BMD Changes Following 2-Year Treatment of Osteoporosis by using BMK to Monitor the Dose of Bisphosphonates

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Reasons for using BMK to adjust dose for Osteoporosis patients: 1) To keep balance between bone formation and bone resorption, 2) To set balance of bone formation to be higher than bone resorption (+10%), 3) To slightly lengthen bone life cycle.

Only 127 out of 197 patients who joined the program of using BMK to monitor Bisphosphonate dose could complete the 2-year follow-up.

The measurement of BMK used before the treatment was compared with that of the 2-year follow-up by using both T-score and PR.

As a result, the adjustment of the Bisphosphonates given period by using BMK can better reinforce both spine and hip T-scores and PR summaries, more increasing and steadier than decreasing. It can be said that using BMK to monitor the dose of bisphosphonates can offer balance between bone formation and bone resorption (balanced with plus and steadiness than minus). Moreover, it can lengthen the bone cell life cycle more than usual (CTx = 80-100% of normal value, 0.31, in women or CTx 0.25-0.31). Besides, it helps the patients to reduce the cost of treatment of bisphosphonate by lengthening the time of administration by up to 3-6 times.

Keywords: Bisphosphonates, Adjusted dose, Bone markers, Osteoporosis

J Med Assoc Thai 2015; 98 (Suppl. 8): S8-S12
Full text. e-Journal: http://www.jmatonline.com

Thai biochemical bone marker (BMK) in the blood was first studied in 2001 by Bunyarathavej N. and reported normal BMK in reproductive Thai females(1).

BetaXLaps** or CTx is the bone resorptive marker.

PINP*** is the bone formation marker.

NMID is the NMID osteocalcin marker of marker bone turnover.

In 2011, the observation of the application and advantages of BMK in osteoporosis by monitoring the dose of anti-resorptive drugs with CTx was reported(2). The change of bone turnover rate after the anti-resorptive therapy for individual patients is very independent and varied. The fluctuated changes depend on many factors such as environments, genes, etc. The time of drugs response evaluated by BMK needed to be assigned within one month during which drug dose adjustments can be made. Later on, it is suggested that the BMK be tested regularly at least every 6 months.

Besides, the proper dose of anti-resorptive drugs, the balance of the bone formation and bone resorption and the rate of bone life cycle should be considered.

Poshyachinda M(3) reported that bone diminution in Thai women began about the age of 40 and the loss was accelerated after the age of 50. The average rate of loss up to age 75 was 0.8% per year in all sites. In this study, any T-score change in BMD

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measurement that is less than 0.8% in 2 years will be considered as a stable state.

The application of BMK to monitor the dose of drugs in the treatment of osteoporosis has been practiced in the Rehabilitation Medicine Clinic, Chulalongkorn Hospital since 2007.

Objective
To study the BMD change after 2-year treatment of osteoporosis with application of BMK to monitor the dose of drugs.

Material and Method

Method
There were 192 female patients coming to the clinic during 2013-2015, but only 127 patients attended the clinic regularly.

Twenty-three patients were 50-60 years old, 48 patients were 60-70 years old and 56 patients were over 70 years old.

Inclusion criteria
Women who were diagnosed as osteoporosis volunteered to attend the study.

Exclusion criteria
- History of spinal or hip deformity
- History of fracture of hips or spine
- History of endocrinological disease
- History of steroid therapy of herps
- History of ankylosing spondylitis
- History of dementia or unable to follow the drug administration program
- History of alcohol addiction

Intervention
Example showing how to monitor drug dose.
Thai woman, age 55, postmenopausal for 4 years.

1st BMK study: PINP 60.5, CTx 0.45
A) CTx 0.45 - PINP 60.55
   Normal CTx 0.31 - PINP = 60.55x0.31 = 41.6
   Normal CTx 0.31 40
   PINP 0.45
   PINP = 0.45

B) Normal PINP 40.0
   41.6 = 100%
   41.6 = 100x41.6 = 104%
   40

C) Normal CTx 0.31
   0.45 = 100%
   0.45 = 100x0.45 = 145%
   0.31

Bone formation and bone resorption were not in balance. The bone resorption was more than bone formation = 145-104 = 41%

The rate of bone life cycle was shorter than normal.

Prescription:
- Ibandronate 150 mg 1 tablet/month
- Milk 250 ml 1x2
- CDR 1x1
- Vitamin K2 15 mg 1x3

One month later

Table 1. The change of T-score of lumbar spine before and after 2 years of treatment

<table>
<thead>
<tr>
<th></th>
<th>Increased 72 cases</th>
<th>Stable 13 cases</th>
<th>Decrease 36 cases</th>
<th>Very high increased 6 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56.7%</td>
<td>10.3%</td>
<td>28.3%</td>
<td>4.7% were cut off</td>
</tr>
</tbody>
</table>

Table 2. The change of T-score of hip before and after 2 years of treatment

<table>
<thead>
<tr>
<th></th>
<th>Increased 49 cases</th>
<th>Stable 21 cases</th>
<th>Decrease 56 cases</th>
<th>Very high increased 1 case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39.2%</td>
<td>15.9%</td>
<td>44.1%</td>
<td>was cut off</td>
</tr>
</tbody>
</table>

Table 3. The mean and standard deviation of change of T-score of lumbar spine after 2 years of treatment

<table>
<thead>
<tr>
<th></th>
<th>Spine T-score pre</th>
<th>Spine T-score post</th>
<th>Diff T-score spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>n valid</td>
<td>127</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>Mean</td>
<td>-1.55</td>
<td>-1.38</td>
<td>0.17</td>
</tr>
<tr>
<td>Std deviation</td>
<td>1.12</td>
<td>1.17</td>
<td>0.76</td>
</tr>
<tr>
<td>Minimum</td>
<td>-3.70</td>
<td>-3.60</td>
<td>-1.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>2.50</td>
<td>2.40</td>
<td>1.20</td>
</tr>
</tbody>
</table>

95% CI of diff

Table 4. The mean and standard deviation of change of T-score of hip after 2 years of treatment

<table>
<thead>
<tr>
<th></th>
<th>Hip T-score pre</th>
<th>Hip T-score post</th>
<th>Diff T-score hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>n valid</td>
<td>127</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>Mean</td>
<td>-1.0619</td>
<td>-1.0801</td>
<td>-0.182</td>
</tr>
<tr>
<td>Std Deviation</td>
<td>.91926</td>
<td>.89674</td>
<td>.34848</td>
</tr>
<tr>
<td>Minimum</td>
<td>-3.20</td>
<td>-3.10</td>
<td>-1.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.20</td>
<td>1.30</td>
<td>1.40</td>
</tr>
</tbody>
</table>
Table 5. The change of T-score of the spine after 2 years of treatment was statistically significant ($p<0.01$)

<table>
<thead>
<tr>
<th>Paired differences</th>
<th>Mean</th>
<th>Std deviation</th>
<th>Std error</th>
<th>95% confidence interval of the difference</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changing spine T-score post-pre</td>
<td>0.170</td>
<td>0.376</td>
<td>0.033</td>
<td>0.142 - 0.236</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hip T-score post-pre</td>
<td>0.130</td>
<td>1.547</td>
<td>0.1372</td>
<td>-0.141 - 0.402</td>
<td>0.334</td>
</tr>
<tr>
<td>Df T-score spine-df T-score hip</td>
<td>0.039</td>
<td>1.556</td>
<td>0.1381</td>
<td>-0.233 - 0.313</td>
<td>0.774</td>
</tr>
</tbody>
</table>

Table 6. The change of PR of lumbar spine was considered not more than ±2% after 2 years of treatment

<table>
<thead>
<tr>
<th>Change</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>26</td>
<td>20.4%</td>
</tr>
<tr>
<td>Stable</td>
<td>55</td>
<td>43.3%</td>
</tr>
<tr>
<td>Decreased</td>
<td>46</td>
<td>36.3%</td>
</tr>
</tbody>
</table>

Table 7. The change of PR of the hip after 2 years of treatment

<table>
<thead>
<tr>
<th>Change</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>18</td>
<td>14.2%</td>
</tr>
<tr>
<td>Stable</td>
<td>76</td>
<td>60.6%</td>
</tr>
<tr>
<td>Decreased</td>
<td>33</td>
<td>25.2%</td>
</tr>
</tbody>
</table>

2nd BMK study: PINP 34.2, CTx 0.234
- PINP 34.2 = 113.2\%  
- CTx 0.234 = 75.4\%  
Bone formation was more than resorption = 113.2-75.4 = 37.8\%.  
Bone formation and bone resorption were not in balance.  
The rate of bone life cycle was much longer than normal.  
The treatment was adjusted:  
- Discontinued Ibandronate  
- Milk 250 ml 1x2  
- Calcium D Redoxon (CDR) 1x1  
- Vit K2 15 mg 1x3  
One month later

3rd BMK study: PINP 36.5, CTx 0.29
- PINP 36.5 = 97.5\%  
- CTx 0.29 = 93.5\%  
Bone formation was slightly more than bone resorption = 97.593.5 = 4.0\% which was a positive in balance.  
The rate of bone life cycle was slightly longer than normal (CTx 93.5\%).  

In conclusion, the optimal treatments for this case were:  
- Ibandronate 150 mg 1 tablet every 2 months  
- Milk of 250 ml 1x2  
- Calcium D Redoxon (CDR) 1x1  
- Vit K2 15 mg 1x3

Outcome measurement  
The measurement was performed under the following items:  
1) Blood test for BMK prior to the program of the treatment.  
2) BMD study of anterior and lateral lumbar spine and femoral neck prior to the program of the treatment.  
3) 2nd BMK study one month after the treatment.  
4) Repeat BMK study every month until the optimum and balance of drugs accomplished.  
5) Repeat BMK study in 3 months to confirm the optimal dose and balance.  
6) Repeat BMK study every 6 month until the end of the study.  
7) Second BMD study.

Statistic outcome  
A paired t-test was used to assess within-group changes of pre- and post-treatment of BMD T-score at spine and hip. The level of significance was set at $p<0.05$.

Results  
The change of T score was not more than 0.8% measurement(3).
Data analysis

The results of this report using the change of T-score reduction which is less than 0.8% in two years as a standard measurement revealed that:

T-score of the spine increased 56.7% and was stable 10.3%. So, the total was = 67.0%.

T-score of the hip was stable 15.9% and increased 36.2%. The total was = 55.1%.

The change of T-score of the hip after 2 years of treatment was not statistically significant ($p>0.05$).

And T-score change of the lumbar spine compared to T-score change of the hip after 2 years of treatment was also not statistically significant ($p>0.05$).

The changes of PR of lumbar spine after 2 years of treatment increased 20.4% and was stable 43.3% = 63.7%, which were much more than decreasing.

The changes of PR of the hip after 2 years of treatment increased 14.2% and were stable 60.6% = 74.8%, which were also more than decreasing.

Discussion

BM Blake$^{(4)}$ reported that BMD change of 4.5% was required to register statistically significant changes. In this study, the BMD of 2.0% was preferred to render the results more accurate in judgment. The result after 2 years of treatment using BMK to monitor the dose of drugs revealed the BMD were more stable and increased more than decreased. These results might be considered as satisfactory because Angello Licata$^{(5)}$ suggested that in clinical practice, patients who show no change in BMD may still be considered as responding to therapy.

The result of this study also revealed that the treatment was more effective in the lumbar spine than in the hip, which went along with and confirmed Dr. Peter R. Ebelling’s report$^{(6)}$. Further more, the use of BMK to monitor the treatments of osteoporosis could be used to adjust the accurate dose of drugs and to set the rate of bone life cycle as it would be. Finally, it might reduce the cost of treatment.

Conclusion

The BMD change from the 2-year osteoporosis treatment by using BMK to monitor the dose of drugs was mainly stable and increased more than decreased. The adjustment of bone life cycle and the balance of bone formation and bone resorption were accomplished.

Acknowledgement

1) Prof. Em. Bunyaratavej N, 2) Rehabilitation Medicine Residents at Chulalongkorn University, 3) Asst. Prof. Boonhong J, 4) Prof. Em. Poshyachinda M and Prof. Chaiwatanarat T.

Potential conflicts of interest

None.

References

การเปลี่ยนแปลงมวลกระดูกของผู้วัยกลางช่วงหลังของปีที่ใช้การรักษายา bisphosphonate คือ bone marker

ผลอัตราอนุรักษ์

จากการใช้ BMK ปรับขนาดกระดูกโดยรวมกระดูกเพิ่มเติม 1) ปรับให้บริเวณกระดูกสมดุลกันการสลายกระดูก, 2) ปรับปรุงสมดุลโดยรวมในการสลายถืมกระดูกในผู้ป่วย (±10%), 3) ปรับปรุงการรักษาระดับมวลกระดูกกว่าปกติ

ปรากฏว่าผู้ป่วย 192 รายที่อยู่ในโปรแกรมการรักษา BMK เป็นค่าผู้ป่วยของข้อเท้าเพียง 127 รายที่สามารถติดตามได้ครั้ง 2 ปี

การวัดผลการรักษา BMK ค่อนข้างและ 2 เช็คการรักษาเริ่มที่ก่อนหน้า T-score และ PR

ส่วนการใช้ bisphosphonates คือการตรวจ BMK สามารถควบคุมได้ทั้ง T-score และ PR ที่ข้อ spine และ hip ดังนี้ ผลการทดสอบ จึงอธิบายการใช้ BMK ปรับขนาดกระดูกสมดุลกันการสลายกระดูกในผู้ป่วย (สูงในที่ระดับ

และดิ่งที่ระดับที่สูง) และยังสามารถยับยั้งการสลายกระดูกในผู้ป่วยที่มีค่าปกติ (ที่ Ctx อยู่ที่ 80-100% ของค่าปกติ 0.31 ในผู้ป่วยหรือ Ctx 0.25-0.31) นอกจากนี้ยังมีการใช้ให้ที่ผ่านในการรักษาโรคกระดูกผู้ป่วยได้มากโดยสามารถใช้ยา bisphosphonates ออกเป็นปี 3-6 เท่าใด

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J Med Assoc Thai Vol. 98 Suppl. 8 2015