GROWTH, PUBERTY AND SKELETAL DYSPLASIA IN BETA THALASSEMIA MAJOR

Thesis submitted in partial fulfillment of the Master Degree **in Pediatrics.**

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Ahmed Sobhi Abd El-Gawad

LIST OF ABBREVIATION

BMD	=	Bone mineral density – content BMC.
BMT	=	Bone marrow transplantation.
B-Thal	=	B-thalssenia major
C.H.F	=	Congestive heart failure.
DFO	=	Desferrioxamine.
DXA	=	Dual energy x-ray absorpitometey
ECHO	=	Echocardiography.
GH	=	Growth hormone
GHRH	=	Gonadotrophin releasing hormone
GHRH	=	Growth hormone – releasing hormone.
HBV	=	Hepatitis B-virus.
HCV	=	Hepatitis C-virus.
HLA	=	Human leukocyte antigen
H-P axis	=	Hypothalmic pituitary axis.
IGF-1	=	Insulin growth factor-1
IGF-BF-3	=	Insulin growth factor binding protein -3
LDL	=	Low density lipoprotein.
LHRH	=	Leutinizing hormone releasing hormone.
LIC	=	Liver iron content
M.R.I	=	Magnetic resonance imaging
MCH	=	Mean corpuscular hemoglobin
MCV	=	Mean corpuscular volume.
PCR	=	Polymerase chain reaction.
RDW	=	Red cell distribution width
SA	=	Secondary amenorrhea.
SPSS	=	Statistical package for social science.
SQUID	=	Super conducting quantitative interference device.
STFR	=	Soluble transferring receptors.
T	=	Testosterone.

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INTRODUCTION

The cause of growth retardation in the inherited blood disorder β-thalassemia major (β-thal) has long been a subject of debate. This has become an issue since children with β-thal are undergoing hypertransfusion and iron chelation therapy, and now living well into their thirties and forties. Therefore, in addition to growth retardation, many of the endocrinopathies such as hypogonadism, hypothyroidism, hypoparathyroidism and diabetes mellitus, which were not apparent before, are now being diagnosed and treated **(Spiliotis, 1998)**.

Normal growth of β-thal children during the first 10 years of life depends upon the maintenance of hemoglobin levels above 8.5 g/dl. During this period of the child's life hypoxia may be the main factor retarding growth. If deferoxamine, which is used for iron chelation therapy, is used before the age of 3 years it also produces marked stunted growth with a clinical and radiologic rickets-like syndrome. This is because, before there is iron overload from the blood transfusions, deferoxamine is thought to also chelate other essential minerals besides iron **(De Virgilis et al, 1988).**

In addition to short stature, an abnormal sitting height has been reported in studies on thalassemic patients from Australia and Italy. Among the short Italian patients with thalassemia, the majority (77%) of the patients had disproportionate short stature with short trunk but with less severe impairment of subischial leg length. This abnormality of body proportion was due to platyspondyly as revealed by skeletal radiology and was present as early as 4 years of age but was more common in adolescence. It is now recognised that short stature and skeletal dysplasia can be induced by injudicious use of desferrioxamine. Clinically, the patients with desferrioxamine-induced skeletal dysplasia have short trunk, genu valgum, metaphyseal widening of long bones, joint stiffness and a decreased growth velocity. Radiological changes include thickened growth plate with widening and cupping of the metaphyses of long bones, sclerosis of subchondral bone, osteoporosis and small radioluscent metaphyseal lesions.

The studies on growth hormone (GH) secretion in patients have shown both normal and reduced response to a variety of pharmacological stimuli. It is likely that as the patients survive

longer, the prevalence of GH deficiency or neurosecretory dysfunction among these patients will increase with advancing age. The present evidence of normal GH reserve and serum GHBP levels with low serum IGF-1 and IGFBP-3 concentrations suggests that a partial secondary GH insensitivity state exists in patients with transfusion-dependent thalassemia major and that supraphysiological doses of GH can overcome this resistance and lead to an improvement in the growth of such patients. **(Low, 2005)**.

Hypogonadism is the most frequent endocrine complication in patients with thalassemia and is an important cause of growth retardation in adolescence. Even in patients who have gone through spontaneous puberty, secondary amenorrhoea and hypogonadism will invariably develop with time. Hypogonadotropic hypogonadism is due to damage from iron deposition in the hypothalamus and pituitary gland but occasionally primary gonadal failure can also occur. The pituitary gonadotropes are particularly sensitive to oxidative damage induced by iron overload. Magnetic resonance imaging (MRI) of the anterior pituitary has shown that a decrease in