BONE MASS AND PARATHYROID STATUS IN 208 BELARUSSIAN CHILDREN AFTER TOTAL THYROIDECTOMY BECAUSE OF A THYROID CARCINOMA

This study analyzes the consequences of the development of hypoparathyroidism after total thyroidetomy because of a thyroid carcinoma on Ca-P metabolism and bone accrual during childhood and adolescence.
Two hundred eight children and adolescents (119 girls and 89 boys) from Gomel city (Belarus) and its rural surroundings were referred to our institution after having undergone a total thyroidectomy as a treatment for an advanced papillary thyroid cancer. A soubgroup of the children with a demonstrated primary hypoparathyroidism was given a dihydrotachysterol (AT-10) and / or Ca supplement. Among routine procedures over a follow-up period of 5 years, scans of the whole body were taken using dual energy X-ray absorptiometry (DXA) at each visit in order to determine the whole-body bone mineral content (TBMC).
Despite of the AT-10 / Ca supplementation, the average serum Ca, P and AP concentrations over the whole observation period were significantly different between the groups. However, the TBMC z-scores for all the studied children were statistically similar in all visits, regardless of the AT-10 / Ca administration. The TBMC values did not differ from normal reference data throughout the observation period, suggesting that the total bone mass accrual was not impaired by PTH deficiency in the studied conditions. No reduction in growth gain was observed in both groups of boys and girls throughout the study.
Results indicate that the primary impairment in parathyroid function and bone metabolism indicators in these thyroidectomized children, despite of not having been completely corrected by the AT-10 / Ca supplementation in the most severe cases, were not associated to measurable disturbs in bone mass accrual or mineralization after 5 years.

Introduction

Hypoparathyroidism has been reported as a relatively frequent complication of total thyroidectomy that may disturb the 1,25(OH)2-Vit D3 synthesis and consequently the intestinal Ca absorption [1,2]. Considering that the skeleton accumulates more than 1 kg of Ca during the second decade of life (average over 270 mg / day), the maintenance of Ca homeostasis (critical for many electrophysiological functions) would require an important mobilization of Ca from the skeleton within that period. Calcium supplementation in adolescents has been shown to increase bone mineral mass but this effect rapidly reversed after withdrawal [3]. Bone mass accrual has been shown related to both, Ca intake and exercise [4]. However, there is little information on the long-term influence of hypoparathyroidism or hypocalcemia on the young skeleton.
In a previous study we had reported no remarkable effects on BMD and serum calcitonin levels in thyroidectomized adults that had subnormal total and serum ionized Ca levels [5], presumably due to alternative sources of this hormone. In this study we have investigated the bone mass in 208 Belarussian children and adolescents who had undergone total thyroidectomy because of a papillary thyroid carcinoma [6]. They had either normal or significantly subnormal serum Ca levels not accompanied by neurological symptoms. Our aim was to determine whether the acquired hypoparathyroidism (not adequately compensated in many cases by the administration of

a Ca and / or calciferol supplementation) had lead or not to a measurable deficit in bone mass during a long-term observation in those particular circumstances.

Material and Methods

Two hundred eight children and adolescents (119 girls and 89 boys) from Gomel city (Belarus) and its rural surroundings were referred to our institution after having undergone a total thyroidectomy as a treatment for an advanced papillary thyroid carcinoma, most of them in stage pT4; 4 in pT3; 17 in pT2; 3 in pT1, and 4 in pTx [6,7]. Most of the patients were periodically submitted (up to 9 times) for follow-up procedures and radioiodine treatment over 72 months. The follow-up protocol included ultrasonography and scintigraphy of the neck, thorax X-ray or spiral CT scan, computerized test for pulmonary function, serum determinations of thyroglobulin, TSH, free T4, T3, total Ca, P, iPTH [Nichols Institute Diagnostics, San Juan Capistrano, USA], serum alkaline phospatase (AP) [Roche, Mannheim, Germany] and blood cell counts. The replacement therapy with levothyroxine had been withdrawn 4 weeks before treatment and was restarted 2 days after the control procedures or the application of radioiodine. Urinary Ca excretion was not determined because the urine contamination with 131-iodine would have complicated the sample handling. The children with a demonstrated hypoparathyroidism (defined by at least one serum iPTH value lower than 10 pg/ml in at least two of the visits) were given 0.2 - 0.9 mg dihydrotachysterol (AT-10, 1mg/ml solution, 6-26 drops) per day and 500 mg of Ca gluconate 3-4 times per day.

In addition, whole-body measurements were performed by dual energy X-ray absorptiometry (DXA; DPX-L and Prodigy, LUNAR Radiation, Madison, Wisconsin) at each visit in order to determine the whole-body bone mineral content (TBMC). The TBMC was compared within and between groups employing a reference set of data from normal Argentine Caucasian children for calculation of the corresponding z-scores [8]. Quality control of the scanner was ensured during the whole period using the both the manufacturers' standard and the European spine phantoms. Precision, accuracy and stability of this procedure have been described elsewhere [9].

The average time between referrals of the children to our hospital was 6 months. The numbers of children seen were 208 at visit 1, 60 at visit 5, and 17 at visit 9.

All the patients were annually examined in the Central Hospital, Gomel, including neck ultrasound, chest X-ray, ECG, EEG, and serum and urine laboratory determinations comprising thyroid-related antibodies, thyroid hormones, hTG, and Ca. Additional checkups including only neck ultrasound and thyroid status (serum thyroglobuline and thyroid hormones) were done annually at the University Clinic, Minsk. Eighty to 90% of the children underwent the follow-up examinations in their home Country.

The patients were divided into two groups, one with demonstrated hypoparathyroidism (n = 91, 35 boys and 56 girls) which was given the AT-10 / Ca supplementation (unavailable in Belarus), and other without a demonstrable hypoparathyroidism (n = 117, 54 boys and 63 girls) which was given no supplement and untreated otherwise. The AT-10 supply was provided by our hospital in batches large enough for a 6-month supplement. Calcium supplementation was given in Belarus. A suppressive T4 dose was given to every child in their Country. This was calculated accordingly to the evolution of serum TSH values, and resulted somewhat higher in the boys receiving the AT-10 / Ca supplementation.

There was a clear tendency of the children from rural areas to be lesser compliant than the others in taking their supplementation regularly, as determined by availability

troubles, lack of patient care, education, and economic situation. Despite of the adequate prescription, most of the hypoparathyroid patients either did not take or were unable to afford the AT-10 supplement in Belarus after consuming the initial supply from our hospital.

Standard, one-way ANOVA tests and regression analyses [StatisticaTM] were performed for evaluation of the data. The Tukey Honest Significance Test (HST) for unequal sample sizes was used to test group range differences in the TBMC z-scores. The z-scores were calculated using a polynomial fit function based on the means and standard deviations of the normal reference BMC values for boys and girls. Significance levels were set at $p<0.05$ in all instances.

Results

At the first follow-up instance (visit 2) no differences were detected in body weight and height between the groups (Table 1).

Table 1

Anthropometric data at visit 2 and daily oral levothyroxine dose

Variable	Boys		girls	
	No supplementation n at visit 1 =54	AT10 + Ca n at visit 1 =35	No supplementation n at visit 1 =63	AT10 + Ca n at visit 1 =56
weight (kg)	51.2±16.8	51,7±17.9	49.7±16.8	47.5±12.6
height (kg)	156.6±16.0	159.7±16.1	153.2±14.1	153.9±13.1
levothyroxine dose daily (µg)	140±32*	150±43*	139±37	136±35

*sign. different at p<0.001.

Table 2

Mean +/- SD values of serum parameters of the combined groups (boys n=89 and girls n=119) with hypoparathyroidism and normal parathyroid function corresponding to the last visit of each subject

Variable	Ref. range	No supplementation	AT-10 + Ca supplementation	P value
Ca [mmol/l]	2.0 - 2.7	2.33±0.16	1.82±0.37	<0.001
Phosphate [mmol/l]	0.87- 1.45	1.56±0.22	2.19±0.56	<0.001
AP [U/l] boys girls	86 - 390 69 - 330	297±149	245±129	0.002
iPTH(1-84) [pg/ml]	10 - 65	31.4±20.3	6.3±8.5	<0.001

Table 3

Mean±standard deviation of age and total bone mineral mass (TBMC) of the whole groups of boys and girls studied at visit 1–9

visit	Age (boys) years	Age (girls) years	TBMC (boys) grams	TBMC (girls) grams	n (boys)	n (girls)
1	12.7±2.4	12.5±2.5	1949±594	1977±550	89	119
2	13.3±2.4	13.0±2.5	2148±640	1965±521	87	107
3	13.8±2.6	13.3±3.0	2228±748	1986±575	53	63
4	13.8±2.6	13.5±2.9	2364±833	1988±633	35	43
5	14.6±2.7	13,9±2.9	2333±852	2012±640	27	33
6	15.5±3.3	14,7±3.1	2445±874	2097±602	22	27
7	15.0±1.3	15.1±2.7	2426±641	2285±508	15	18
8	16.3±1.3	16.0±3.5	2652±694	2413±546	13	11
9	17.5±1.5	16.3±3.2	2795±684	2445±481	8	9

Despite of the substitution therapy installed, the average serum Ca, P and AP concentrations over the whole observation period were significantly different between groups ($p<0.001$, Table 2). Nevertheless, at visit 2 68% of the supplemented boys and 55% of the supplemented girls failed to reach normal serum Ca levels ?2mmol/l despite a good compliance and regardless of their place of residence. They ranged within 1.1 – 1.9 mmol/l serum Ca.

On analyzing the whole sample altogether, the negative correlation observed between serum P and iPTH values showed that the high-P / low-iPTH cases corresponded to individuals who had also a serum Ca concentration below 2.0 mM (Fig. 1). The serum AP correlated positively but weakly with the serum iPTH (Fig. 2), showing a particular distribution of the AT-10 / Ca supplemented individuals within the low-AP / low-iPTH region.

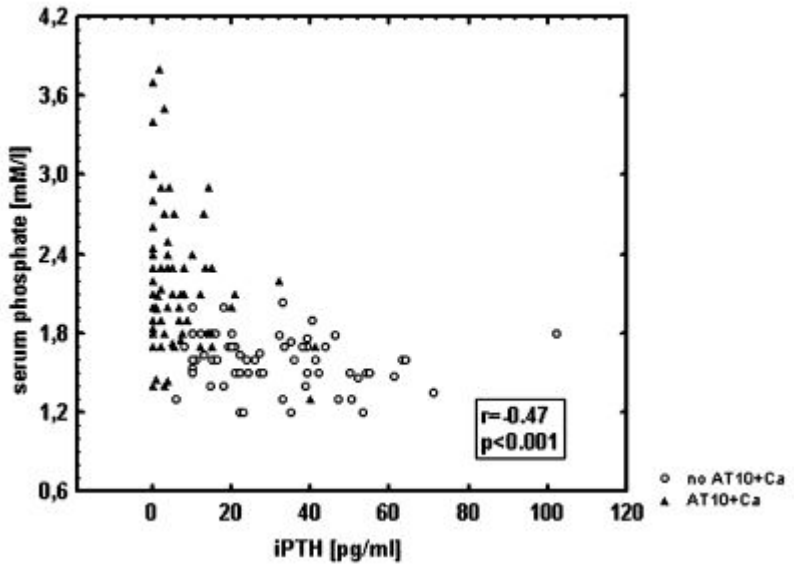

Fig.1: Correlation between serum P and iPTH values. The high-P / low-iPTH cases (triangles) corresponded to individuals who had also serum Ca concentrations below 2.0 mM.

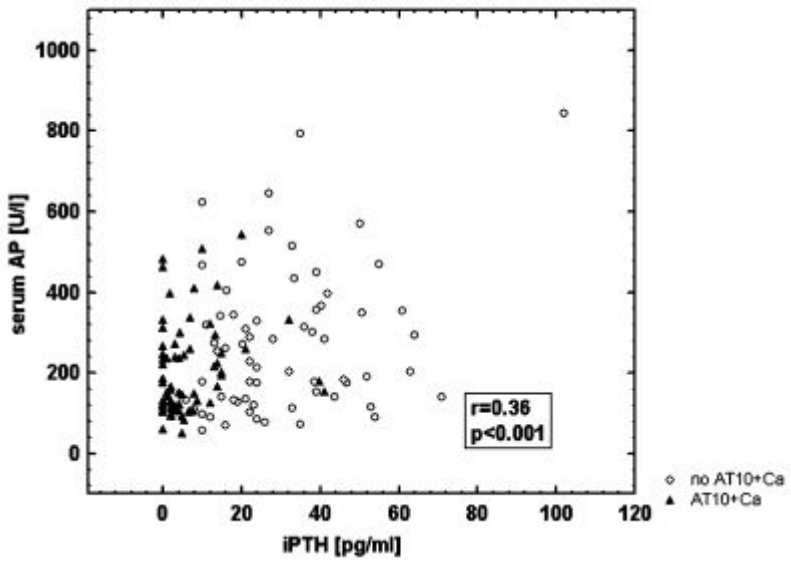

Fig.2: Weak correlation between serum AP and serum iPTH values. The AT10 / Ca–supplemented patients showed a low iPTH level.

The bone status of the patients was analyzed regarding the evolution of the cohortrs TBMC z-scores in the course of the visits. No correlation was detected between the TBMC (DXA) or their corresponding z-scores and the serum iPTH values (Fig. 3). A concentration of the AT-10 / Ca supplemented cases towards the lowest end of the serum iPTH range was observed.

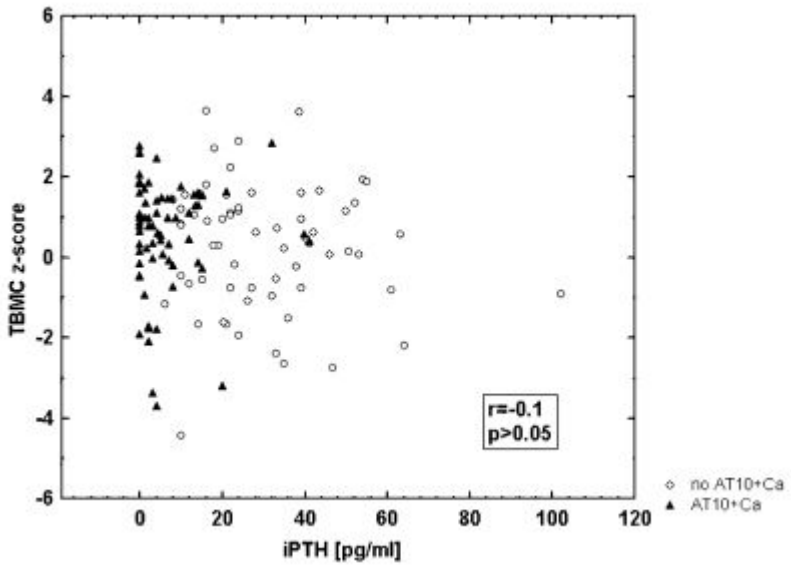

Fig.3: Lack of correlation between the TBMC z-scores and the serum iPTH activity showing relatively low iPTH values for the AT10 / Ca–supplemented patients.

The Tukey HST showed that the TBMC z-scores for boys and girls (Table 3) did not differ significantly throughout the control period (Fig. 4), regardless of the AT-10 / Ca administration and the parathyroid condition. The spline function graphs only indicated unsignificant trends. The TBMC values fitted well into the reference plot of the reference normal Argentine data (Fig. 5), suggesting that the total bone mass accrual would not have been impaired by PTH deficiency.

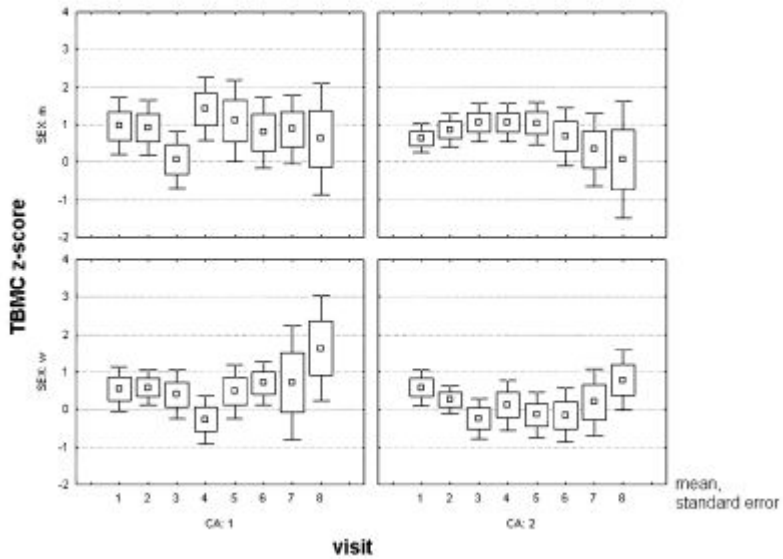

Fig.4: Means, SD and SE values of TBMC z-scores in boys and girls receiving or not the AT10 / Ca–supplementation along the 9 visits (n at each visit corresponds to table 3). The Tukey HSD test revealed no significant differences in TBMC z-scores between any of the visits within the same box.

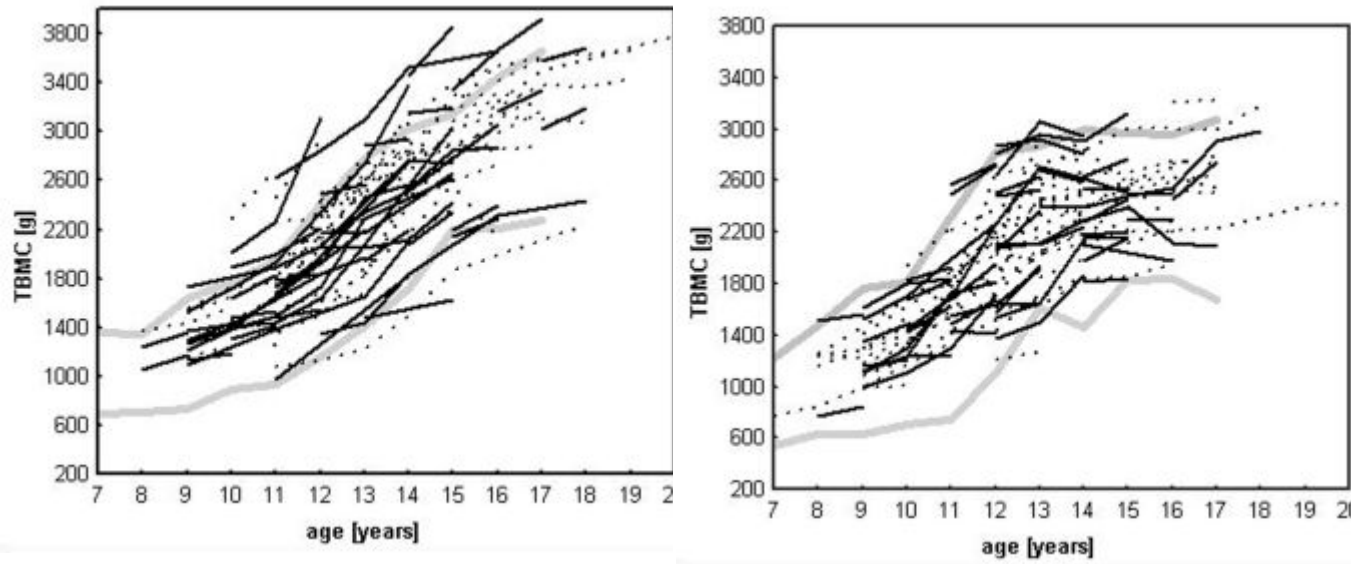

Fig.5: Evolution of the individual TBMC values of the boys (a) and girls (b) during the study follow-up. The 95% CI for the reference sample of normal Argentine children and adolescents [8] is shown between dashed lines. Values corresponding to visits for the same child are connected by lines.

From visit 1 to 9 no differences in growth gain were observed between both groups of boys and girls (data not shown).

Discussion

The data show the primary (surgical) nature of the hypoparathyroidism observed in the first group of patients, especially evident from the correlation graph between serum P and iPTH (coincidence of hyperhosphatemia and hypocalcemia). The incidence rate of permanent hypocalciemia or hypoparathyroidism was 6-14% higher in ours than in others' reports [2].

In a previous study in adults we had demonstrated a tendency of this type of patients to show a higher urinary Ca / creatinine excretion ratio than that of normal controls [5]. This observation suggests that the low serum Ca values of some of our children could be explained by a raise in the urinary excretion of Ca resulting from an impaired tubular resorption. Additionally, an impairment of the intestinal Ca absorption because of a reduction in calciferol metabolic rate poorly compensated by an incomplete supplementation with AT-10 may have contributed to that condition in some instances.

Expectedly, this associated deficit of parathyroid function and Ca availability would have chronically induced a greater reduction in bone formation (indicated by the correlative variation of serum AP and iPTH) than in bone resportion. As a result, the TBMC should have tended to decrease in correspondence with the serum iPTH level. However, there were no inter-group differences in TBMC large enough to alter the BMD data, proposedly because bone growth in length and width (bone modeling) were not reduced in the hypoparathyroid children.

Interestingly, the bone mass balance (as determined by the DXA-assessed «areal» BMD) seemed not to have been significantly impaired by the parathyroid malfunction in these children. Results suggest that changes in bone mineral followed those eventually induced in bone growth in length or width (bone modeling). Therefore, little or no impact on bone mineralization (i.e. the «true», volumetric BMD of the calcified tissue) and hence in bone material «quality» (i.e., intrinsic stiffness, elastic modulus) in mechanical terms would have been induced.

The study followed an intention-to-treat concept. Thus, patients who did not need a further course of radioiodine therapy were considered as „drop-outs“ and may have potentially influenced the primary goal to assess the TBMC. The noticeable but nonsignificant trend of bone mass to fall in the children that did not receive AT-10 / Ca supplementation may only have reflected some variation within the cohort. At variance with our findings, Pettifor et al. [10] showed that a low dietary Ca intake led to a lower apparent bone mineral density of the appendicular skeleton in 651 boys and girls 1-20 years of age. However, this observation may not be compatible with the mechanism involving parathyroid malfunction and consecutive hypocalcemia.

The impact of suppressive doses of T4 on bone in adults has not been clearly established yet [11]. There is no information available on the impact of high doses of T4 in a maturing skeleton. Nevertheless, although no control group of normal children treated with T4 was included in this study, our data do not suggest any negative T4 effect on bone mass development.

Comparability of the BMD data of our children with those shown by the Argentine reference database [8] may have been affected by the known technical differences between the two densitometer devices employed. However, the accuracy error in the densitometric estimation of the TBMC was determined to be below 4% [12]; the accuracy of the device used to measure the Argentine children was comparable with that of our densitometer [8,9,12,13], and the Argentine children were ethnically similar (Caucasian) to our patients. Moreover, the bone mass accrual of our patients fitted the expected magnitude according to Zanchetta’s data. Faulkner et al. reported TBMC values 10% lower than those obtained by Zanchetta et al. in girls and boys aged 8-16 years [14], but the reported numbers of children per comparable age groups were substantially lower than those in the Argentine study. A further study of 79 children aged 3-14 years, in

addition to confirm an accurate calibration of a scanner using dual photon absorptiometry (DPA) [15], showed very similar TBMC-values to those in the Argentine study.

In conclusion, our study shows that the primary impairment in parathyroid function and the subsequent hypocalcemia in these thyroidectomized children were not associated to measurable disturbs in the growth-related rate of bone mass accrual or mineralization as detected by the evolution of DXA t-scores in the studied conditions.

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