thyrotropin, thyroid hormone, densitometry, bone mineral density, children

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THYROID HORMONE AND THYREOTROPIN (TSH) ASSOCIATION WITH DENSITOMETRIC PARAMETERS IN CHILDREN

The influence of TSH on bones is still vastly unknown and the information that is known is considered controversial. This important relationship has not been studied in detail. The aim of our research was to assess the correlation between TSH, thyroid hormone and bone mineral density in children measured by DXA scanning. Our study group included 36 children (16 girls and 20 boys) mean age 12.9 ± 3.3 years. Basic anthropometrical measurements were performed (height, weight, body mass index-BMI), in all subjects. Blood was collected and measured for TSH and FT4. Bone mineral density of lumbar spine (L2-L4 BMD) and total body (Total Body BMD) were measured by DXA and expressed as bone mineral content (BMC [g]) and bone mineral density (BMD [g/cm^2]). BMD Z-Score was also calculated. Correlation between the parameters obtained by DXA and anthropometrical data, TSH and thyroid hormone concentration were calculated. A statistically significant positive correlation was observed between height, weight and BMI and BMD which was calculated. Weight and BMI also had a statically significant correlation with Z-Score and total bone mineral content (BMC – expressed in grams). There was a statistically significant positive correlation between TSH level and Z-Score for both L2-L4 lumbar spine and for total body. TSH did not correlate significantly with BMD [g/cm^2] and BMC [g]. FT4 was negatively and significantly correlated with Z-Score for both L2-L4 lumbar spine and for total body. There was also no significant correlation between FT4 and BMD [g/cm^2] and BMC [g]. Conclusion: 1. Thyroid stimulating-hormone (TSH) appears to be associated with maintenance of bone mineral density in children. 2. BMD Z-Score especially from L2-L4 lumbar spine assessed by DXA scanning is correlated best with hormonal and biochemical factors potentially influencing bone mineralization in children.

1. INTRODUCTION

Peak bone mass is essential for well functioning skeletal structures in adults, adolescents and children. Ninety percent (90%) of peak bone mass is achieved usually after the age of 18. The remaining ten percent (10%) of peak bone mass increases during what is called the consolidation phase. Consolidation phase occurs when bones no longer grow in length rather growth per se is only intensive bone remodelling. Bone mass achieves the state of equilibrium in the third decade of human life. Peak bone mass is a major risk factor for osteoporosis and fractures in the elderly population and it is obtained by the end of sexual development [7,8,15]. Peak bone mass is dependent on physical activity and adequate intake of calcium and vitamin D [25]. There are several risk factors which can have a negative impact on bone maturation. Factors which might disturb correct growth, bone function and ultimately peak bone mass are chronic malnutrition, chronic steroid exposure, lack of physical activity, teenage pregnancy, genetic disorders such as Ehlers-Danlos, Fibrous Dysplasia and Marfan's syndrome [17,23]. Chronic diseases such as Anorexia Nervosa [24], Celiac Disease [21], and Diabetes Mellitus Type 1 [16], endocrine disorders such as growth hormone deficiency[10] and immobilization diseases such as Spina Bifida and Muscular Dystrophy [2,5], all have be reported to have a negative impact on bone mass.

The influence of thyroid hormones on bone metabolism has been well established [18,19].

Hypothyroidism in childhood is connected with decreased skeletal development, while an increased risk of osteoporosis is found in hyperthyroidism.

In children with congenital hypothyroidism characteristic bones alteration i.e. very early inhibition of skeletal maturation and growth in bone length, can be observed. In adults decreased thyroid hormone leads to a reduction of bones cells growing and their activity. Thyroid hormones influence growth plates, restrain chondrocytes proliferation and activates differentiation and promote bone matrix synthesis, mineralization and angiogenesis. Thyroid hormones activate osteoblasts proliferation, differentiation and apoptosis. Osteoblasts have specific nuclear receptors for thyroid hormones and IL-6, RANKL-L gene expression has also been revealed.Triiodothyronine binding to nuclear receptor forms the complex which activates the gene which is responsible for mRNA synthesis and the end result is proteins of bone matrix. In addition, triiodothyronine causes increased synthesis and secretion of growth factors and cytokines [3,9].

The influence of TSH on bones has not clearly been elucidated. The information that is currently known is controversial at best, and firm conclusions have not been determined. The conventional point of view indicates that a direct effect on bones is made only by the actions of T3. Unfortunately, this point of view has been complicated by studies showing TSH as a negative regulator of bone turnover [3]. There is limited data regarding TSH impact on bones in the developmental period of human life. Because of these issues and perhaps to provide clarity to this topic in general, the aim of our study includes all of these variables.

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2. THE AIM OF THE STUDY

The aim of our research was to assess correlation between TSH, thyroid hormone and bone mineral density in children measured by DXA scanning.

3. MATERIAL AND METHODS

Our study was performed in a group of 36 children (16 girls and 20 boys), mean age 12.9 ± 3.3 years. Inclusion criteria for this study were all the patients diagnosed in the Department of Paediatric Endocrinology with suspicion of calcium-phosphorus balance disturbances. Children with negative result of the diagnostics procedures were included to the study group as well. Basic anthropometrical measurements were performed (height, weight, body mass index-BMI) in all study subjects. Blood was collected and measured for TSH and FT4. TSH and FT4 levels remained within normal limits. Bone mineral density of lumbar spine (L2-L4 BMD) and total body (Total Body BMD) were measured by dual energy X-ray absorptiometry (DXA) with the Lunar analyzer. These values were expressed as bone mineral content (BMC [g]) and bone mineral density (BMD [g/cm^2]). Z-Score (number of standard deviation from mean BMD for age, sex and race matched group) was also calculated. Previous research indicated that a correlation existed between the parameters obtained by DXA and anthropometrical data, TSH and thyroid hormone concentration. Statistical analysis was performed by Statistica PL 5.18 software. In all statistical analyses $p < 0.05$ was considered significant.

4. RESULTS

Anthropometrical measurements

Our results indicated that a statistically significant positive correlation existed between height, weight, BMI and bone mineral density (BMD – expressed by g/cm^2). This statistically significant positive correlation was observed at both sites of scanning (lumbar spine and total body). Weight and BMI also have statistical significant correlation with Z-Score and total bone mineral content (BMC – expressed by grams). However, there was no statistically significant correlation between height, calculated Z-Score and total bone mineral content. Detailed correlation coefficients and *p*-values were showed in Table1.

Table 1. Correlations of densitometrical parameters vs. anthropometrical measurements

	BMD [g/cm^2] (L2-L4)	**Z-Score (L2-L4)**	**BMD [g/cm^2] (Total Body)**	**Z-Score (Total Body)**	**BMC [g] (Total body)**
Height [cm]	0.502 ***	NS	0.599 ***	NS	NS
Weight [kg]	0.794 ***	0.434 **	0.741 ***	0.254 *	0.845 ***
BMI [kg/m2]	0.773 ***	0.477 **	0.495 ***	0.265 *	0.522 ***

*p< 0,05 ;**p< 0,01 ; ***p< 0,001 (Pearson correlation)

Thyrotropin (TSH) and free thyroxin (FT4)

There was a statistically significant positive correlation between TSH level and Z-Score for both L2-L4 lumbar spine and for total body. TSH did not correlate significantly with BMD [g/cm^2] and BMC [g]. FT4 was negatively and significantly correlated with Z-Score for both L2-L4 lumbar spine and for total body (fig.1).There was also no significant correlation between FT4 and BMD [g/cm^2] and BMC [g] (fig.2).

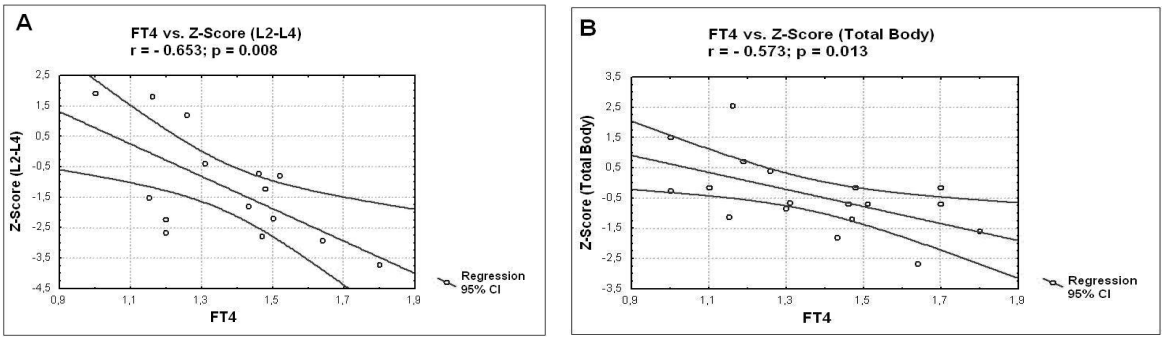

Fig. 1. Correlation between FT4 vs. Z-Score in L2-L4 of lumbar spine (A) and vs. Z-Score in Total Body (B).

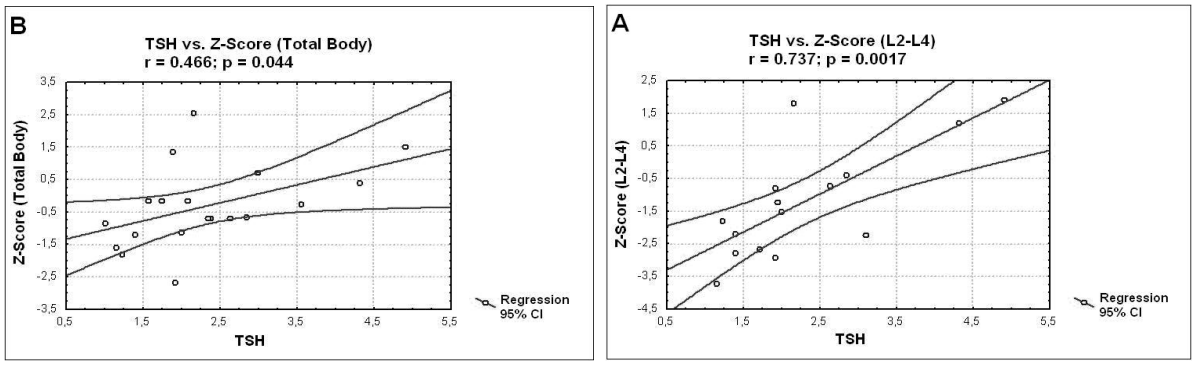

Fig. 2. Correlation between TSH vs. Z-Score in L2-L4 of lumbar spine (A) and vs. Z-Score in Total Body (B).

5. DISCUSSION

Clinical studies indicated that euthyroid status in children is essential for normal skeletal development and achievement of peak bone mass. Thyroid hormones regulate osteoblast proliferation, differentiation and function directly via nuclear receptor TRα. On the other hand they may regulate osteoclast proliferation, differentiation and function either directly or via osteoblast-mediated effects [3]. An important step in understanding these relationships was the discovery of the thyrotropin (TSH) receptor (TSHR) in bone [1,12]. Historically, the decreased BMD observed in patients with hyperthyroidism was attributed to elevated levels of thyroid hormone; a direct effect of TSH suppression was not suggested until 2003 [9]. TSH was shown to influence both osteoclast formation and survival, as well as osteoblast differentiation by the influence on progenitor cells commitment for both osteoclasts and osteoblasts [3,20]. Additional important information was obtained from a study by Sun et al. who demonstrated the association between TSH receptor deficiencies resulted in osteoclastogenesis and increased tumor necrosis factor-α (TNF-α) production [22]. Our study was designed to examine whether TSH level obtained from euthyroid children correlated with bone mineral density assessed by DXA scanning. Dual X-ray absorptiometry is a "gold standard" in the assessment of bone mineralization during the developmental period. Interpretation of results of the DXA examination must include the relevant parameters such as the numeric results, gender, ethnicity, height, weight, body composition, and physiologic maturity (measured by bone age). All of these parameters should be considered in the interpretation of the study [6]. Our study indicated that basic anthropometrical measurements may significantly influence the DXA numeric result interpretation. In our patients there was strong positive correlation with all of the anthropometrical parameters and bone mineral density (BMD [g/cm^2]) and bone mineral content (BMC [g]). The correlation was much weaker when bone mineral density was expressed as number of standard deviation from mean adjusted for gender, age and race (Z – Score) and height correlation. Similar observation was made in prepubertal girls. In this study Malecka-Tendera et al. suggested that, a better way for numeric results interpretation is the calculation of volumetric BMD (expressed as g/cm^3) or plotting of BMD and BMC on the special percentile charts [14]. Therefore, Z-Scores seem to be good parameters to correlate with the other factors which can have a potential impact on bone mineralization. Our data revealed that there existed a significant negative correlation between free thyroxin (FT4) and BMD Z-Score for both lumbar spine and total body. However thyroid stimulating-hormone (thyrotropin –TSH) correlates significantly with BMD Z-Score in a positive manner and the correlation coefficient was even stronger for L2-L4 lumbar spine. The strongest correlation vs. lumbar spine may be due to the highest bone turnover caused by higher amount of trabecular bone in vertebral bodies which is more metabolically active. Our data confirmed the findings of Heemstra et al., which established the existence of an independent association between serum TSH levels and indicators of bone turnover [11]. Biochemical markers of bone turnover correlated negatively with TSH level in postmenopausal women in the study conducted by Zofkova et al. However, the authors did not find a significant correlation between TSH and BMD assessed by DXA scanning. They used hip (low metabolic rate – large amount of cortical bone) and spine (in the elderly osteofits on vertebral bodies may give false results) BMD expressed as g/cm^2 [25]. Nevertheless, a recent study made by Bassett et al. [2] showed that in patients with hypothyroidism, their skeletal abnormalities were rather caused by lack of thyroid hormones as opposed to thyrotropin excess [4]. All of our patients were in an euthyroid state. It is feasible that the TSH modulatory influence on bones which is important in physiology has a much different impact in pathological situation like hypo or hyperthyroidism, where the direct thyroid hormone effects or bone metabolism are already known. Further research into mechanism of TSH in bone metabolism (especially in children) should be carried out. In our research study FT3 was not measured and therefore the clinical use of this research data is limited.

6. CONCLUSIONS

1. Thyroid stimulating-hormone (TSH) appears to be associated with maintenance of bone mineral density in children.
2. BMD Z-Score especially from L2-L4 lumbar spine assessed by DXA scanning correlated best with hormonal and biochemical markers potentially influencing bone mineralization in children.

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