



CHANGES IN BONE MINERALIZATION IN CHILDREN WITH HYPOTHYROIDISM ON REGULAR TREATMENT WITH THYROID REPLACEMENT THERAPY

Thesis

*Submitted for Partial Fulfillment
of M.Sc. E Degree in Pediatrics*

By

Mohamed Abu-El Fadl Hagagi Mohamed
(M.B.B. CH)
Assuit University

Under the Supervision of

Prof. Heba Hassan El Sedfy

Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Prof. Lerine Bahy El Din El Shazly

Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Dr. Mohamed Shaker Kahzy

Assistant Professor of Radiology
Faculty of Medicine - Ain Shams University

Faculty of Medicine - Ain Shams University

2010



التغيرات في التركيب المعدني للعظام في الأطفال الذين يعانون من نقص هرمون الغدة الدرقية

دراسة

للحصول على درجة الماجستير في طب الأطفال

مقدمة من

الطبيب / محمد أبو الفضل حجاجي محمد
بكالوريوس الطب و الجراحة - جامعة أسيوط

تحت إشراف

أ. د / هبة حسن الصدفي
أستاذ طب الأطفال - جامعة عين شمس

أ. د / ليرين بهي الدين الشاذلي
أستاذ طب الأطفال - جامعة عين شمس

د / محمد شاكر غازي
أستاذ مساعد الأشعة التشخيصية - جامعة عين شمس

كلية الطب - جامعة عين شمس

٢٠١٠



First of all, I thanks "*Allah*" to whom I relate any success in achieving any work in my life.

I am greatly indebted to *Prof Dr. Heba Hassan El Sedfy*, Professor of Pediatrics, Ain Shams University for her supervision, and honest assistance in every step of this work and for providing me a lot of encouragement and support throughout the work.

Special acknowledgement and deep thanks to *Prof Dr. Lerine Bahy El Din El Shazly*, Professor of pediatrics, Ain Shams University for her generous time, valuable advice and constructive supervision.

I wish to express my deepest gratitude to *Dr. Mohamed Shaker Kahzy*, Assistant Professor in Radiology, Faculty of Medicine Ain Shams University for his kind supervision, help, continuous guidance and encouragement.

Finally. I would like to convey my warmest gratitude to my professors, *my colleagues and patients* in the Pediatrics Department, Ain Shams University for their kind cooperation.

Last but not least, I have thank *my family* for lending me their help and support, which enabled me to carry out this work.

بسم الله الرحمن الرحيم

اقْرَأْ بِاسْمِ رَبِّكَ
الَّذِي خَلَقَ *
خَلَقَ الْإِنْسَانَ
مِنْ عَلَقٍ *
اقْرَأْ وَرَبُّكَ
الْأَكْرَمُ

صدق الله العظيم
سورة العلق
الآيات
(٣-١)

List of Contents

Title	Page No.
<i>Introduction.....</i>	<i>1</i>
<i>Aim of the Study.....</i>	<i>3</i>
<i>Review of Literature.....</i>	<i>4</i>
<i>Embryology:</i>	<i>4</i>
<i>Anatomy:.....</i>	<i>7</i>
<i>Histology:.....</i>	<i>8</i>
<i>Thyroid Follicular Cells:.....</i>	<i>10</i>
<i>Blood Supply</i>	<i>12</i>
<i>Thyroid physiology:</i>	<i>13</i>
<i>Synthesis of thyroid hormones:</i>	<i>14</i>
<i>Regulation of thyroid hormone synthesis:.....</i>	<i>24</i>
<i>Actions of thyroid hormones:.....</i>	<i>30</i>
<i>Assessment of thyroid Function.....</i>	<i>40</i>
<i>Lab Studies:.....</i>	<i>40</i>
<i>Thyroid Ultrasonographic Studies.</i>	<i>56</i>
<i>Radionuclide Studies.</i>	<i>57</i>
<i>Thyroid Auto antibodies:</i>	<i>60</i>
<i>Thyroid function in preterm babies:.....</i>	<i>61</i>
<i>Congenital Hypothyroidism</i>	<i>64</i>
<i>Pathophysiology:.....</i>	<i>64</i>
<i>Etiology.....</i>	<i>70</i>
<i>Clinical Manifestations of CH.....</i>	<i>83</i>
<i>Management of Congenital Hypothyroidism</i>	<i>93</i>
<i>Treatment</i>	<i>116</i>
<i>Follow Up.....</i>	<i>125</i>
<i>Therapy Monitoring.....</i>	<i>127</i>
<i>Prognosis</i>	<i>131</i>
<i>Bone Mineralization In Congenital Hypothyroid Children</i>	<i>133</i>
<i>Dual Energy X-Ray Absorptiometry (DEXA).....</i>	<i>143</i>
<i>Patients and Methods</i>	<i>148</i>
<i>Results.....</i>	<i>154</i>
<i>Discussion</i>	<i>176</i>
<i>Summary and Conclusion</i>	<i>184</i>
<i>Recommendations.....</i>	<i>187</i>
<i>References.....</i>	<i>188</i>
<i>Appendix</i>	<i>226</i>
<i>Arabic Summary</i>	

List of Tables

Table No.	Title	Page No.
Table (1):	Pediatric Reference Intervals for T4, T3, TSH, and Free T4	44
Table (2):	Causes of concordant and divergent changes in serum thyroxine (T4) and tri-iodothyroxine (T3) levels	49
Table (3):	Normal Range for Thyroxine, Tri-iodothyronine, Thyroxine-Binding Globulin, and Thyrotropin in Infancy and Childhood	53
Table (4):	Tests of thyroid Function	63
Table (5):	Etiologic Classification of Congenital Hypothyroidism.....	69
Table (6):	Signs and symptoms of CH.....	92
Table (7):	Screening and Evaluation Strategies for CH Quebec Guidelines, 2001.....	94
Table (8):	Management should include the following:	112
Table (9):	Management of CH.	113
Table (10):	Screening approach using ultrasound, serum T4, and serum TG to confirm diagnosis in newborns with elevated TSH	115
Table (11):	Guidelines for Maintenance Sodium L-Thyroxine Therapy	123
Table (12):	Measurements should be performed:	126
Table (13):	Conditions that alter Levothyroxine requirements.....	130
Table (14):	World Health Organization Criteria For Osteoporosis.....	153
Table (15):	Clinical and biochemical parameters of patients	154
Table (16):	Correlation between BMD SDS and clinical and biochemical parameters of the patients.....	156

List of Tables (Cont...)

Table No.	Title	Page No.
Table (17):	Correlation between age and clinical and biochemical parameters of patients.....	157
Table (18):	Correlation between age at start of treatment and clinical and biochemical parameters of patients.	158
Table (19):	Correlation between mean TSH level during treatment and clinical and biochemical parameters of patients.....	159
Table (20):	Correlation between mean T4 level during treatment and clinical and biochemical parameters of patients.....	160
Table (21):	Correlation between mean FT4 level during treatment and clinical and biochemical parameters of patients.....	161
Table (22):	Correlation between duration of treatment and clinical and biochemical parameters of patients.	162
Table (23):	Correlation between height SDS and clinical and biochemical parameters of patients.....	163
Table (24):	Correlation between weight SDS and clinical and biochemical parameters of patients.....	164
Table (25):	Correlation between mean dose of T4/m ² ug and clinical and biochemical parameters of patients	165
Table (26):	Correlation between BMI SDS and clinical and biochemical parameters of patients.....	166
Table (27):	Correlation between BMC and clinical and biochemical parameters of patients.....	167
Table (28):	Correlation between serum alkaline phosphatase and clinical and biochemical parameters of patients.....	168
Table (29):	Correlation between fasting urinary calcium / creatinine ratio and clinical and biochemical parameters of patients.	169

List of Figures

Fig. No.	Title	Page No.
Fig. (1):	Structure of thyroid hormone and related compounds.....	15
Fig. (2):	Synthesis of Triiodothyronine and Thyroxine	19
Fig. (3):	Structures of thyroid hormones	20
Fig. (4):	Hypothalamic Pituitary-thyroid axis	28
Fig. (5):	Regulation of thyroid hormone synthesis	29
Fig. (6):	Normal thyroid scan	60
Fig. (7):	Congenital hypothyroidism in an infant 6 mo of age.....	88
Fig. (8):	Flow chart of suggested approach to the NB infant with CH	96
Fig. (9):	Steps in diagnosis of hypothyroidism	109
Fig. (10):	Congenital hypothyroidism.....	116
Fig. (11):	Pelvis X – Ray photography Before and 3 years after regular treatment.....	127
Fig. (12):	Distribution of the BMD SDS in patients.....	155
Fig. (13):	DEXA of Spine of the patient number 1.....	170
Fig. (14):	DEXA of Femur of the patient number 1.....	170
Fig. (15):	DEXA of the forearm of the patient number 1	171
Fig. (16):	DEXA of Spine of the patient number 2.....	171
Fig. (17):	DEXA of Femur of the patient number 2.....	172
Fig. (18):	DEXA of Forearm of the patient number 2	172
Fig. (19):	DEXA of Spine of the patient number 5.....	173
Fig. (20):	DEXA of Femur of the patient number 5.....	173
Fig. (21):	DEXA of Forearm of the patient number 5	174
Fig. (22):	DEXA of Spine of the patient number 9.....	174
Fig. (23):	DEXA of Femur of the patient number 9.....	175
Fig. (24):	DEXA of Forearm of the patient number 9	175

List of Abbreviations

ACTH	<i>Adrenocorticotrophic hormone</i>
ATPase	<i>Adenosine triphosphatase</i>
BMD	<i>Bone mineral density</i>
BMI	<i>Body mass index</i>
CAMP	<i>Cyclic adenosine monophosphate</i>
CH	<i>Congenital hypothyroidism</i>
CLT	<i>Chronic lymphocytic thyroiditis</i>
D3	<i>1,25 Dihydroxy cholecalciferol</i>
DEXA	<i>Dual Energy X-Ray absorptiometry</i>
DIT	<i>Di-iodinated tyrosine</i>
DNA	<i>Deoxy ribonucleic acid</i>
DPA	<i>Dual photon absorptiometry</i>
EPO	<i>Erythropoietin</i>
ER	<i>Rough endoplasmic reticulum</i>
FDH	<i>Familial dysalbuminemic hyperthyroxinemia</i>
FSH	<i>Follicular stimulating hormone</i>
FT3	<i>Free T3</i>
FT4	<i>Free T4</i>
FTI	<i>Free T4 index</i>
GA	<i>Golgi apparatus</i>
GD	<i>Graves' disease</i>
H₂O₂	<i>hydrogen peroxide</i>
¹²³I	<i>Iodine 123</i>
I⁻	<i>Iodide</i>
IO³⁻	<i>Iodate</i>
IQ	<i>Intelligence quotient</i>
LH	<i>Luteinizing hormone</i>
L-thyroxin	<i>Levothyroxine</i>
Ly	<i>Lysosome</i>
MIT	<i>Monoiodotyrosine</i>
mRNA	<i>Messenger ribonucleic acid</i>
mv	<i>Milli volt</i>

List of abbreviations (Cont.)

NADPH	<i>nicotinamide adenine dinucleotide phosphate oxidase</i>
NIS	<i>sodium-iodide symporter</i>
Oc	<i>Osteocalcin</i>
OPG	<i>Osteoprotegerin</i>
PAX-8 gene	<i>Paired-box gene 8</i>
PCR	<i>Polymerase chain reaction</i>
Pit - 1	<i>Pituitary specific transcription factor (Homeobox protein)</i>
RNA	<i>Ribonucleic acid</i>
rT3	<i>Reverse T3</i>
RTH	<i>Thyroid hormone resistance</i>
SDS	<i>Standard deviation score</i>
T3	<i>Triiodothyronine</i>
T4	<i>Thyroxin</i>
TG	<i>Thyroglobulin</i>
TBG	<i>Thyroxin binding globulin</i>
99TmTC	<i>Technetium 99m</i>
TH	<i>Thyroid hormone</i>
THBR	<i>Thyroid hormone binding ratio</i>
TPO	<i>Thyroid peroxidase</i>
TRH	<i>Thyrotropin-releasing hormone</i>
TRs	<i>thyroid hormone receptors</i>
TSH	<i>Thyroid stimulating hormone</i>
TSH RAb	<i>Thyrotropin receptor antibodies</i>
TTF1	<i>Thyroid transcription factor 1</i>
TTF2	<i>Thyroid transcription factor 2</i>
TTR	<i>Transthyretin</i>

INTRODUCTION

Thyroid hormones exert a critical influence on the development of the skeleton. Thyroid hormone deficiency in children results in retarded skeletal development, delayed bone age, and growth arrest accompanied by epiphyseal dysgenesis (**Bassett and Williams, 2008**).

Thyroid hormones are essential for bone development. Thyroid hormone deficiency results in developmental delay, whereas thyroid hormone excess accelerates bone formation and growth. Thus, euthyroid status during childhood is essential for normal linear growth and to establish peak bone mass in early adulthood (**Williams, 2009**).

Thyroid hormone seems to be more determinative to cortical bone (found in the hip and forearm) than to trabecular bone found in the spine (**Ross, 2001**).

Thyroid hormones are required for growth and establishment of peak bone mass. Thyroid hormones are required to maintain optimal bone strength. Hypothyroidism and hyperthyroidism are both associated with increased fracture risk. Mild degrees of thyroid hormone excess, characterized by suppressed levels of TSH, are associated with increased fracture risk in children (**Dare et al., 2009**).

Decreased growth and skeletal abnormalities in children with congenital hypothyroidism are one of the

spectacular examples of thyroid hormone importance in bone mineral metabolism. In patients with hyperthyroidism, bone loss and increased levels of bone specific markers may occur (**Matusik et al., 2010**).

Levothyroxine (LT4) therapy, particularly in suppressive doses, may be associated with reduced bone mass and increased levels of bone metabolism (**Mohammadi et al., 2007**).

Prolonged suppressive L-thyroxin treatment may result in mild sub clinical hyperthyroidism with adverse effects on bone (**Ross et al., 2000**).

The development of non invasive techniques for diagnosing bone loss and the availability of the second and third generation assays for thyroid stimulating hormone (TSH) led to better understanding of the sequences of thyroid hormone over treatment with respect to bone loss (**Ross et al., 2001**).

Hyperthyroidism results in bone resorption, whereas successful treatment of the disorder improves bone mineral density (BMD). Moreover, subclinical hyperthyroidism, i.e., suppression of thyroid-stimulating hormone (TSH) without an elevation in thyroid hormones, has also been associated with bone loss. These clinical situations suggested that it is the suppressed TSH rather than the elevated thyroid hormones that exert a deleterious effect on bone density (**Karga et al., 2004**).

AIM OF THE STUDY

The purpose of this study was to evaluate the effect of thyroid hormone treatment in congenital hypothyroidism on skeletal integrity; to correlate the BMD with the average TSH levels.

REVIEW OF LITERATURE

Embryology:

The thyroid gland originate as a derivative of the digestive tract and starts to develop 3 weeks after conception. The primordial thyroid, an epithelial thickening, is connected by the thyroglossal duct to the pharynx. Thirty days after conception, the bilobar structure of the organ can be recognized (Gruters, 1992).

The development of the thyroid gland starts with an invagination of the ventral endoderm of the future oral cavity (median anlagen). This invagination develops into a bilobar structure, and subsequently each lobe fuses with an ultimobranchial body (lateral anlagen) derived from the fourth pharyngeal pouches while migrating to the distal part of the neck. Thyroid follicles appear at 10 weeks of gestation, indicating that the thyroid follicular cells can synthesize thyroglobulin. At the same time, iodine accumulates in the fetal thyroid, indicating that thyroid oxidase and peroxidase are active. By mid-gestation the thyroid is able to secrete substantial amounts of T4. Serum free T4 concentrations gradually increase until adult values are reached at about 36 weeks of gestation (Thomas Vulsma et al., 2005).

It is the first endocrine structure that becomes recognizable in humans. This thickening, the so-called median anlagen, is located between the first and second branchial arches and is adjacent to the newly differentiating myocardium. The anlagen appear as a visible bud on day 16 or day 17 in humans. The bud expands ventrally as a diverticulum, with rapid proliferation of the cells at its distal end, but it remains attached to the pharyngeal floor by a tubular stalk called the thyroglossal duct. The thyrocyte progenitor cells continue to proliferate distally and then begin to proliferate laterally, which leads to the formation of the characterized bilobed structure connected by an isthmus. Because of its close association with the embryonic heart, the thyroid can be viewed as being pulled downward by the heart during its descent. This caudal migration is accompanied by rapid elongation of the thyroglossal duct, which eventually fragments and degenerates. This migration occurs from day 24 to day 32 in humans (Stone, 2000).

It descends as a bilobed diverticulum in front of the pharyngeal gut, still connected to it by a canal – the thyroglossal duct. Migration continues in front of the hyoid bone and laryngeal cartilages to the definitive position in front of the trachea by 7th week gestation (Kelner, 1998).