Bone Mineral Density Trends in Indian Patients with Hyperthyroidism – Effect of Antithyroid Therapy

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Abstract

Background: Hyperthyroidism is associated with bone loss, which is reversible after treatment. The extent of reversibility of loss of bone mass density (BMD) in hyperthyroid patients after treatment especially at forearm is not clear. Therefore, the present study was conducted to assess degree of reversibility in bone mineral density following one-year medical treatment in Indian patients with hyperthyroidism.

Methods: A total of 30 consecutive patients with hyperthyroidism were included in this one year study at All India Institute of Medical Sciences, New Delhi, India. All the patients were assessed for parameters of bone mineral homeostasis such as calcium, phosphorous, alkaline phosphatase, 25-hydroxy vitamin D [25 (OH) D], parathyroid hormone (PTH) at the time of diagnosis and after one year medical treatment. Bone mineral density was measured using Hologic DDX scan at hip, spine and forearm. All the patients received medical therapy with carbimazole. The parameters of bone homeostasis and bone mineral density at base line and after one year medical treatment was compared.

Results: All patients attained euthyroid status after eight weeks of carbimazole therapy. Parameters of bone homeostasis such as calcium, phosphorous, 25 (OH) D and PTH did not show any significant change from base line. Bone mineral density expressed as bone mineral content in gm/cm² at left hip neck, trochanteric and intertrochanteric region was significantly higher after carbimazole therapy (745.2±127.6 gm/cm² vs. 688.2±123.5 gm/cm²; p=0.02, 573.4±109.9 gm/cm² vs. 641.0±138.0 gm/cm²; p=0.005 and 1008.6±185.5 gm/cm² vs.938.0±145.3 gm/cm² p=0.0131 respectively). Bone mineral density at lumbar spine expressed as either T and Z score was significantly higher after treatment (10 months of euthyroid state) (-0.6±1.3 vs. -1.7±1.2, p=0.013 and -0.4±1.2 vs. -1.4±1.2, p=0.012 respectively). However Bone mineral measures as T and Z score at left forearm decreased significantly after one year of medical therapy.

Conclusion: In Indian patients with hyperthyroidism, the pattern of recovery of bone loss after one year of antithyroid therapy suggests early recovery at hip and lumbar spine and deterioration at forearm.

Introduction

Thyroid hormones are required for skeletal development and establishment of peak bone mass. In adults, Thyronine T₃ regulates bone turnover and bone mineral density, and normal euthyroid status is essential to maintain optimal bone strength. The patients with hyperthyroidism both overt and subclinical are at increased risk of osteoporosis related to catabolic effects of excess thyroid hormones. Such alterations in bone mineral homeostasis are observed with much greater frequency in Indian patients with thyrotoxicosis. Previously, we have documented disturbances in bone mineral homeostasis in patients with hyperthyroidism. Briefly, the results indicated that 26.6% of Indian patients with hyperthyroidism are vitamin D deficient as demonstrated by subnormal 25(OH) D levels. The bone mineral density expressed as either T and/or Z score or bone mineral content in gm/cm² was significantly lower in them when compared to the Caucasian population as per norms provided by WHO. The results also suggested that vitamin D deficiency aggravates bone loss in patients with hyperthyroidism. Studies conducted in Western countries have documented that parameters related to bone mineral density are reversed with antithyroid treatment 4 at hip and lumbar spine. The extent of reversibility of loss of bone mass density (BMD) in hyperthyroid patients especially at forearm after treatment is not clear. Only one published study from India has shown increase in BMD after treatment of thyrotoxicosis. In this study BMD was measured at spine only. Patients with active thyrotoxicosis in India are at increased risk of osteomalacia or osteoporosis due to associated vitamin D deficiency. Therefore, the present study was conducted to assess degree of reversibility in bone mineral density following one-year medical treatment with carbimazole in patient with hyperthyroidism. In the background of high prevalence of vitamin D deficiency in population this study assumes significance.

Materials and Methods

Thirty consecutive patients with hyperthyroidism attending endocrine clinic of All India Institute of Medical Sciences, (AIIMS), New Delhi were included in the study after taking appropriate ethical clearance and informed consent. All patients were subjected to detailed history and clinical examination. History included assessment of severity of hyperthyroidism using Wayne’s score, osteomalacia / osteoporosis discriminatory score described by McKenna et al.11 Fasting venous samples of all study subjects were drawn at 0800-0900 hrs without venostasis in calcium free test tubes. Serum was separated in a refrigerated centrifuge at 800 x g for 15 minutes at 4°C, and stored in multiple aliquots at –20°C for serum T₄, TSH, 24 (OH) D and PTH assays. All hormone assays were batched together. Serum calcium, phosphorous and alkaline phosphatase were estimated on the day of collection. Serum T₄ and serum 25 (OH) D estimation were done by radioimmuno assay. Serum intact PTH and TSH concentration were measured by IRMA technique. Intra-assay coefficient of variation ranged from 4.0% to 7.2% for T₄ and TSH and 3.4% to 6.4% for serum PTH. The normal range in our lab is 52-167nmol/L for serum total T₄, 0.3-3.0mmol/L for TSH. Normal kit range for PTH is 13-54ng/l. Normal level of serum calcium, phosphorous, serum alkaline phosphatase are 2.15-2.7mmol/l, 0.8-1.5mmol/l and 3-13KA units respectively.

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Received: 09.06.2010; Revised: 27.08.2010; Re-revised: 27.11.2010; Accepted: 29.11.2010

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After basal investigation, all patients were started on carbimazole therapy in the dose of 30-45 mg/day. After achieving euthyroidism a maintenance dose of 10-20 mg/day was continued. Euthyroidism was achieved between 6-10 weeks as indicated by Wayne’s clinical score for thyrotoxicosis (<19) and normal serum total T4. All subjects also received propranolol 60-120 mg/day in three divided doses. None of these patients received calcium and vitamin D supplementation along with antithyroid therapy. During follow up all patients were assessed clinically and biochemically at two monthly intervals. Euthyroid status was maintained in all subjects during follow up. Repeat study was conducted in 15 patients on carbimazole therapy during same month to avoid seasonal variation in 25 (OH) D and PTH. Beside 25 (OH) D and PTH repeat biochemical parameters included serum calcium, phosphorous alkaline phosphatase. Bone mineral density was measured at left hip, lumbar spine and left forearm using the same machine i.e., Hologic DR 4500 A densitometry. Bone mineral density at hip was also separately analyzed at trochanteric, intertrochanteric and neck region. Data was represented as mean ± SD. Paired “t” test was used to compare mean of various indices before and after treatment. A “p” value less than 0.05 was considered significant.

**Results**

**Clinical and Biochemical Indices**

Clinical characteristic and biochemical indices of thyrotoxic state and bone homeostasis before and after treatment are given in Table 1. All patients achieved clinical and biochemical euthyroidism after eight weeks of carbimazole therapy as reflected by normal Wayne’s score and normal total T4 levels in euthyroid range (T4, 131.7±13.6 nmol/l). Euthyroidism was maintained in all patients during the study period. At the end of one-year antithyroid therapy, mean weight at treatment was significantly lower and normalized (45.3±9.2 kg; p<0.05) (Table 2). Similarly mean Wayne’s score after one-year treatment was significantly lower and normalized as compared to baseline (8.14±5.8 vs. 24.5±5.3; p=0.0012). At end of one year of carbimazole therapy, the mean total T4 and TSH value were also in euthyroid range. Five each of the patients at presentation had hypocalcemia and elevated serum alkaline phosphatase levels and one had hyperphosphatemia. Thirty six percent patients had osteomalacia based upon osteomalacia/osteoporosis discriminatory index score. At the end of one year treatment with carbimazole patients did not have significant change in parameter related to bone mineral homeostasis such as serum calcium, phosphorous, alkaline phosphatase, 25(OH) D and PTH.

**Bone Mineral Measures**

Changes in bone mineral density in patient with

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>49.3±9.2</td>
<td>51.1±7.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Wayne’s Score</td>
<td>25.5±5.3</td>
<td>8.14±5.87</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum total T4 (nmol/l)</td>
<td>28±88.8</td>
<td>117.5±20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum Calcium (mmol/l)</td>
<td>2.15±0.19</td>
<td>2.26±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Phosphorous (mmol/l)</td>
<td>1.25±0.23</td>
<td>1.27±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Alkaline Phosphorous (KAU)</td>
<td>12.9 ± 5.3</td>
<td>13.9 ± 5.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 1: Clinical characteristic and biochemical indices of thyrotoxic state in patients with hyperthyroidism before and after treatment

Table 2: Indices of bone mineral measure in patients with hyperthyroidism before and after treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip BMC (gm/cm²)</td>
<td>773.13±150.7</td>
<td>831.6±149.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hip T score</td>
<td>-1.7±1.4</td>
<td>-1.1±1.3</td>
<td>0.023</td>
</tr>
<tr>
<td>Hip Z score</td>
<td>-1.6 ± 1.3</td>
<td>-0.8 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip neck BMC (gm/cm²)</td>
<td>688.2±123.5</td>
<td>745.2±127.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Trochanteric BMC (gm/cm²)</td>
<td>573.4±109.9</td>
<td>641.0±138.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intertrochanteric – BMC (gm/cm²)</td>
<td>938.8±145.3</td>
<td>1008.6±185.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Forearm – BMC (gm/cm²)</td>
<td>506.4 ± 96.8</td>
<td>472.1 ± 74.2</td>
<td>NS</td>
</tr>
<tr>
<td>Forearm T score</td>
<td>-1.5 ± 1.7</td>
<td>-2.3 ± 1.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Forearm Z score</td>
<td>-1.4 ± 1.7</td>
<td>-2.0 ± 1.1</td>
<td>0.071</td>
</tr>
<tr>
<td>Lumbar spine BMC (gm/cm²)</td>
<td>902.2±149.6</td>
<td>986.3±145.8</td>
<td>0.070</td>
</tr>
<tr>
<td>Lumbar spine T score</td>
<td>-1.7±1.2</td>
<td>-0.6±1.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lumbar spine Z score</td>
<td>-1.4±1.2</td>
<td>-0.4±1.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Bone mineral density expressed as bone mineral content in gm/cm² at hip tended to be higher after one year of antithyroid treatment (831.6±149.6 vs. 773.13±150.7; p=0.0621) as compared to their pretreatment value. The bone mineral density at hip expressed as either T and Z score was significantly higher after one-year treatment (1.7±1.4 vs. 1.2±1.3; p=0.0027 and -0.8±1.0 vs. -1.6±1.3; p=0.006). Bone mineral density expressed as bone mineral content in gm/cm² at left hip neck, trochanteric and intertrochanteric region was significantly higher after carbimazole therapy (745.2±127.6 gm/cm² vs. 688.2±123.5 gm/cm²; p=0.005 and 1008.6±185.5 gm/cm² vs. 938.8±145.3 gm/cm² p=0.0131 respectively). Bone mineral density at lumbar spine expressed as either T and Z score was significantly higher after treatment (10 months of euthyroid state) (+0.6±1.3 vs. -1.7±1.2; p=0.013 and -0.4±1.2 vs. -1.4±1.2; p=0.012 respectively). The mean bone mineral density expressed as bone mineral content in gm/cm² at left forearm deteriorated after attainment of euthyroid status when compared to values obtained before treatment (472.1±74.2 gm/cm² vs. 506.4±96.8 gm/cm²; p=0.7036). However, difference did not attain statistical significance. Similarly, BMD expressed as either T score at left forearm was significantly lower after medical therapy (-1.5±1.7 vs. -2.3±1.1; p<0.05).

Overall, bone mineral content increased by 7.4 and 9.3% at hip, spine respectively. However, the BMC reduced by 6.7% at forearm.

**Discussion**

The present study was designed to assess the reversibility of parameters related to bone mineral homeostasis and density among Indian patient with hyperthyroidism at hip, spine and forearm following medical treatment with carbimazole therapy. The key findings of study are improvement in bone density measures at hip and spine and deterioration at forearm.

Hyperthyroidism is an important cause of secondary osteoporosis and is associated with significant bone loss at hip, forearm and lumbar spine. Thyrotoxicosis related loss of bone mass tend to recover following treatment with antithyroid drugs. In the present study at the end of one year of antithyroid therapy there was a significant improvement in bone mineral density expressed as T and Z score at left hip neck, trochanteric and intertrochanteric region after treatment. The pattern of
recovery of bone loss at hip and lumbar spine among patients with thyrotoxicosis in India is similar to that reported by investigators from the Western countries. Diamond et al, 1994 has reported reversibility of bone loss at lumbar spine in a group of postmenopausal women after one year of euthyroidism.12 Similarly Mora et al, 1999 has reported significant improvement in BMD at spine and whole body bone density after one year of treatment.13 Recent studies from Netherland and China also show a similar trend of change in bone density after treatment in hyperthyroidism.14,15 The mean BMD of lumbar spine, femoral neck, Ward triangle and total hip bone density increased by 5.9, 3.8, 3.0 and 6.7%, respectively, after one year of treatment, all significant increases except the increase in Ward triangle bone mass density.14 Zhang et al has reported that the course of disease and menopause has an effect on the BMD in female patients with hyperthyroidism

Interestingly, in the present study the bone density at forearm expressed either as bone mineral content in gm/cm² or as T and Z scores worsened after one year of carbimazole therapy. Such paradoxical deterioration of bone density at forearm despite antithyroid drug treatment has been reported earlier. Oikawa et al, 1997 assessed bone density by DEXA in 79 thyrotoxicosis patients and demonstrated persistent bone loss despite three years of antithyroid drug therapy.9 Toh et al studied 23 patients with thyrotoxicosis and demonstrated a trend of continuous decline of bone density at forearm despite improvement at hip and forearm after two year of carbimazole therapy.8 Fraser et al, (1971) reported increased fracture rate at forearm in postmenopausal women with hyperthyroidism treated with different modalities even after five years of euthyroidism.9 The reasons for delayed recovery or failure to show recovery at forearm has been attributed to predominance of cortical bone at forearm, which has slower activation frequency time.16 Activation frequency indicates how often a given site of bone surface undergoes resorption and subsequent formation. In contrast to trabecular bone cortical bone has less surface to volume area for bone remodeling.

The pattern of bone loss in the present study is also consistent with that seen in osteomalacia. Patients with hypovitaminosis D and secondary hyperthyroidism demonstrated increased bone loss at lumbar spine and hip. Mezquita et al (2001) studied 161 postmenopausal females. Thirty nine percent of females with vitamin D levels less than <15ng/ml had significant osteoporosis at lumbar spine.17 Collin et al (1998) also reported similar results in postmenopausal females.18 In studies conducted by Mezquita et al19 and Collin et al20 bone mineral density at lumbar spine correlated with 25 (OH) D levels. There is a paucity of data on BMD at forearm in patients with osteomalacia. Serhan et al assessed BMD at forearm in 110 Asians Indian residents in UK Bone mineral density was significantly reduced in them at forearm.19 In the previous study we had observed that 26% patients with hyperthyroidism in India had concomitant vitamin D deficiency. Patients with thyrotoxicosis and concomitant vitamin D deficiency had significantly higher bone loss at hip and forearm when compared to thyrotoxic patients who did not have associated vitamin D deficiency.3 As there was no change in status of parameters related to bone mineral homeostasis such as 25(OH)D and PTH levels, the changes observed in this study are due to antithyroid therapy.

There are a few limitations of this study. We have followed up these patients for a period of one year only. The reversibility of bone loss at forearm needs to be studied for a longer duration of treatment. The effect of combination of medical therapy and vitamin D supplementation also needs to be evaluated in view of widespread hypovitaminosis in Indian population.

To conclude, Indian patients with hyperthyroidism have significant reduced bone mineral density during thyrotoxic state and the pattern of reversal of bone loss after one year of antithyroid therapy with carbimazole suggests early recovery at hip and lumbar spine and deterioration at forearm.

References