

Acknowledgement

Thanks to Allah, the most merciful and most compassionate, for completing this work.

I am delighted to express my thanks and appreciation to Prof. Dr. Laila El Sayed Ziada, Professor of Hematology, Medical Research Institute, University of Alexandria for her precious guidance, wise instruction, continuous constructive advice, close supervision and sincere help during the progress of my work. It is a great honor for me to work under her supervision.

My deepest thanks and gratitude are to Prof. Dr. Nadia Ali Sadek, Professor of Hematology, Medical Research Institute, University of Alexandria whose valuable suggestions, meticulous supervision, patience and encouragement helped me all through the steps of this thesis. Actually, I find no words of appreciation for the time she spent and her tremendous effort until the delivery of this study.

I am also grateful to Dr. Maher Abdel Naby Kamel, Assistant Professor of biochemistry, Medical Research Institute, University of Alexandria who gave me much of his effort and experience . His generous assistance and meticulous laboratory work had a pivotal role in the completion of this study.

I am deeply indebted to Dr .Ola Ali Balbaa, Fellow of Hematology, Medical Research Institute, University of Alexandria for her constant support, motivation and guidance all through the steps of the study.

I am also grateful to Dr. Gihan Nabil Mohamed, Lecturer of Hematology, Medical Research Institute, University of Alexandria for her help and support from the start of the work.

Last but not least, i would like to express my deepest thanks to my family for their continuous guidance and encouragement.

My great appreciation is extended to all those who shared either practically or morally in the accomplishment of this work.

Table of contents

Chapter	Page
Acknowledgment	I
List of contents	ii
List of tables	iii
List of figures	v.
List of abbreviations	viii.
1.Introduction <ul style="list-style-type: none">• Pathophysiology of β –thalassemia• Body iron pathways• Oxidative stress in βThalassemia• Haptoglobin• Clinical complications in repeatedly transfused βTM	1. 8. 14. 18. 24.
2.Aim of work	27.
3.Subjects	28.
4.Methods	29.
5.Results	37.
6.Discussion	81.
7.Summary	89.
8.Conclusions	92.
Recommendations	93.
9.References	94.
Protocol	
Arabic summary	

List of Tables

Table NO		Page
1.	Comparison between the two studied groups according to demographic data.	38
2.	Comparison between the two studied groups according to anthropometrics.	39
3.	Distribution of studied cases according to clinical findings	42
4.	Comparison between the two studied groups according to CBC.	44
5.	Comparison between the two studied groups according to ABO blood group and Coombs' test.	50
6.	Comparison between the studied groups according to Hb Electrophoresis.	51
7.	Comparison between the two studied groups according to iron profile.	54
8.	Serum ferritin levels in thalassemic patients.	57
9.	Comparison between the two studied groups according to laboratory profile.	59
10.	Comparison between the two studied groups according to haptoglobin Polymorphism.	62
11.	Correlation between haptoglobin genotype with iron profile.	64
12.	Correlation between haptoglobin genotype with serum MDA and Serum Haptoglobin in thalassemic group.	65
13.	Correlation between haptoglobin Polymorphism with hepatitis C.	68
14.	Correlation between Coombs' test with Retic count and serum haptoglobin in thalassemic group.	69
15.	Relation between splenectomy with demographic data.	71

16.	Relation between splenectomy with ABO Blood groups, Coombs' test and Hepatitis C.	72
17.	Relation between splenectomy with CBC.	74
18.	Relation between splenectomy with iron profile.	75
19.	Relation between splenectomy with laboratory profile.	76
20.	Relation between splenectomy with haptoglobin polymorphism.	77
21.	Correlation between NLR with CRP and ALT in cases group.	78
22.	Correlation between CRP and Serum ferritin in cases group	80

List of Figures

Figure NO		Page
1.	Pathophysiology of b-thalassemia	2
2.	Factors that modify the β thalassaemia phenotype	7
3.	Body iron pathways	8
4.	Cells regulating body iron homeostasis	10
5.	Signal pathways in systemic regulation of hepcidin	12
6.	Hepcidin regulation by erythroid -iron and hypoxia related signals.	14
7.	The oxidant/antioxidant balance	15
8.	Reactions associated with the generation of reactive oxygen species	16
9.	The role of free-iron species in generation of oxidative stress	17
10.	differences between Hp phenotypes	19
11.	Typical electrophoretic patterns of Hp phenotypes	19
12.	Schematic representation of the organization of the Hp gene	20
13.	ID-Card "LISS/Coombs	30
14.	Grading of Reactions	31
15.	Stander curve of MDA	33
16.	Partial structure of haptoglobin alleles Hp 1 and Hp 2.	35
17.	Agarose gel electrophoresis of genotyping of Haptoglobin polymorphism	35
18.	Comparison between the two studied groups according to weight .	40
19.	Comparison between the two studied groups according to height .	40
20.	Comparison between the two studied groups according to BMI .	41

21.	Distribution of studied cases according to clinical findings.	42
22.	Comparison between the two studied groups according to Hb.	45
23.	Comparison between the two studied groups according to PCV	45
24.	Comparison between the two studied groups according to MCV.	46
25.	Comparison between the two studied groups according to MCH.	46
26.	Comparison between the two studied groups according to RBCS.	47
27.	Comparison between the two studied groups according to retic count.	47
28.	Comparison between the two studied groups according to Platelets.	48
29.	Blood film showing red blood cells morphology in thalassemia.	49
30.	Comparison between the studied groups according to Hb electrophoresis	52
31.	Comparison between the studied groups according to Hb electrophoresis	52
32.	Comparison between the two studied groups according to serum iron.	55
33.	Comparison between the two studied groups according to TIBC.	55
34.	Comparison between the two studied groups according to TS .	56
35.	Comparison between the two studied groups according to serum ferritin.	56
36.	Comparison between the two studied groups according to CRP.	60
37.	Comparison between the two studied groups according to ALT.	60

38.	Comparison between the two studied groups according to serum haptoglobin .	61
39.	Comparison between the two studied groups according to serum MDA.	61
40.	Comparison between the two studied groups according to haptoglobin.	63
41.	Comparison between the two studied groups according to allele frequency.	63
42.	Correlation between haptoglobin genotype with serum MDA in thalassemic group	66
43.	Correlation between haptoglobin genotype with serum haptoglobin in thalassemic group	67
44.	Correlation between Coombs' tests with retic count in thalassemic group.	70
45.	Correlation between Coombs' tests with serum haptoglobin in thalassemic group	70
46.	Correlation between NLR with CRP in cases group.	78
47.	Correlation between NLR with ALT in cases group.	79
48.	Correlation between CRP and serum ferritin in cases group.	80

List of abbreviations

A	Alpha
ALT	Alanine Transaminase
β	Beta
BMPs	Bone morphogenetic proteins
β TM	Beta -Thalassemia Major
C	Cytosine
Ca ²	Calcium
CBC	Complete Blood Count
CD	Cluster of Designation
CKII	Casein Kinase II
CO	Carbon monoxide
COL1A1	Collagen Type 1a 1 gene
CRP	C-reactive protein
C282Y	Cys282Tyr
Dcyt-b	Duodenal cytochrome b
DFO	Desferrioxamine
DFP	Deferiprone
DFX	Deferasirox
DMT1	Divalent Metal Transporter 1
DNA	Deoxyribonucleic Acid
EDTA	Ethylenediamine tetra acetic acid
EPO	Erythropoietin
Fe	Iron
Fe+2	Ferrous Iron

Fe ⁺³	Ferric Iron
FLVCR	Feline leukemia virus subgroup C receptor
γ	Gama
GDF-15	Growth Differentiation Factor -15
GSH	Reduced Thiol Glutathione
GPI linked protein	Glycosylphosphatidylinositol
H63D	His63Asp
H ₂ O ₂	Hydrogen Peroxide
Hb	Hemoglobin
HbE	Hemoglobin E
Hb F	Fetal Hemoglobin
HCl	Hydrochloric acid
HClO	Hypochlorous acid
HCV	Hepatitis C Virus
HepG2	Human hepatocellular liver carcinoma cell line
HFE	Hemochromatosis gene
HIFs	Hypoxia Inducible transcription factors
HJV	Hemojuvelin gene
HLA-DR	Human Leukocyte Antigen –DR
Hp	Haptoglobin
Hp0	Anhaptoglobinemia
Hpr	Haptoglobin-related Protein
ICAM-1	Inter -Cellular Adhesion Molecule-1
IFN-γ	Interferon Gamma
Ig	Immunoglobulin
IGF-1	Insulin-like Growth Factor-1

IL-6	Interleukin-6
Jak2	Janus kinase 2
Kb	Kilo base
KDa	Kilo Dalton
LCR	Locus control regions
LPI	Labile Plasma Iron
LIP	Labile iron pool
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDA	Malondialdehyde
mRNA	Messenger Ribonucleic Acid
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NLR	Neutrophil to Lymphocyte ratio
NTBI	Non-Transferrin-bound Iron
O ₂ •-	Superoxide Ion Radical
1O ₂	Single Oxygen
OH•	Hydroxyl Radical
O ₃	Ozone
PCV	Packed cell Volume
PCFT/HCP1	Proton-coupled folate transporter/heme carrier protein 1
Plts	Platelets
RBCs	Red Blood Cells
Retic	Reticulocytes
RO•	Alkoxyl Radicals
ROO•	Peroxyl Radicals

ROS	Reactive Oxygen Species
SDS	Sodium dodecylsulphate
SOD	Superoxide Dismutase
STAT 3	Signal transducer and activator of transcription 3
T	Thymine
TA	Thymine, Adenine
TBA	Thiobarbituric acid
TCA	Trichloroacetic acid
TF	Transferrin
TfR	Transferrin Receptors
TFR	Transferrin receptor gene
TGF- β	Transforming Growth Factor $-\beta$
Th	T helper lymphocyte
TIBC	Total Iron Binding Capacity
TLF	Trypanosome Lytic Factor
TMP	Tetramethoxy propane
TNF	Tumor-necrosis factor
TGF- β	transforming growth factor beta
TRPC	Transient Receptor Potential Canonical protein
TWSG1	Twisted Gastrulation 1
UGTIA	Uridine diphosphate-glucoronyl transferase IA
VDR	Vitamin D Receptor

obeykandl.com