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

Thesis

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

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بسم الله الرحمن الرحيم
اقْرَأْ بِاسْمِ رَبِّكَ
الَّذِي خَلَقَ *
خَلَقَ الإِنْسَانَ
مِنْ عَلَقٍ *
اقْرَأْ وَرَبُّكَ
الأَكْرَمُ
صدق الله العظيم
سورة العلق
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List of Abbreviations

ACTH	*Adrenocorticotropic hormone*
ATPase	*Adenosine triphosphatase*
BMD	*Bone mineral density*
BMI	*Body mass index*
CAMP	*Cyclic adenosine monophosphate*
CH	*Congenital hypothyroidism*
CLT	*Chronic lymphocytic thyroiditis*
D3	*1,25 Dihydroxy cholecalciferol*
DEXA	*Dual Energy X-Ray absorptiometry*
DIT	*Di-iodinated tyrosine*
DNA	*Deoxy ribonucleic acid*
DPA	*Dual photon absorptiometery*
EPO	*Erythropoietin*
ER	*Rough endoplasmic reticulum*
FDH	*Familial dysalbuminemic hyperthyroxinemia*
FSH	*Follicular stimulating hormone*
FT3	*Free T3*
FT4	*Free T4*
FTI	*Free T4 index*
GA	*Gologi apparatus*
GD	*Graves' disease*
H2O2	*hydrogen peroxide*
^{123}I	*Iodine 123*
I-	*Iodide*
IO^{3-}	*Iodate*
IQ	*Intelligence quotient*
LH	*Luteinizing hormone*
L-thyroxin	*Levothyroxine*
Ly	*Lysosome*
MIT	*Monoiodotyrosine*
mRNA	*Messenger ribonucleic acid*
mv	*Mille volt*

List of abbreviations (Cont.)

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

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 determinal 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).**