

Antioxidants in Chronic Pediatric Liver Diseases

Submitted for Partial Fulfillment of
The Requirements of the
Master Degree in
Pediatrics.



By

Usama Beshara Morid

M.B., Bch

Faculty of Medicine

Alex. University

618-923623
u. B.

Supervisors

Dr. Zenab Anwar El Kabbany

Assistant Professor of Pediatrics

Faculty of Medicine

Ain Shams University

رسالة
2012/10

Dr. Eman Ahmed Zaki

Assistant Professor of Pediatrics

Faculty of Medicine

Ain Shams University

Dr. Amina Mohamed El gharieb

Lecturer of Biochemistry

Faculty of Medicine

Ain Shams University

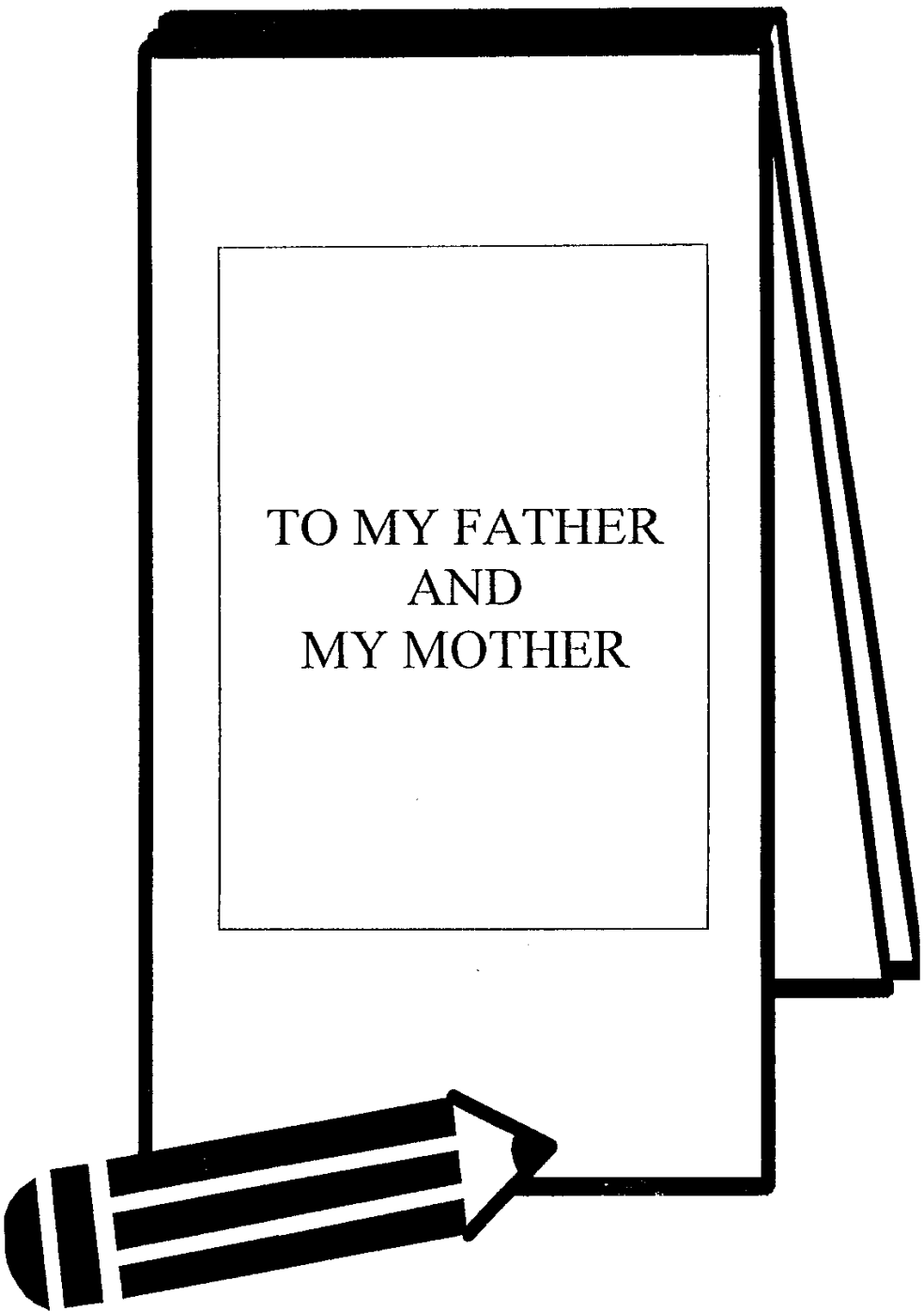


Faculty of Medicine

Ain Shams University

1999





ACKNOWLEDGMENTS

First and foremost, I thank my **GOD** who is my strength and my shield.

It is a great honor to me to express my sincere gratitude to **Dr. Zenab Anwar El Kabbany**, Assistant professor of pediatrics, Faculty of Medicine, Ain Shams University, for his masterly teaching, valuable advice, kind supervision and continuous encouragement throughout the work.

I am particularly indebted to **Dr. Eman Ahmed Zaki**, Assistant professor of pediatrics, Faculty of Medicine, Ain Shams University, for her meticulous supervision, continuous support, honest assistance and unlimited help throughout the whole work.

I wish to express my gratitude to **Dr. Amina Mohamed Elgharieb**, Lecture of Biochemistry, Faculty of Medicine, Ain Shams University, for her kind and active participation in the laboratory part of the work.

I wish to thank the patients and their parents for being cooperative during our study, and I wish them all best of health.

Also, I would like to thank my family without whom this thesis would never have been seen light.

Lastly, sincere appreciation is extended to every body who has shared in a way or another in the performance of this work.

LISTS

		Page
List (1)	Disorders producing chronic liver disease....	2
List (2)	Causes of cholestasis.....	22
List (3)	Etiology of chronic hepatitis.....	42

LIST OF TABLES

	Page
Table (1) : Hepatic involvement in glycogen storage diseases.....	20
Table (2) : Endogenous and Exogenous antioxidants.....	100
Table (3) : Synthetic antioxidants and scavengers.....	101
Table (4) : Statistical comparison between our cases and controls as regards age distribution.....	131
Table (5) : Statistical comparison between cases and controls as regards sex distribution.....	131
Table (6) : Incidence of different presenting symptoms recorded among our cases.....	132
Table (7) : Ultrasonographic findings in our studied patients with chronic liver diseases.....	134
Table (8) : Needle liver biopsy findings encountered in studied cases with chronic liver diseases.....	135
Table (9) : Etiological classification of our studied cases with chronic liver diseases.....	136
Table (10) : Statistical comparison between cases before treatment and controls (group II) as regards serum liver enzymes.....	136
Table (11) : Statistical comparison between group Ia and controls as regards plasma level of enzymatic antioxidants.....	138
Table (12) : Statistical comparison between group Ia and controls as regards MDA.....	138

Table (13) :	Comparison between group Ia and group Ib as regards hepatic transaminases.....	140
Table (14) :	Statistical comparison between group Ia and group Ib as regards enzymatic antioxidants.....	141
Table (15) :	Statistical comparison between group Ia and group Ib as regards MDA.....	143
Table (16) :	Statistical comparison between group Ib and group II as regards hepatic transaminases.....	143
Table (17) :	Statistical comparison between group Ib and group II as regards enzymatic antioxidants.....	145
Table (18) :	Statistical comparison between group Ib and group II as regards MDA.....	145

LIST OF FIGURES

	Page
Figure (1) : Metabolic pathways involved in glycogen synthesis.....	7
Figure (2) : Causes of neonatal cholestasis.....	26
Figure (3) : Hepatic portoenterostomy for an extrahepatic biliary atresia involving the main right and left hepatic ducts and the common bile duct (Type 3).....	32
Figure (4) : Diagrammatic representation of surgically correctable extrahepatic biliary atresia (Type 1).....	33
Figure (5) : The effect of exposure to hepatitis B virus.....	44
Figure (6) : T-lymphocyte lysis of infected hepatocytes and mechanisms of failure of lysis in chronic hepatitis.....	47
Figure (7) : Phases of hepatitis B-infection.....	50
Figure (8) : Structure of HCV genome.....	55
Figure (9) : The metabolism of molecular oxygen.....	61
Figure (10) : Scheme of the L-arginine / NO ⁻ pathway.....	66
Figure (11) : Formation of oxygen radical in the hypoxanthine - xanthine oxidase system.....	69
Figure (12) : Hypoxia - Reoxygenation injury.....	70
Figure (13) : Cytochrome oxidase system.....	72
Figure (14) : Pathway for lipid peroxidation induced by oxygen and other radicals.....	77
Figure (15) : Initiation and propagation of lipid peroxidation.....	78
Figure (16) : The reaction sequence for peroxidation of polyunsaturated fatty acids (PUFAS) in cell membrane.....	79

Figure (17) :	DNA damage by free radicals.....	81
Figure (18) :	The action of antioxidant enzymes.....	88
Figure (19) :	Antioxidant enzymatic pathways for reduction of superoxide to water.....	89
Figure (20) :	Generation of pro-oxidants and enzymatic detoxification of hydrogen peroxide (H ₂ O ₂).....	90
Figure (21) :	Cytochrome oxidase system and enzymatic antioxidants.....	91
Figure (22) :	The chain breaking action of vitamin E that terminates lipid peroxidation in cell membrane.....	96
Figure (23) :	Mechanisms of hepatocyte necrosis by toxic bile salts.....	114
Figure (24) :	Frequency of different presenting symptoms recorded among cases.....	134
Figure (25) :	Comparison between group Ia and controls as regards serum liver enzymes.....	137
Figure (26) :	Statistical comparison between group Ia and controls as regards MDA.....	139
Figure (27) :	Comparison between cases before and after treatment as regards GSH reductase.....	142
Figure (28) :	Statistical comparison between group Ia and controls as regards hepatic transaminases.....	144
Figure (29) :	Statistical comparison between group Ia and controls as regards MDA.....	146

LIST OF ABBREVIATION

SOD	Superoxide dismutase
GSH	Reduced glutathione
GSD	Glycogen storage disease
EHBA	Extrahepatic biliary atresia
I.V.C	Inferior vena cava
SLE	Systemic lupus erythematosus
DIC	Disseminating intravascular coagulopathy
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBc-antibody	Hepatitis B core antibody
HLA	Human leukocytic antigen
Ts	T suppressor cell
Tc	T cytotoxic cell
HCV	Hepatitis C virus
RIBA	Radio immune blot assay
PCR	Polymerase chain reaction
IFN	Interferon
GGT	Gamma glutamyl transferase
DNA	Deoxy ribonucleic acid
RNA	Ribonucleic acid
m-RNA	Messenger - ribonucleic acid
ALT	Alanine transaminase
AST	Aspartate transaminase
NS	Non Structure protein
Fig.	Figure
O₂	Oxygen
$\dot{O}_2$ or $O_2^{\cdot}$	Superoxide radical
H₂O₂	Hydrogen peroxide
CT	Computed tomography
OH$\cdot$	Hydroxyl radical
H₂O	Water
e$'$	Electron
Fe⁺⁺	Ferrous ion
Fe⁺⁺⁺	Ferric ion

NO[•]	Nitric oxide radical
ONOO⁻	Peroxynitrite
HOCl	Hypochlorous acid
Cl⁻	Chloride ion
H⁺	Hydrogen ion
EDRF	Endothelium derived relaxing factor
GTP	Guanosine tri-phosphate
cGMP	Cyclic guanosine monophosphate
ATP	Adenosine tri-phosphate
AMP	Adenosine mono-phosphate
IMP	Inosine mono-phosphate
CSF	Cerebrospinal fluid
Ca⁺²	Calcium ion
NOS	Nitric oxide synthetase
Hx	Hypoxanthine
EAA	Excitatory amino acids
XDH	Xanthine dehydrogenase
XO	Xanthine oxidase
Cu	Copper
-C[•]-	Carbon centered radical
-C(O₂)[•]-	Peroxyl radical
-C(H₂O)[•]-	Lipid hydroperoxides
PUFA	Polyunsaturated fatty acid
MDA	Malondialdehyde
HIV	Human immune deficiency virus
Zn	Zinc
Mg	Magnesium
GSH-PX	Glutathione peroxidase
Se	Selenium
GSSG	Oxidised glutathione
TH	Tochopherol (Vitamin E)
T[•]	Tochopherol radical
BPD	Bronchopulmonary dysplasia
LD	Lactic dehydrogenase
GCDC	Glycochenodeoxycholic acid