Endocrine, *vol. 10, no. 1, 53–56, February 1999* 0969–711X/99/10:53–56/$11.00

Acute and Early Effects of Triiodothyronine Administration on Serum Markers of Bone and Mineral Metabolism

Naofumi Kobe, Junta Takamatsu, Mitsuru Ito, Sadaki Sakane, and Nakaaki Ohsawa

First Department of Medicine, Osaka Medical College, Takatsuki, 8686, Japan

There have been few studies on acute changes of bone metabolism in humans by thyroid hormone. This study aimed to examine the effects of triiodothyronine on serum markers of bone and mineral metabolism during a 7-d course of daily 75 μg therapy in 14 normal volunteers by drawing blood on 1, 2, 3, 5, and 7 d of therapy.

Serum calcium concentrations did not significantly change during the course of therapy, while serum phosphorus concentrations were significantly ($p < 0.05$) decreased from 3.21 ± 0.43 mg/dL (mean ± SD) to 2.85 ± 0.46 mg/dL on the 7th d. Serum PTH concentrations were significantly decreased from 339 ± 116 pg/mL to 316 ± 29 pg/mL. Serum concentrations of alkali-phosphatase and bone-specific alkali-phosphatase were not significantly changed, but serum osteocalcin concentrations were significantly increased from5.71 ± 1.98 mg/dL to 6.73 ± 2.24 mg/dL. Serum carboxy-terminal propeptide of type I collagen concentrations were significantly decreased from 137.8 ± 33.7 μg/L to 119.2 ± 33.6 μg/L. Serum pyridinoline cross-linked telopeptide domain of type I collagen concentrations, a bone resorption marker, were significantly increased from 3.40 ± 0.77 to 3.87 ± 1.05 μg/L, and such significant increase was obtained from the 3rd day. The results indicate that some of bone and mineral markers change rapidly in response to triiodothyronine-induced acute thyrotoxicosis, but the manner of change is not the same as that of chronic thyrotoxicosis.

Key Words: Thyroid hormone; triiodothyronine; bone markers; thyrotoxicosis; bone; mineral.

Introduction

In patients with hyperthyroidism, bone mineral density is decreased *(1–3)*. The similar decrease is also seen in long-term suppressive therapy with thyroxine (T4) for prevention of thyroid neoplasms *(4)*, and the major cause is reported to be an accelerated turnover of bone metabolism *(2,5)*. However, acute and early effects of thyroid hormone on bone and mineral metabolism have not been well studied. There were an in vitro study using cultured fetal rat bone *(6)* and an in vivo study using rats by thyroxine for 3 wk *(7)*. In humans, Hasling et al. *(8)* determined some relative classical markers of bone metabolism including serum alkali phosphatase and osteocalcin after 1 wk of pharmacological dose of triiodothyronine (T3). Rosen et al. *(9)* recently investigated bone loss induced by 7-d administration of T3 with or without associated pamidronate therapy. The present study also examined in vivo changes of serum markers of bone and mineral metabolism by serial blood sampling in humans during administration of excessive T3, and the results have shown that some novel markers exhibit significant changes even within such short period of T3 therapy.

Results

During the T3 administration, 11 of 25 subjects were found not to take thyroid hormone sufficiently, because their serum T3 concentrations to monitor the drug compliance did not show the appropriate increase during the period. Similarly, the serum TSH concentrations were not appropriately suppressed. Thus, the data of the remaining 14 normal volunteers were further analyzed. Among them, five had palpitations, and seven had increased appetite, but the symptoms were not serious, and they completed receiving thyroid hormone. As shown in Fig. 1, serum free T3 concentrations were increased into a thyrotoxic range in the 14 subjects. Serum TSH concentrations were markedly suppressed to below 0.3 mU/L in these subjects. Serum free T4 concentrations were decreased to about 70% from the basal value on the 7th d of therapy (data not shown).

Serum calcium concentrations did not significantly change during the course of T3 therapy. As shown in Fig. 2A, the values were 9.29 ± 0.43 mg/dL before T3 therapy and

Received August 13, 1998; Revised October 22, 1998; Accepted October 22,1998.

Author to whom all correspondence and reprint requenst should be addressed: Dr. Junta Takamatsu, MD, First Department of Medicine, Osaka Medical College, 2–7, Daigakumachi, Takatsuki, Osaka, 569-0801, Japan; E-mail: juntat@cb3.so-net.or.jp.

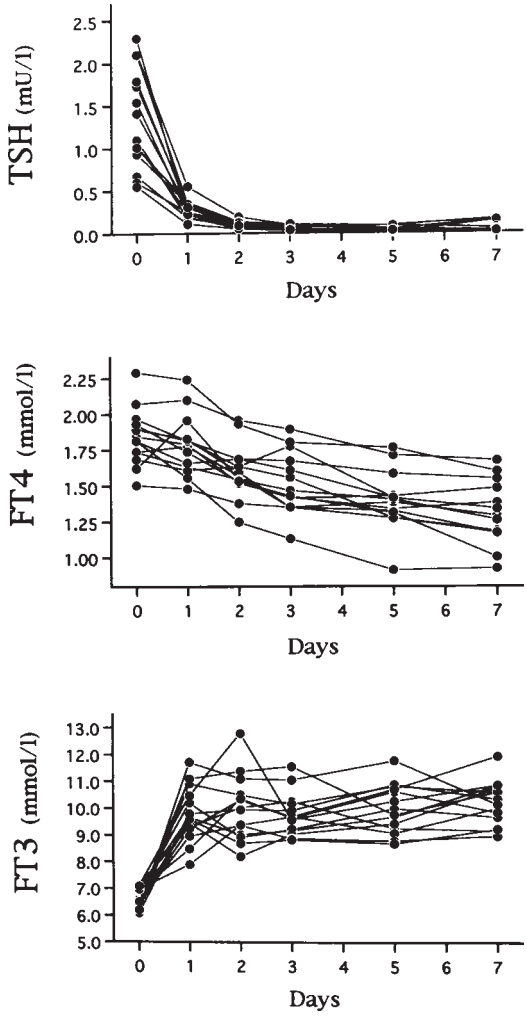

Fig. 1. Changes in serum TSH, free T4 and free T3 concentrations after administration of daily 75 μg of T3 for 7 d. The data before and after 1, 2, 3, 5, and 7 d of treatment were shown. Data of individual subjects are lined.

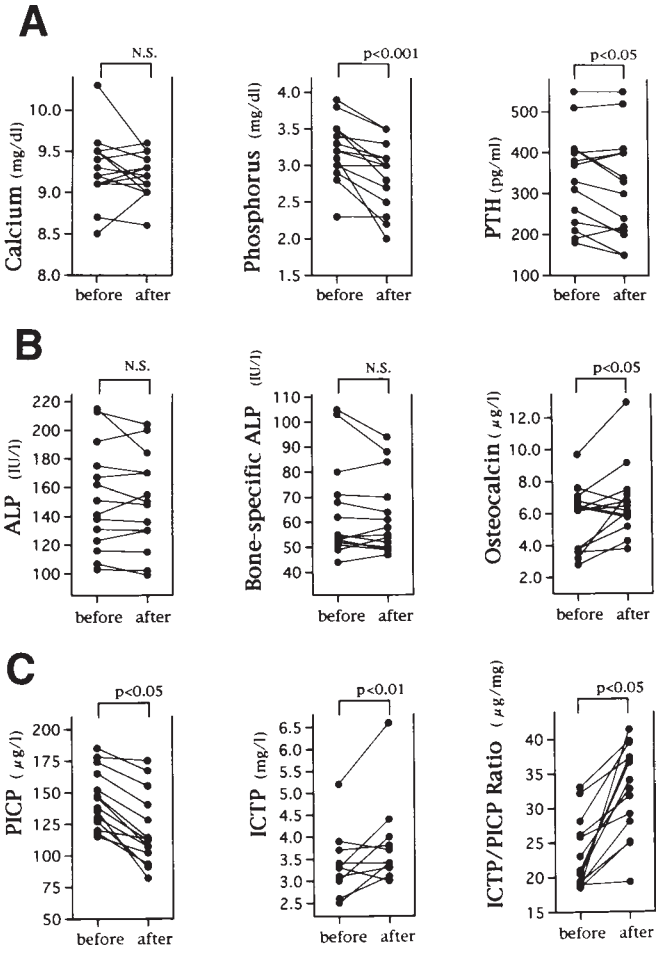

Fig. 2. Changes in serum markers of bone and mineral metabolism before and after administration of 75 μg of T3. The data before and after 7 d of T3 administration were shown; serum Ca, P and PTH in **(A)**, serum ALP, bone-specific ALP, and osteocalcin concentrations in **(B)**, and serum PICP and ICTP concentrations and ICTP/PICP ratios in **(C)**.

9.20 ± 0.26 mg/dL on the 7th d of therapy. Serum phosphorus concentrations were significantly ($p < 0.001$) decreased from 3.21 ± 0.43 mg/dL to 2.85 ± 0.46 mg/dL. Serum PTH concentrations were significantly ($p < 0.05$) decreased from 339 ± 116 pg/mL to 316 ± 129 pg/mL. As shown in Fig. 2B, serum ALP concentrations were not significantly changed after 7th d of T3 therapy (from131 ± 35 IU/L to 127 ± 31 IU/L). Similarly, serum bone-specific ALP concentrations were not significantly changed (from 65.2 ± 23.1 IU/L to 61.9 ± 18.0 IU/L). While, serum osteocalcin concentrations were significantly ($p < 0.05$) increased from 5.71 ± 1.98 mg/dL to 6.73 ± 2.24 mg/dL. As shown in Fig. 2C, serum PICP concentrations were significantly ($p < 0.05$) decreased from 137.8 ± 33.7 μg/L to119.2 ± 33.6 μg/L on the 7th d of therapy. Serum ICTP concentrations were significantly ($p < 0.01$) increased from 3.40 ± 0.77 μg/L to 3.87 ± 1.05 μg/L. As the result, serum ratios of ICTP/PICP (μg/mg) were significantly ($p < 0.05$) increased from 25.57 ± 6.2 to 33.50 ± 7.15.

When serum PICP and ICTP concentrations were further examined serially on 0, 1, 2, 3, 5, and 7th d, and the percent changes from the basal value were calculated, as shown in Fig. 3, a significant decrease of serum PICP was obtained on the 5th d, and significant increase of ICTP on the 3rd d. Accordingly, the significant increase of the ICTP/PICP ratios were obtained on the 5th d.

Discussion

The increase of serum free T3 concentrations together with suppressed serum TSH concentrations during T3 administration in 14 out of 25 normal volunteers indicates that the compliance of T3 intake was sufficient, which is based on our previous report on suppression of serum TSH with the same protocol of T3 administration *(10)*. The decrease of serum free T4 concentrations was also obtained, which indicates the suppression of thyroid hormone secretion from the thyroid gland as the consequence of TSH suppression by the T3 therapy.

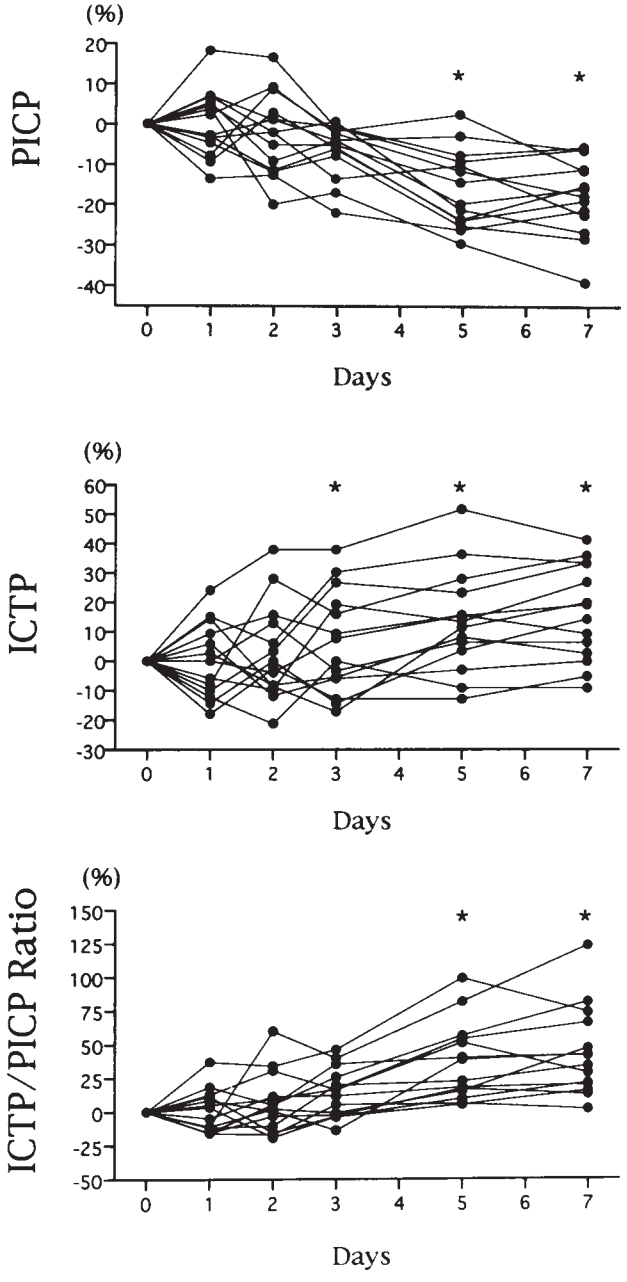

Fig. 3. Percent changes in serum PICP and ICTP concentrations and ICTP/PICP ratios during T3 administration. The data before and after 1, 2, 3, 5, and 7 d of treatment were shown. Data are lined in individual patient. *, significant difference ($p < 0.05$) from the pretreatment value.

There are many papers on bone changes during thyroid hormone replacement for hypothyroidism, but thyroxine was administered for long time, and we cannot get the data of triiodothyronine administration , particularly to normal volunteers, like our study. Only one study by Rosen et al. *(9)* used triiodothyronine for 7 d to observe the effect of an antiosteoporotic drug. Their study was in part similar to our study, but they measured bone markers only on d 1 and 8, and aimed to analyze chronic phase of triiodothyronine administration to observe effects of antiosteoporotic drug, pamidronate, whereas our study focused on very early phase of changes of bone markers. There have been no reports, as far as we know of, on acute effects by administration of T4 , not T3. Although the dose potency of T4 and T3 is not easy to compare, the present study is dealing with considerably greater dosage of thyroid hormone regimen.

It is reported that serum phosphorus concentration is increased in patients with chronic state of thyrotoxicosis *(2)*, but in this study, serum phosphorus concentrations were decreased. The reason of such discordance is not clear, but there might exist different mechanisms between persistent thyrotoxicosis such as hyperthyroidism and acute thyrotoxicosis such as T3 therapy of this study. Regarding the failure of increase in serum calcium concentrations, an increase in urinary calcium excretion might have been observed in our subjects *(9)*, although the measurement was not performed. Increased bone resorption and release of the calcium into the serum is the likely cause of decrease in serum PTH obtained in this study. Also, the decreased serum phosphorus concentrations obtained in our subjects may contribute the PTH suppression.

Serum ALP as the osteoblastic marker is increased in patients with hyperthyroidism *(2,11,12)*. In the present study, however, serum ALP, as well as bone-specific ALP having more specificity to the bone than the total ALP *(13)*, were not changed. The reason is not clear, but we previously reported that serum concentrations of sex-hormone binding globulin and ferritin, reliable peripheral markers of thyroid hormone action on peripheral tissue, were not significantly increased after 7 d of T3 therapy *(14)*, and it was assumed that the period of T3 therapy was too short to exhibit increases of serum sex-hormone binding globulin and ferritin. The similar mechanism can be considered in the case of serum ALP and bone-specific ALP. Indeed, it is frequently observed that the increased serum ALP concentrations in patients with hyperthyroid Graves' disease are not rapidly decreased to normal but persistently elevated even when euthyroidism is achieved after antithyroid therapy. Serum osteocalcin concentrations were rapidly increased, which was compatible to previous reports *(15)*, suggesting that the response of production of this protein is more rapid than that of ALPs.

The increase in serum ICTP concentrations, the recently developed reliable marker of bone resorption, was compatible to previous reports *(16–18)*. One of the prime purposes of the present study was to know the time of the initiation of changes of markers during the course of T3 administration by serially drawing blood on d 1, 2, 3, 5, and 7, and serum ICTP concentration did not exhibit significant changes until the second day, but became significant on the third day. The decrease in serum PICP concentration is inverse to previous reports showing the increase in chronic hyperthyroidism *(17,18)*. The reason is not clear, but it may be speculated, from the data of initiation of ICTP changes, that bone resorption is initially activated by T3 , but the bone formation is not yet

activated within 7 d: the bone formation might initiate to enhance in later days as the subsequent response to the preceding bone resorption.

Finally, determination of biochemical markers of bone turnover, either classical or new, have brought new insights on the activity of bone, but careful interpretation of the data of these markers is required in practical medicine, particularly in patients whose thyroid function is changing rapidly.

Materials and Methods

Subjects

Twenty-five normal volunteers (16 men and 9 women with the mean ± SD age of 29 ± 8 yr) participated in the study. They had no clinical or biological evidence of thyroidal or bone diseases. After a written consent on this study was obtained from each subject, 75 μg of T3 daily in three divided doses were orally administered for 7 d to 25 normal volunteers. During the T3 therapy the subjects were assigned not to change their usual daily lives including meals. Blood was drawn at fasting before and after 1, 2, 3, 5, and 7 d of T3 therapy.

Determinations

Serum concentrations of calcium, inorganic phosphorus (phosphorus), high-sensitive PTH ,and alkali-phosphatase were determined. Serum concentrations of bone-specific ALP were determined by iso-ALP kit, Boehringer-Mannheim, with reference value of less than 100 IU/L and osteocalcin were measured by IRMA assay (Yuka Medics, Japan) with reference value of 2.5–13 μg/L. The determinations extended to serum concentrations of carboxy-terminal propeptide of type I collagen (PICP) (Orion Diagnostica Co.) with reference value of 30–182 μg/L, and serum concentrations of pyridinoline cross-linked telopeptide domain of type I collagen (ICTP) (Chugai Pharmaceutical Co.) with the reference value of 0.76–5.24 ng/mL.

Statistical Analysis

Grouped data were expressed as the mean±SD. The data on T3 therapy were compared with those of untreated state. Statistical analysis was performed using Student's paired *t*-test, and *p* value of less than 5% was considered to be statistically significant.

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