Medical Study Department

# Hypoparathyroidism in Beta-Thalassemia Children in Relation to Bone Mineral Density

Thesis

*Submitted for Partial Fulfillment of Ph.D Degree in Childhood Studies (Child Health and Nutrition)*
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Irene Mokhtar Kamel

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# List of Abbreviation

| | |
|---|---|
| **ALP** | Alkaline phosphatase |
| **BMD** | Bone mineral density |
| **BMT** | Bone marrow transplantation |
| **Ca** | Calcium |
| **CIC** | Circulating immune complexes |
| **CT** | Computerized topography |
| **DFO** | Desferrioxamine |
| **DPA** | Dual photon absorpiometry |
| **DPA** | Dual photon absorpiometry |
| **DXA** | Dual X-ray absorpiometry |
| **GIT** | Gastrointestinal tract |
| **Hb** | Haemoglobin |
| **$IGF_1$** | Insulin growth factor-1 |
| **LIC** | Liver iron content |
| **OPG** | Osteoprotegrine |
| **P** | Phosphorus |
| **PBM** | Peak bone mass |
| **PIH** | Pyrodoxal isonicotinoyl hydraxone |
| **PTBCs** | Packed transfused red blood cells |
| **PTH** | Parathyroid hormone |
| **RANKL** | Receptor activator of nuclear factor Kappa-B ligand |
| **rHu EPO** | Recombinant human erythropoietin |
| **Sc – DFO** | Subcutaneous infusions of desferrioxamine |
| **SCD** | Sickle cell disease |
| **SHAM** | Salicylate hydranoxamic acid |
| **TCRN** | North American thalassemia clinical research network |
| **TM** | Thalassemia major |

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# Introduction

Thalassemias are groups of heterogenous inherited disorders in which there are varying degrees of diminished systhesis of one or more of the normal haemoglobin polypeptide chains. Different types exist according to these defective chains as:

Beta-thalassemia which is the most common variety with defective β chain synthesis and α-thalassemia with defective α chain formation ***(Steddon et al., 2005).***

Treatment of thalassemia depends mainly on frequent, repeated blood transfusion with a new problem taking place which is iron overload, which leads to multiple endocrinopathies including hypoparathyroidism. There is significant drop in the parathyroid hormone level with decreased total and ionized calcium while phosphorous level is elevated ***(Morbito et al., 2007).***

Since the concentration of ferritin is not a valuable tool in the prediction of the development of hypoparathyroidism, parathyroid function should be tested periodically, particularly when other iron overload associated complications occur ***(Perifanis et al., 2007).***

***Cohen et al. (2008)*** reported significant reduction in bone mineral density in β-thalassemia major patients which affects mainly the femur, lumbar spines and iliac bones.

This study also related this reduction in bone density with changes in biochemical parameters mainly calcium, phosphorus and total alkaline phosphatase.

# Aim of the Study

The aim of this work is to estimate the level of serum parathyroid hormone and to find its relation to bone mineral density in transfusion dependent beta-thalassemia major children.

# The Normal Human Hemoglobin

Hemoglobin is the oxygen carrier protein in vertebrate red blood cells and also found in some invertebrates and in the root nodules of legumes. The molecule is tetrameric, each subunit is composed of a polypeptide chain, globin and a prosthetic group, heme, which is an iron-containing pigment that combines with oxygen and gives the molecule its oxygen-transporting ability ***(Voskairdou et al., 2009).***

The six known different globin polypeptides chains in man are designated α, β, γ, δ, ε, and ξ. The α-chains contains 141 amino acids, while β, γ, δ, and ε chains have 146 residues. The ε, γ and δ chains are more similar to β-chain than to α-chains differing from β at 36, 39 and 10 positions, respectively. The two globin chains, ε & ξ are found in the embryonic erythrocytes. Both The ε gene and ξ sequence encodes an embryonic β-like chain ***(Soliman et al., 2008a).***

The hemoglobin molecular weight is 64500 daltons. It consists of two α-and two non α globin polypeptide chains, each of which has a single covalently bond heme group. Each of the 4 heme groups is made up of an iron atom bound within a protoporphyrin type IX ring ***(Weatherall, 2005).***

In normal adults, the major component, comprising about 97% of the total is HbA ($\alpha_2\beta_2$), with the reminder being $HbA_2$

($\beta_2\delta_2$) comprises 2-3.5% of the total Hb. The main Hb in fetal life is Hb F($\alpha_2\gamma_2$), and this is preceded in embryos by Hb Gower 1 ($\varepsilon_2\xi_2$) and Gower 2 ($\varepsilon_2\varepsilon_2$) and Hb Portland ($\xi_2\gamma_2$). Traces of Hb F(~0.5 percent) are found in adults ***(Enas et al., 2010)***. Figure (1) show the changes in globin chain during human development.

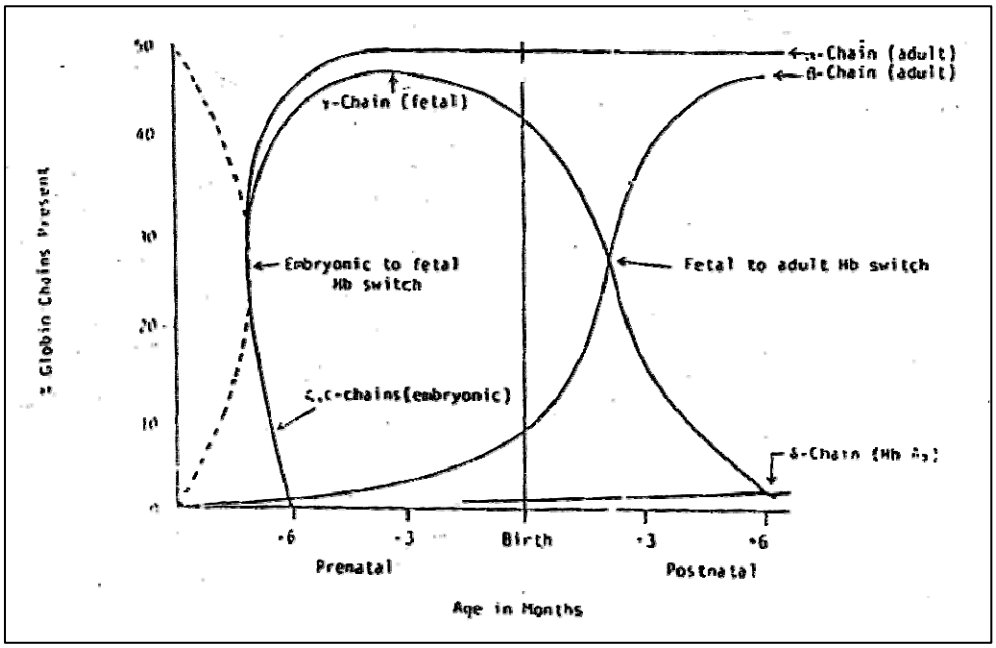


**Figure (1):** Qualitative and quantitative changes in globin chains during human development ***(D'Ascoka et al., 1998).***

# Thalassemia

## Definition:

The thalassemia syndromes are a heterogenous groups of inhereted anaemias characterized by defect in the synthesis of one or more of the globin chain subunits of the hemoglobin tetramer. The clinical syndromes associated with thalassemia arise from the a combined sequence of inadequate hemoglobin and accumulation of globin subunits. The former causes hypochromia and the later leads to ineffective erythropoises and hemolytic anaemia ***(Weatherall, 2005).***

Absent globin synthesis is designated with an "$_o$" superscript e.g $\beta^o$-thalassemia, while the presence of some (but not enough) of the gene product is noted by a "$_+$" superscript e.g. $\beta^+$-thalassemia. When there is partial synthesis of the affected globin chain, it is usually structurally normal, therefore, the defect is a quantitative one secondary to unbalanced globin gene synthesis. This contrast with the hemoglobinopathies in which the variant hemoglobins are qualitatively or structurally abnormal ***(Vogiatzi et al., 2009a).***

Thalassemia is one of the most common single gene disorders and is widely distributed in the Mediterranean region. Thalassemia syndromes are a heterogeneous group of inherited anaemias characterized by defects in the synthesis of one or more

of the globin chain subunits of the hemoglobin tetramer ***(Cohen et al., 2006).***

In 1925, Thomas Cooley and Pearl Lee described homozygous β-thalassemia. They recognized similarities in the disease entity and clinical course of severe anaemia, spleenomegaly, severe growth retardation, and bone changes affecting four children of Greek and Italian origin. As all early cases were reported in children with Mediterranean background the disease was termed "Thalassemia" from the Greek word "Thalassos" meaning "sea" and "emia" which means "related to blood". Over the years, the disease proved to be widely occurring throughout tropical countries ***(Cooley et al., 1925).***

The first case of β-thalassemia in Egypt was reported in 1940 by Professor El Diwany, ever since there has been increasing interest to reveal the extent of occurrence of this problematic disease in Egypt ***(Khalifa et al., 2004).***

## Prevalence and Geographical Distribution:

Thalassemia is considered the most common genetic disorder worldwide, about 3% of the world population (150 million people) carry β-thalassemia genes and in Southeast Asia 5-10% of the population carries genes for α-thalassemia ***(Honig, 2004).***

According to ethnic group, α-thalassemia trait is most prevalent in South East Asia, affects 2.7% of American black

newborns and less common in the Mediterranean region, β-thalassemia occurs in 5% in certain areas of Italy, Greece, Sardinia, India and 8% in American blacks ***(Weatherall, 2001).***

The position of Egypt in the center of the Middle East contiguous with the Mediterranean countries, has facilitated genetic admixture of Egyptians with several populations of a diverse geographic and ethnic origin. Since thalassemia and sickle cell anaemia prevail among some of those intermixing populations, it is anticipated that the two inheritable blood disease could as wel1 be propagating among Egyptians. In Egypt the carrier rate of thalassemia was reported to be 1.3-4.5% ***(Hashem, 1978).***

In a study done by ***Shawky et al. (1997),*** the incidence of consanguineous marriages was 75 % of the studied families. There is a high consanguinity rate in Egypt. Consanguinity rate is up to 28% in Egypt, which helps to accumulate deleterious genes in families ***(Hafez et al., 1983).*** Abd Elsalam and associates found in (1985) a consanguinity rate of a 36.2 % in rural areas and of 20.37 % in urban areas in Egypt.

## Classification of Thalassemia:

I. β-thalassemia.

II. α-thalassemia.