Clinical observation of bone metabolism before and after $^{131}$I treatment in premenopause adult female hyperthyroidism patients with low bone mass

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ABSTRACT

Objective: To observe the bone metabolism before and after $^{131}$I treatment in premenopause female hyperthyroidism patients with low bone mass patients of different age. Methods: A total of 78 premenopause female patients hyperthyroidism with low bone mass were divided into two different age groups: premenopause female patients less than 35 years old in group A ($n=38$). Patients above 35 in group B ($n=40$). 78 healthy adults of same age were enrolled as the control group. The bone mineral density (BMD) and bone turnover markers including type I procollagen N-terminal propeptide (PINP), $\beta$-C-terminal telopeptides of type 1 collagen ($\beta$-CTX) of two groups were measured before and 6 months and 12 months after $^{131}$I treatment to observe the bone metabolism and the restorability of BMD. Results: After prolonged treatment with $^{131}$I, PINP and $\beta$-CTX of group A decreased and BMD increased gradually in a time-dependence way. And there was no significant difference when compared to the normal after 12 months. PINP and $\beta$-CTX of group B decreased gradually, after 12 months, BMD of group B restored when compared to the level of before treatment but lower than group A. Conclusions: In young female hyperthyroidism patients with low bone mass (<35 years), BMD can be restored to normal levels as reversing of high bone turnover after $^{131}$I treatment. Short-term clinical observation showed that high bone turnover was reduced partly in premenopause female patients (>35 years) treated only with $^{131}$I, but still at a high level, BMD can not restored completely.

1. Introduction

Graves disease is the most common cause of hyperthyroidism, accounting for about 85% of the cases of hyperthyroidism. In hyperthyroidism patients excessive systemic thyroid hormones interferes with normal bone metabolism, causing high bone turnover and negative calcium balance, losing of bone mass, results in low level of bone mass even up to osteoporosis, seriously affects the health and quality of life of the patients. In order to better guide the clinical diagnosis and treatment, PINP, $\beta$-CTX, and BMD in 78 premenopausal women patients with hyperthyroidism and low bone mass were measured continuously and repeatedly before and after $^{131}$I treatment in our study. The main results were described as follows.

2. Materials and methods

2.1 Objects of study

A total of 243 cases of hyperthyroidism patients to be receiving $^{131}$I treatment who were firstly diagnosed by the Department of nuclear medicine of the First Affiliated Hospital of Hainan Medical University between 2013-2015 consists of 51 male patients and 192 female patients. All patients received dual energy X-ray absorptiometry measurements before $^{131}$I treatment. 78 premenopausal patients with low bone mass ranged from 19-54 (34±11) ages. They were divided into two groups by the age of 35, patients less than 35 years old were in group A ($n=38$), patients above 35 in group B ($n=40$). 78 same age healthy volunteers or physical check-up adults were enrolled as control group(group A1:...
2.2 Instruments

ASY-00409 dual energy bone density measuring instrument (Hologic company of America) with high precision (CV<1.0%) was used. Roche chemiluminescence instrument was used for PINP and β-CTX detection. The normal range of reference value for β-CTX: premenopausal women were less than 0.573 ng/mL, and postmenopausal women were between 1.008 mg/mL, for PINP, premenopausal women were between 15.13-58.59 ng/mL, and postmenopause women were between 16.27-73.87 ng/mL. Because the main affected regions of osteoporosis are lumbar vertebrae and hips bone, the bone mineral density of femoral neck and L1-L4 were measured.

2.3 Research method

Inclusion criteria: All patients had typical clinical manifestations of thyrotoxicosis, and the thyroid function and iodine uptake rate test met the diagnostic criteria for Graves hyperthyroidism. No smoking history, no past medical history of liver and kidney disease, rheumatic diseases, diabetes or other endocrine diseases were reported. No usage history of calcium supplements, vitamin D preparations and hormone were reported. Osteoporosis patients were grouped by the diagnostic criteria depending on the T value[1]: Normal group of bone mass (T>-1.0), Osteopenia group (-2.5<T≤-1.0), osteoporosis group (T≤-2.5). 78 premenopausal women were less than 35 years old increased significantly compared with that before treatment (P<0.05), and it returned to normal level at 12 months showing no significant difference compared with A1 group (P>0.05). BMD of femoral neck and L1 to L4 from group A premenopausal patients less than 35 years old increased significantly compared with that before treatment (P<0.05). And it returned to normal level at 12 months showing no significant difference compared with A1 group (P>0.05). BMD of femoral neck and L1 to L4 from group A premenopausal patients less than 35 years old increased significantly compared with that before treatment (P<0.05). And it returned to normal level at 12 months showing no significant difference compared with A1 group (P>0.05).

2.4 Statistical analysis

The data were analyzed by statistical software. The measurement data were expressed as the mean ± standard deviation (Mean ± SD). The difference between groups was compared by student’s t test. The difference was considered statistically significant when P<0.05.

3. Results

3.1 BMD Changes in two groups of patients before and after 131I treatment

There was no significant difference in BMD value (P>0.05) between two control groups A1 and B1 before treatment, 6 months and 12 months after treatment. Before treatment, there was no significant difference in BMD value between the two treatment groups (P>0.05). BMD of femoral neck and L1 to L4 from group A premenopausal patients less than 35 years old increased significantly compared with that before treatment (P<0.05). And it returned to normal level at 12 months showing no significant difference compared with A1 group (P>0.05). BMD in group B recovered after treatment with 131I, and BMD at 6 months and 12 months was significantly different from that before treatment (P<0.05). BMD at 12 month was similar to that at 6 month, still lower than control group, no significant difference was found between them. BMD of group B at 12 month was significantly different from that of group A and control group A1, B1 at 12 month (P<0.05). For details, see Table 1.

3.2 Changes of PINP and β-CTX of two groups before and after 131I treatment

The value of PINP and β-CTX detected at 0 month, 6month, 12 month from group A1, group B1 changed scarely, showing no significant difference (P>0.05). There was no significant difference between PINP and β-CTX from two patients group A, B (P>0.05) before treatment. Both patients group significantly were higher than corresponding control group A1 and B1 (P<0.05). After 131I treatment, the values of PINP and β-CTX of the two groups at 6 month were significantly lower than those corresponding group values before treatment (P<0.05) and almost back to normal level, PINP and β-CTX from group A at 12 month was similar to that at 6 month. β-CTX from group A continued to decrease, PINP from group A continued to increase, significantly higher than that at 6 month (P<0.05). PINP and β-CTX of group A at 12 month were significantly different from that of control group A1, B1 and group A

Table 1.

The BMD changes of the two patients groups before and after treatment.

<table>
<thead>
<tr>
<th>Group</th>
<th>0 month</th>
<th>6 month</th>
<th>12 month</th>
<th>0 month</th>
<th>6 month</th>
<th>12 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=38)</td>
<td>0.895±0.10^a</td>
<td>0.996±0.12^a</td>
<td>1.122±0.11^a</td>
<td>0.780±0.11^*</td>
<td>0.841±0.08^*</td>
<td>0.902±0.09^*</td>
</tr>
<tr>
<td>A1 (n=38)</td>
<td>1.118±0.13</td>
<td>1.111±0.08</td>
<td>1.115±0.07</td>
<td>0.901±0.10</td>
<td>0.907±0.07</td>
<td>0.906±0.08</td>
</tr>
<tr>
<td>B (n=40)</td>
<td>1.120±0.09</td>
<td>1.117±0.08</td>
<td>1.118±0.10</td>
<td>0.909±0.07</td>
<td>0.905±0.09</td>
<td>0.908±0.08</td>
</tr>
<tr>
<td>B1 (n=40)</td>
<td>0.901±0.08^a</td>
<td>0.995±0.09^a</td>
<td>0.999±0.07^a</td>
<td>0.782±0.09^a</td>
<td>0.837±0.09^a</td>
<td>0.841±0.08^a</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, ^P<0.05; Compared between group A and B, *P<0.05, compared with control group, &P<0.05.
At present, many studies have shown that hyperthyroidism has a higher prevalence of low bone mass and osteoporosis as to 54.1%. Relevant studies show that hyperthyroidism leads to bone mineralization time reduction, bone matrix synthesis reduction, susceptibility to low bone mass, and even osteoporosis. TSH stimulates mesenchymal stem cell self-renewal and cartilage differentiation, and directly participates in formation of bone and cartilage[6]. The plenty of thyroid hormones in hyperthyroidism patients promote osteoclasts more than osteoblasts, leading to bone mineralization time reduction, bone matrix synthesis reduction, susceptibility to low bone mass, and even osteoporosis. Relevant studies show that hyperthyroidism has a higher prevalence of low bone mass and osteoporosis as to 54.1%(7). The importance and role of \(^{131}\)I therapy has been more and more recognized for the treatment of hyperthyroidism[8]. At present, many studies have been done on the diagnosis and treatment of hyperthyroidism with osteoporosis or low bone mass and find that with the recovery of thyroid function, bone mineral density will be improved. However, the degree of improvement and the time required and the need for treatment of low bone mass/osteoporosis still remains controversial. No international guidelines and expert consensus have been put forward.

**PINP, \(\beta\) -CTX and BMD taken as monitoring indicators , can reflect the metabolism of bone tissue[9], can help to provide a good basis to study bone metabolism characteristics in patients with hyperthyroidism and low bone mass. Peak bone mass means the highest value of bone mass, usually attains at the age of 20-35[10]. Attainment of peak bone mass at young age is closely related to the occurrence of low bone mass and osteoporosis. Chinese medical classics “Su Wen Ancient Naive Theory” elucidate: Women seven years old(at first seven year), Shen qi increases , teeth  renews , hairs grows…… Women seventy-five years old (at fifth senven year) , Yang Ming declines, face begins to turn dark , the hair begins to fall ; Women forty-two years old ( at sixth seven year ) , The three Yangs decline, face turns darker , hair begins to turn white……, reveals that the 35 age for woman is an important turning point of body function. Chinese scholars have observed the difference of bone mineral density between the non menopausal group and the menopausal group after \(^{131}\)I treatment for female Graves patients presenting statistical significance (\(P<0.05\))[11]. Therefore, considering Chinese people inherent physical characteristics, growth, development, aging and peak bone mass characteristics, our study choose age 35 as an important time point to classify premenopausal patients with hyperthyroidism and low bone mass into <35 years old group, >35 years old group who were observed continuously and dynamically the changes of bone metabolism before and after treatment. It helped to eliminate the related effects of sex hormones. Our study found that bone turnover indicators returned to normal level 6 months after \(^{131}\)I treatment. BMD also recovered 12 months after \(^{131}\)I treatment, The \(\beta\) -CTX continued to decrease. PINP rised , the BMD returned to normal level, these were not observed in patients >35 years old , The reasons may be related to the following factors: 1) hyperthyroidism patients have hyper thyroid function, the synthesis and secretion of thyroid hormones rise , in addition to thyroid enlargement and high metabolic syndrome, the balance between osteoblasts and osteoclasts was also be broken, bone turnover of osteoblasts and osteoclasts went up. After \(^{131}\)I treatment, following the thyroid hormone restored to normal level, the state of the high conversion of bones was also corrected. Younger women who did not reach peak bone mass had higher regulation and repair ability. the ir activity of osteoblast was significantly higher than that of osteoclast. Younger women could restore and correct unbalanced bone metabolism with low bone mass/osteoporosis. Patients above 35 years old have reached the time points of peak bone mass, followed by a decline in the body regulation functions , the ability to maintain steady state of osteoclasts and osteoblasts which were significantly lower than that of young people especially in postmenopausal patients with low bone mass 2) hyperthyroidism patients had little awareness of low bone mass and osteoporosis. Studies have shown that few hyperthyroidism patients receive calcium supplements . Only 2% of patients know that hyperthyroidism can lead to calcium deficiency, causing osteoporosis[12]. 3) Chinese population has

<table>
<thead>
<tr>
<th>Group</th>
<th>Before</th>
<th>6 month</th>
<th>12 month</th>
<th>Before</th>
<th>6 month</th>
<th>12 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=38)</td>
<td>0.79±0.21*</td>
<td>0.43±0.10</td>
<td>0.18±0.22*</td>
<td>158.4±28.7*</td>
<td>44.4±11.2*</td>
<td>58.5±15.1*</td>
</tr>
<tr>
<td>A1 (n=38)</td>
<td>0.42±0.17</td>
<td>0.42±0.15</td>
<td>0.42±0.13</td>
<td>43.7±12.1</td>
<td>44.9±11.5</td>
<td>45.1±10.9</td>
</tr>
<tr>
<td>B1 (n=40)</td>
<td>0.43±0.15</td>
<td>0.43±0.17</td>
<td>0.43±0.14</td>
<td>42.9±11.8</td>
<td>43.2±12.1</td>
<td>44.5±12.3</td>
</tr>
<tr>
<td>B (n=40)</td>
<td>0.80±0.18*</td>
<td>0.42±0.16*</td>
<td>0.40±0.15*</td>
<td>46.9±18.9*</td>
<td>41.2±10.9*</td>
<td>45.4±11.3*</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, \(P<0.05\); Compared between group A and B, *\(P<0.05\), compared with control group, **\(P<0.05\).
insufficient nutrition supplements, relatively high proportion of lactose intolerance, and less dairy products consumption. The recent dietary nutrition survey shows that the average calcium intake from the elderly dietary is about 338 mg/d\(^{[13]}\). The proportion of vitamin D deficiency in Graves patients is as high as 59.77%\(^{[14]}\). Therefore, when hyperthyroidism is treated, the occurrence of hyperthyroidism osteopathy should be actively prevented. Studies have shown that \(^{131}\)I combined with calcium and vitamin D to treat hyperthyroidism with low bone mass, the recovery time and curative effect is better than the \(^{131}\)I treatment alone, it can effectively prevent further bone loss and reduce the incidence of osteoporosis\(^{[15]}\). Alendronate can be used to treat hyperthyroidism osteoporosis with high efficacy and safety, and it can effectively increase bone mineral density and not increase the side effects\(^{[16]}\).

Although the limitations of few observation cases and shorter observation time of our study, it suggests that there is age difference factors in bone metabolism before and after \(^{131}\)I treatment in female patients with hyperthyroidism and low bone mass. Therefore, for patients with premenopausal >35 years of age, attention should be paid to BMD changes and bone turnover while hyperthyroidism is treated. Actively adding nutritional supplements and necessary medication therapy will bring great benefits to hyperthyroidism patients.

Reference


\[2\] Bai Bihui, Xie Xingwen, Li Dingpeng. Epidemiological studies on osteoporosis in the past five years in China. Chin J Osteoporosis 2018; 24(2): 253-258.


