

**STUDY OF GROWTH  
DIFFERENTIATION FACTOR 15  
EXPRESSION IN PATIENTS WITH  
BETA THALASSEMIA  
INTERMEDIA**

*Thesis*

*Submitted for fulfilment of the M.Sc. Degree in Pediatrics*

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## **Abstract**

**Background:** The thalassemia syndromes represent the most common causes of ineffective erythropoiesis . The increased but ineffective erythropoiesis resulting in tissue iron overload induces numerous endocrine diseases, hepatic cirrhosis, cardiac failure and even death .

**Objectives:** we aim to study GDF15 levels in  $\beta$ - thalassemia intermedia patients and to correlate its level to their iron status and different clinical and laboratory disease parameters.

**Method:** This is case control study conducted on 25 pediatric patients under 18 years with beta thalassemia intermedia and 30 healthy children taken as control group . GDF 15 level was performed using ( ELISA) kit in serum samples that obtained from children of both groups . Abdominal examination , frequency of blood transfusion , Complete blood picture , Reticulocytic count , liver function tests , serum ferritin were done in case group to assess severity of beta thalassemia intermedia .

**Result:** . Our results showed that GDF 15 levels were statistically higher in cases compared to control ( P Value < 0.05 ).

**Conclusion:**GDF15 level in our study represent a first step for its use as biomarker in thalassemia patients although future studies may be needed before its routine use.

**Key words:** Thalassemia intermedia (TI), Growth Differentiation Factor 15 (GDF 15),Ferritin

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## List of Abbreviations

<b>3'UTR</b>	3' untranslated region
<b>AFSC</b>	Control sample containing A, F, S, and C hemoglobins
<b>ALT</b>	Alanine transaminase
<b>AST</b>	Aspartate transaminase
<b>ATO</b>	Arsenic trioxide
<b>BM</b>	Bone marrow
<b>BMPRs</b>	Bone morphogenic protein receptors
<b>BMPs</b>	Bone morphogenic proteins
<b>CBC</b>	Complete blood count
<b>CT scanning</b>	Computerised tomography
<b>d</b>	Day
<b>DFO</b>	Desferoaxamine
<b>DFP</b>	Deferiprone
<b>DNA</b>	Deoxyribonucleic acids
<b>DVT</b>	Deep vein thrombosis
<b>ECG</b>	Electrocardiogram
<b>EDTA</b>	Ethylene diamine tetra-acetic acid
<b>EMH</b>	Extramedullary hematopoiesis
<b>EPO</b>	Erythropoietin
<b>ESR</b>	Erythrocyte sedimentation rate
<b>g</b>	Gram

<b>GDF15</b>	Growth differentiation factor 15
<b>Hb</b>	Hemoglobin
<b>Hb A</b>	Adult hemoglobin
<b>Hb F</b>	Fetal hemoglobin
<b>HbE</b>	Hemoglobin lepreux
<b>Hct</b>	Hematocrit
<b>HFE</b>	HFE gene product
<b>HJV</b>	Haemojuvelin
<b>HPFH</b>	Hereditary persistence of fetal hemoglobin
<b>HPLC</b>	High-performance Liquid chromatography
<b>HSCT</b>	Hematopoietic stem cell transplantation
<b>HSM</b>	Hepatosplenomegaly
<b>HU</b>	Hydroxyurea
<b>ICL 670</b>	Iron chelator 670 (Deferasirox)
<b>IL-1</b>	interleukin -1
<b>IL6R</b>	IL-6 receptor
<b>IVS</b>	Intervening sequence
<b>Kg</b>	Kilogram
<b>L</b>	Liter
<b>L 1</b>	Deferiprone
<b>LIC</b>	liver iron concentrations
<b>m</b>	Millimeter
<b>MCH</b>	Mean corpuscular hemoglobin

<b>MCHC</b>	Mean corpuscular hemoglobin concentration
<b>MCV</b>	Mean corpuscular volume
<b>mg</b>	Milligram
<b>MIC-1</b>	Macrophage inhibitory cytokine – 1
<b>min</b>	Minute
<b>mmHg</b>	Millimeter mercury
<b>MMP</b>	Mitochondrial membrane potential
<b>mo</b>	Month
<b>Mr</b>	Monomer molecular mass
<b>MRI</b>	Magnetic résonance imaging
<b>mRNA</b>	Messenger ribonucleic acid
<b>NAG-1</b>	Nonsteroidal anti-inflammatory drug activated gene
<b>ng</b>	Nanogram
<b>nt</b>	Nucleotide
<b>PB</b>	Peripheral blood
<b>PCR</b>	Polymerase chain reaction
<b>PDF</b>	Prostate derived factor
<b>pg</b>	Pico gram
<b>PHT</b>	pulmonary hypertension
<b>PLT</b>	Platelets
<b>PTGFb</b>	Placental transforming growth factor-b
<b>RBC</b>	Red blood cell
<b>RE</b>	Reticuloendothelial



<b>SCF</b>	Stem cell factor
<b>sec</b>	Second
<b>sHJV</b>	Soluble form of Haemojuevelin
<b>Smad</b>	Small molecules against decapentaplegic proteins
<b>TF</b>	Transcription factor
<b>Tf</b>	Transferrin
<b>TGF-β</b>	Transforming growth factor-β
<b>TI</b>	β-thalassemia intermedia
<b>TLC</b>	Total leucocytic count
<b>TM</b>	Thalassemia major
<b>TWSG1</b>	Twisted gastrulation
<b>Tx</b>	Thromboxne
<b>U</b>	Unite
<b>USA</b>	United States of America
<b>WBC</b>	White blood cells
<b>WHO</b>	World Health Organization
<b>yrs</b>	Years

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**Introduction**  
**and**  
**Aim of the Work**

## **Introduction**

The thalassemia syndromes (**alpha and beta thalassemia**) represent the most common causes of ineffective erythropoiesis (**Tanno et al., 2010**). The increased but ineffective erythropoiesis resulting in tissue iron overload (**Casanovas et al., 2011**) induces numerous endocrine diseases, hepatic cirrhosis, cardiac failure and even death (**Weatherall and Clegg, 2001**).

Hepcidin regulated intestinal iron absorption represents a principal mechanism for iron homeostasis in humans (Donovan et al., 2006). It is commonly believed that ineffective erythropoiesis inhibits expression of hepcidin, a hepatic peptide hormone secreted from liver that regulates the release of iron into the blood stream from duodenal enterocytes, hepatocytes and macrophages (**Ramey et al., 2010**). It was shown that hepcidin levels are decreased in individuals with beta thalassemia syndromes (**Kattamis et al., 2006**).

It's hypothesized that the erythroid expansion could influence the regulation of hepcidin expression through systemic release of transforming growth factor  $\beta$  (TGF- $\beta$ )