8):	Head circumference measurement	73
Figure (9):	Mid upper arm circumference measurement	73
Figure (10):	Holtain skin fold caliper	74
Figure (11):	Triceps skinfold thickness measurement using Skin fold caliper	75
Figure (12):	Subscapular skin fold thickness measurement using skin fold caliper	75
Figure (13):	Sex distribution in both patient and control groups.	79
Figure (14):	Mean age of both patient and control groups.	79
Figure (15):	Age groups distribution in patient group.	80
Figure (16):	Distribution of patients according to the presence or absence of cholestasis.	80
Figure (17):	Distribution of patients according to the Child Pugh score.	82
Figure (18):	Percentage of patients with anthropometric parameters z scores below -2SDS.	84
Figure (19):	Mean of IGF-1 level in patient and control groups.	90
Figure (20):	Mean of IGF-1 level in different Child Pugh classes.	91
Figure (21):	Mean of IGF-1 level in different etiological groups of CLD.	92
Figure (22):	Mean of 25 (OH) D level in different Child Pugh classes.	95

List of tables

Table	Title	Page
Table (1):	Etiology of chronic liver disease in children	6
Table (2):	Stages of encephalopathy	13
Table (3):	General Investigations of chronic liver disease in children	19
Table (4):	Diagnostic tests in chronic liver disease and cirrhosis	20
Table (5):	Objective signs of specific nutritional deficits	44
Table (6):	Modified Child-Pugh score	77
Table (7):	Frequency (n & %) of cases in different etiological groups of CLD	81
Table (8):	Frequency (n & %) of cases with different degree of liver disease severity (assessed by Child Pugh score) in the etiological groups of CLD	82
Table (9):	Age groups distribution in different etiological groups of CLD	83
Table (10):	Frequency (n & %) of patients with anthropometric parameters z score below -2SDS	84
Table (11):	Z score of anthropometric parameters	85
Table (12):	Comparison of means of anthropometric parameters z scores between Child Pugh classes	86
Table (13):	Comparison of means of anthropometric parameters z scores between etiological groups of CLD	87
Table (14):	Comparison of means of anthropometric parameters z scores between patients aged <2 years old and those aged ≥ 2 years old	88
Table (15):	Comparison of means of anthropometric parameters z scores between cholestatic and non cholestatic group	88
Table (16):	Correlation between anthropometric parameters z scores and (serum albumin, total and direct bilirubin, PT, and INR)	89
Table (17):	Correlation between anthropometric parameters z scores and ALT, AST, ALP, and GGT levels	90
Table (18):	Comparison of means of IGF-1 level between patient and control groups	90
Table (19):	Comparison of means of IGF-1 level between Child Pugh classes	91
Table (20):	Correlation between IGF-1 level and Liver function tests (serum albumin, total bilirubin, direct bilirubin, PT, INR, AST, ALT, ALP and GGT)	92
Table (21):	Comparison of means of IGF-1 level between etiological groups of CLD	92
Table (22):	Correlation between anthropometric parameters z scores and serum IGF-1	93
Table (23):	Comparison of means of IGF-1 level between patients with anthropometric parameters z scores above and below -2SDS	94
Table (24):	Comparison of means of 25 (OH) level between patient and control groups	94
Table (25):	Comparison of means of 25 (OH) D level between Child Pugh classes	95
Table (26):	Comparison of laboratory data between patient and control groups	96

Abstract

Introduction: Malnutrition and growth retardation are important consequences of CLD in childhood. They are associated with frequent complications, hospitalization, poor outcome after liver transplantation, and ultimately death.

Objectives: To evaluate growth and nutritional status of children with CLD and to determine the level of IGF-1 in these patients and to identify the relation between its level to both the degree of malnutrition and the degree of hepatic dysfunction.

Methodology: Fifty children with CLD, recruited from the outpatient clinic of pediatric hepatology and from the pediatric hepatology department of Pediatric Hospital, Cairo University, were enrolled in the present study. Their mean age was 2.05 years (ranged from 0.5 to 5.75 years). Laboratory results were compared with an age and sex-matched children (control group). Anthropometric assessment, measurement of liver function and serum level of IGF-1 were performed. Assessment of severity of liver disease was done using the modified Child-Pugh score. **Results:**

Short stature was identified in 54% of patients, while malnutrition was identified in 70% of patients by TUAA, 62% by MUAC, 56% by TSFT, 56% by SSFT, 52% by MUAFA, 46% by MUAMA, 42% by Wt, 30% by Wt/Ht, and 22% by AFI. Moreover, MUAC was the most affected anthropometric parameter followed by TUAA, TSFT, MUAFA, Wt, MUAMA, SSFT, AFI, Wt/Ht respectively. Regarding serum IGF-1 level, it was significantly lower in patients compared to controls, and was significantly lower in Child Pugh C compared to Child Pugh B and A, and it was significantly lower in Child Pugh B compared to Child Pugh A. Moreover, there was no significant correlation between any of the anthropometric parameters and serum IGF-1. **Conclusion:** Growth retardation and malnutrition are common complications in children with CLD. Moreover, TUAA, MUAC and TSFT represent the best anthropometric parameters that can identify malnutrition in these patients. It was also concluded that in CLD, IGF-I level is affected by the degree of liver dysfunction rather than the degree of malnutrition.

Key words: Growth - Nutritional Status - Children - Chronic Liver Disease - IGF-1.



INTRODUCTION



Introduction

Chronic liver disease (CLD) is a disease process of the liver that involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis. CLD in children are the result of many different diseases including: metabolic, genetic, infectious, toxic and idiopathic causes **(Shepherd, 2008)**.

Malnutrition is an increasingly recognized complication of CLD that has important prognostic implications. Malnourished patients with CLD have a higher rate of complications and, overall, an increased mortality rate. Furthermore, patients who are severely malnourished before transplant surgery have a higher rate of complications and a decreased overall survival rate after liver transplantation **(Alberino et al., 2001; McDiarmid et al., 2002; Tajika et al., 2002; Henkel & Buchman, 2006; Gundling et al., 2007; Tsiaousi et al., 2008)**.

The pathogenesis of malnutrition in CLD is multifactorial and includes a reduction in nutrient and caloric intake, anorexia and dietary restrictions, impaired intestinal absorption, abnormalities in nutrient metabolism (carbohydrate, lipid, and protein), and increased proinflammatory cytokine levels, resulting in a hypermetabolic state **(Sanchez & Aranda-Michel, 2006; Hurtado-López et al., 2007; Nightingale & Ng, 2009; Merli et al., 2010)**.

In view of high prevalence and increased complications resulting from malnutrition it is important to assess the nutritional status and initiate timely intervention in patient suffering from CLD (**Henkel & Buchman, 2006; Pop & Miu, 2010**).

Techniques of assessment of nutritional status such as body weight and weight adjusted for height may not be accurate in patients with liver disease, because of fluid retention manifested by ascites and edema masking the underlying loss of bulk in crucial body compartments. Thus, assessment of malnutrition is best performed using other parameters particularly those less affected by fluid retention, such as triceps skinfold thickness “TSSF” and mid upper arm circumference “MUAC” (**Ramaccioni et al., 2000; Pop & Miu, 2010**).

Insulin-like growth factor-I (IGF-I) is a polypeptide hormone synthesized mainly in the liver and functions as the major mediator of growth hormone (GH)-stimulated somatic growth, as well as a mediator of GH-independent anabolic responses in many cells and tissues. IGF-1 has numerous growth-promoting effects, including mitogenic effects and the promotion of cartilage sulphation (**Bonefeld & Møller, 2011; Clemmons, 2012; Puche & Castilla-Cortázar, 2012**).

The nutritional status has a great influence on IGF-I. Both the energy and protein content of the diet are important in the maintenance of IGF-1. Restriction of dietary nutrients adversely affects IGF-1 synthesis and action by decreasing the number of GH receptors, causing post receptor defects and decreasing the levels of IGF-1 mRNA (**Livingstone, 2013**).

Although IGF is a marker of protein metabolism, that can be used to assess malnutrition. However, in CLD, with impaired IGF synthesis, its use may lead to an exaggeration of the degree of malnutrition (Stephenson et al., 2001; Taylor & Dhawan, 2005; Socha, 2008). Moreover, Colakoğlu et al., 2007; Dehghani et al., 2012; Khoshnood et al., 2013 and Ronsoni et al., 2013 reported a decrease of IGF level in patients with CLD, and they found that its level was correlating to the extent of hepatic dysfunction rather than the degree of malnutrition. The IGF-I deficiency in CLD is thought to result primarily from the reduced synthetic capacity of the hepatocellular mass, combined with a decrease in GH receptors in the cirrhotic liver (Donaghy et al., 2002).



AIM OF THE STUDY

