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 Bishosphonates 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*

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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].

	The mean*	95% CI
BetaXLaps** n = 356	0.310±0.169	0.293-0.328
NMID** n = 123	16.460±0.179	14.9-18.02
PINP*** n = 109	44.500±19.920	40.78-48.35

BetaXLaps or CTx is the bone resorptive marker.

PINP is the bone formation marker.

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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

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 = $\frac{60.55 \times 0.31}{0.45}$ = 41.6

B) Normal PINP 40.0 = 100%

41.6 = $\frac{100 \times 41.6}{40}$ = 104%

C) Normal CTx 0.31 = 100%

0.45 = $\frac{100 \times 0.45}{0.31}$ = 145%

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 K_2 15 mg 1x3

One month later

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

Increased 72 cases	56.7%
Stable 13 cases	10.3%
Decrease 36 cases	28.3%
Very high increased 6 cases	4.7% were cut off

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

Increased 49 cases	39.2%
Stable 21 cases	15.9%
Decrease 56 cases	44.1%
Very high increased 1 case was cut off	

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

	Spine T-score-pre	Spine T-score-post	Diff T-score spine
n valid	127	127	127
Mean	-1.55	-1.38	0.17
Std deviation	1.12	1.17	0.76
Minimum	-3.70	-3.60	-1.00
Maximum	2.50	2.40	1.20

95% CI of diff

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

	Hip T-score-pre	Hip T-score-post	Diff T-score hip
n valid	127	127	127
Mean	-1.0619	-1.0801	-0.182
Std Deviation	.91926	.89674	.34848
Minimum	-3.20	-3.10	-1.70
Maximum	1.20	1.30	1.40

Table 5. The change of T-score of the spine after 2 years of treatment was statistically significant (p<0.01)

	Paired differences					
	Mean	Std deviation	Std error mean	95% confidence interval of the difference		*p*-value
				Lower	Upper	
Changing spine T-score post-pre	0.170	0.376	0.033	0.142	0.236	<0.01
Hip T-score post-pre	0.130	1.547	0.1372	-0.141	0.402	0.334
Df T-score spine-df T-score hip	0.039	1.556	0.1381	-0.233	0.313	0.774

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

Increased 26 cases	20.4%
Stable 55 cases	43.3%
Decreased 46 cases	36.3%

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

increased 18 cases	14.2%
Stable 76 cases	60.6%
Decreased 33 cases	25.2%

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.

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Potential conflicts of interest

None.

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การเปลี่ยนแปลงมวลกระดูกของผู้ป่วยกระดูกพรุนหลังสองปีที่ใช้การปรับขนาดยา bisphosphonate ด้วย bone marker

เสก อักษรานุเคราะห์

จากการใช้ BMK ปรับขนาดยารักษาโรคกระดูกพรุนเพื่อให้ 1) ปรับให้การสร้างกระดูกสมดุลกับการสลายกระดูก, 2) ควรปรับสมดุลให้อยู่ในการสร้างมากกว่าการสลายเล็กน้อย (±10%), 3) ปรับให้วงจรชีวิตของกระดูกยาวกว่าปกติเล็กน้อย

ปรากฏว่าผู้ป่วย 192 รายที่อยู่ในโปรแกรมการรักษาที่ใช้ BMK เป็นตัววัดขนาดของยามีเพียง 127 รายที่สามารถติดตามได้ครบ 2 ปี การวัดผลการรักษาใช้ BMK ก่อนรักษาและ 2 ปีหลังการรักษาเปรียบเทียบกันทั้ง T-score และ PR

สำหรับการปรับระยะเวลาการให้ยา bisphosphonates ด้วยการตรวจ BMK สามารถควบคุมให้ทั้งค่า T-score และ PR ทั้งของ spine และ hip ดีขึ้น + คงที่มากกว่าลดลง จึงนับได้ว่าการใช้ BMK ปรับขนาดยาสามารถปรับให้การสลายกับการสร้างกระดูกอยู่ในสมดุลได้ (สมดุลในทางบวกและคงที่มากกว่าทางลบ) และยังสามารถปรับวงจรชีวิตของเซลล์กระดูกให้อยู่ในช่วงยาวกว่าปกติเล็กน้อยได้ (ค่า CTx อยู่ที่ 80-100% ของค่าปกติ 0.31 ในผู้หญิงหรือค่า CTx 0.25-0.31) นอกจากนี้ยังช่วยให้ผู้ป่วยเสียค่าใช้จ่ายค่ายาในการรักษาโรคกระดูกพรุนลงได้มากโดยสามารถยืดเวลาการให้ยา bisphosphonates ออกไป 3-6 เท่าได้