PATTERN OF TRANSAMINASES AND FERRITIN IN PATIENTS WITH B-THALASSEMIA IN HAEMATOLOGY CLINIC: SINGLE CENTER EXPERIENCE

Thesis

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بسم الله الرحمن الرحيم
وَأَنْزَلَ اللهُ عَلَيْكَ
الْكِتَابَ وَالْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ وَكَانَ
فَضْلُ اللهِ عَلَيْكَ
عَظِيمًا
صدق الله العظيم
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LIST OF CONTENTS

Title **Page No.**

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbrev.	Full Term
Alb	: Albumin
ALP	: Alkaline phosphatase
ALT	: Alanine amino transferase
ARFP	: Alternate Reading Frame Protein
ARMS	: Amplification Refractory Mutation System
AST	: Aspartate aminotransferase
Ccc	: Covalently closed circular
CD	: Cluster of differentiation
DFO	: Desferrioxamine
DFP	: Deferiprone
DNA	: Deoxyribonucleic acid
dsDNA	: Double stranded DNA
EASL	: European Association of the Study of Liver
EMH	: Extramedullary hematopoiesis
ER	: Endoplasmic reticulum
Fpn	: Ferroportin
GIT	: Gastrointestinal tract
H	: Heavy
Hb	: Hemoglobin
HBeAg	: Hepatitis B Virus e antigen
HBsAg	: Hepatitis B surface antigen

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full Term
HBV	: Hepatitis B virus
HBx	: Hepatitis B virus X protein
HCC	: Hepatocellular carcinoma
HCV	: Hepatitis C virus
HDV	: Hepatitis D virus
HIC	: Hepatic iron content
HIV	: Human immunodeficiency virus
ICL 670	: Deferasirox
IQR	: Inter quartile range
IRES	: Internal ribosome entry site
Kb	: Kilobases
L	: light
LDL	: Low density lipoprotein
LFT	: Liver function test
LIC	: Liver iron concentration
LVDd	: Left ventricular end-diastolic dimension
MRI	: Magnetic resonance imaging
mRNA	: Messenger RNA
NS	: Non-structural protein
OPSI	: Overwhelming postsplenectomy infection

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full Term
PCR	: Polymerase-chain-reaction
POL	: Polymerase
PT	: Prothrombin time
RER	: Rough endoplasmic reticulum
RNA	: Ribonucleic acid
SQUID-BLS	: Super-conducting Quantum Interference Device Biomagnetic Liver Susceptometry
TB	: Total bilirubin
TIF	: Thalassemia International Federation
TP	: Total protein
ULN	: Upper limit of normal
US	: United States
UTR	: Untranslated region
β-TI	: β thalassemia intermedia
β-TM	: β-thalassemia major
γGT	: Gamma-glutamyl transpeptidase

INTRODUCTION

β-Thalassemia is the most common congenital hemolytic anemia due to partial or complete lack of synthesis of β-globin chains ***(Gardenghi et al., 2007).***

Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. Iron overload occurs very rapidly in patients who are on chronic transfusion programs ***(Vichinsky et al., 2009).***

There is a particularly high incidence of thalassemia in the Mediterranean basin (2.5%-25%) ***(Giardina et al., 2011).***

Worldwide, from 0.3% to 5.7% of thalassemia patients are hepatitis B surface antigen (HBsAg)–positive and from 4.4% to 85.4% are positive for anti-hepatitis C antibodies. HBsAg and anti-HCV tests are recommended in thalassemia patients with elevated serum aminotransferase levels (ALT, AST) for more than 6 months ***(DiMarco et al., 2010).***

Hemochromatosis is frequently observed in β-Thalassemia major (β- TM) due to an increased rate of iron absorption by the gastrointestinal tract (GIT) and frequent blood transfusions. Excess iron is extremely toxic to all cells of the body and can cause serious and irreversible organic damage such as cirrhosis ***(Estevao et al., 2011).***

Iron chelators are needed for treatment of iron overload. Due to their complications and the route of administration, many patients are noncompliant therefore fail to achieve adequate iron chelation ***(Won et al., 2010).***

Serum ferritin has been found to correlate with body iron stores ***(Galanello et al., 2010).***

AIM OF THE WORK

To assess the pattern of aminotransferases and ferritin and causes of liver dysfunction among patients with β-thalassemia between 2005-2010.

INTRODUCTION TO THALASSEMIA

The word thalassemia comes from the Greek "thalassa", sea referring to the Mediterranean and "haema", blood which means blood disease of the sea. The first description of severe thalassemia as a unique disorder was described in 1925 by a Detroit pediatrician "Thomas Cooley" who described a severe type of anemia in children of Italian origin ***(Rasheed et al., 2009).***

Thalassemias are inherited disorders of hemoglobin (Hb) synthesis that result from an alteration in the rate of globin chain production. A decrease in the rate of production of a certain globin chain or chains (α, β, γ, δ) impedes Hb synthesis and creates an imbalance with the other, normally produced globin chains ***(El-Dakhakhny et al., 2011).***

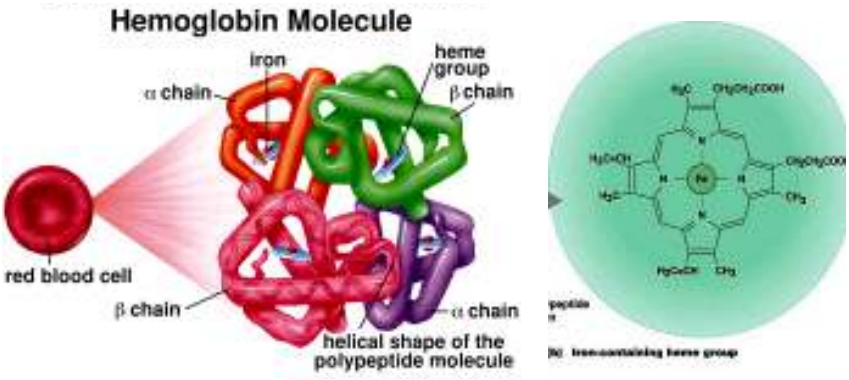

Figure (1): Hemoglobin Molecule with Globin Chains ***(Ghodekar, 2010; Gupta et al., 2011).***

Genetics of β –thalassemia:

The deficiency or absence of β-chains that characterize β -thalassemia could potentially result from defects affecting transcription, ribonucleic acid (RNA) processing or RNA translation, or modifying codons into "nonsense" codons that lead to premature termination of translation. Thalassemia mutations which cause a complete absence of production of normal β-globin chains are called β°-thalassemia and those which cause reduced synthesis are known as β^{+}-thalassemia. The average survival of untreated patients of thalassemia major is <1 year and more than 80% die in first five years of life ***(Porecha et al., 2010).***

More than 200 β thalassemia alleles have been characterized; population studies indicate that about 40 accounts for 90% or more of the β thalassemias worldwide. This is because in the areas in which it is prevalent, only a few mutations are common, with a varying number of rare ones, and each of these populations has its own spectrum of β thalassemia alleles ***(Thein, 2005).***

To date, more than 1000 inherited mutations that affect either the structure or synthesis of the α- and β-globin chains are known. Mutations that result in β or α thalassemia are similar in principle but different in their patterns. Presently, more than 200 molecular defects known to down regulate the expression of β globin have been characterized. Such defects result in various types of β thalassemia ***(Ghodekar, 2010).***

In homozygotes, a shortage of β chains results in an excess of α chains, which precipitate in the red-cell membrane and thereby cause apoptosis of erythroid precursors and ineffective erythropoiesis ***(Cao et al., 2002).***

β-thalassemia is the most common chronic hemolytic anemia in Egypt, it represents 85.1% of all cases of hemolytic anemia ***(El-Dakhakhny et al., 2011).***

Prevalence of thalassemia:

β-thalassemia is prevalent in Mediterranean countries, the Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa and in South America. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia. The high gene frequency of β -thalassemia in these regions is most likely related to the selective pressure from *Plasmodium falciparum* malaria ***(Galanello et al., 2010).***

There is a particularly high incidence of thalassemia (2.5%-25%) in the Mediterranean basin, the Middle East, the tropical and subtropical regions of Africa, the Asian subcontinent, and Southeast Asia, where milder forms of the disease are most commonly seen ***(Giardina et al., 2011).***

Population migration and intermarriage between different ethnic groups has introduced thalassemia in almost every country of the world, including Northern Europe where