

Review Article

The benefits of biochemical bone markers

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Clinical benefits

1. To improve efficiency in Osteoporosis treatment
2. To adjust the dosage of medication for osteoporosis with BMK
3. To adjust bone life cycle as needed
4. To prevent bone necrosis which dentists have been worried.
5. To reduce cost of treatment

BMK test population

1. **Menopausal female group:** there has been fast reducing rate of bone density than normal. Though bone tissue grows, it isn't so much as its reducing rate. It results in rate 3% - 5% decreasing of bone density per year. Gradually, the rate goes on; however, the females of that age don't lose much of it. Years later, they will find a big loss rate of bone density. How do we measure the loss rate of bone resorption and bone formation for those female group? Blood test for BMK is needed for accurate treatment planning.
2. **Senior group:** If BMD and BMK have never been tested. Patients will be given Osteoporosis treatment, both bone antiresorpting and bone formatting drugs. However, many patients found low resorpting rate of bone through BMK blood test, and if antiresorptive drug is prescribed, the rate of resorption will be much lower.

Vice versa, while people at 80s with no sign of any bone balance adjustment still have high bone resorpting rate, they need its antiresorptive treatment, and BMK blood test is needed from time to time to measure the patients adjustment and when lower rate of bone resorption to 70% - 100% they can stop bone antiresorptive drug. In some cases, an automatic increase of bone resorption may show when they need BMK blood tests from time to time.

3. **Group of chronic illness:** The patients will have blood test for BMK to measure the balance of bone resorption and bone formation.
4. Group with Osteoporosis risk need to sometimes have blood tested for BMK.
5. Group of female with hysterectomy but ovary remaining will never know their transitioning to menopause and bone resorpting rate. So they need blood test for BMK.
6. Group of having Bone antiresorptive drug need BMK Blood test to measure the balance.
 - a. Dosage whether too much or too little
 - b. Bone formation at the same time of its resorption.
 - c. Sufficiency of Osteocalcin

Result variation

1. Observing change of bone turnover rate
 - a. High rate on both BMK of bone resorpting and bone formation which means short bone life cycle causing microfracture later on.
 - b. Low rate on both which means long life cycle with little bone loss and little bone formation. The condition won't change but bone quality is poor which is not good.

More Information

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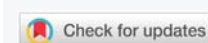
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2. Comparing the rates of bone resorption and bone formation.
 - a. If resorption is more than formation, the condition gradually becomes Osteoporosis.
 - b. If resorption is less than formation, the condition may be from other diseases.
3. Measuring the result of treatment by BMK, comparing between PINP and CTx or Betacrosslops numbers, if the result between bone formation and bone resorption is less than $\pm 10\%$ difference, considering the result is in balance.

There has been long use of Bisphosphonates for bone antiresorption; for example,

Alendronate 10 mg: 1 tablet/day

Alendronate 70 mg: 1 tablet/week

Risedronate 5 mg: 1 tablet/day

Risedronate 35 mg: 1 tablet/week

Risedronate 150 mg: 1 tablet/month

Ibandronate 150 mg: 1 tablet/month

However, effectiveness of the dosage and appropriate length of time have never been evaluated.

After blood test for Biological Bone Marker, studies have been gathered for more than 10 years or since 2005-2017, and surprisingly, remarkable results have been found out.

First of all, BMK blood test must be correct throughout its process, for reliable and accurate results [1,2]

1. No food, is allowed for patients from 8 pm to 8 am (12 hrs.)
2. Blood sample is taken between 8 am to 9 am only.
3. Blood Test by the Laboratory needs to be done immediately as result value varies by time.
4. Solution used for running the BMK blood test must be calibrated every morning.

Normal value of BMK for Thai people specified by Prof. Dr. Narong B [2,3]

1. Normal P1NP represents for bone formation = 40.
2. Normal CTx or Betacrosslap represents for bone resorption = 0.31 for female, 0.4 for male .
3. Normal NMID represents for Osteocalcin resorption = 15.

How to convert the value of BMK into percentage

Results of BMK test alone cannot answers many questions. The ideas to clear these answers are very simple by converting the result into percentage.

The way of converting the BMK results in to percentage is followed.

Example: Results of BMK of one patient are

Pretreatment - CTx = 0.434
 - PINP = 34.2
 - NMID = 16.2
 Calculation $CTx \ 0.31 - PINP = \frac{34.2 \times 0.31}{0.434} = 24.4$
 a. at $CTx \ 0.434 - PINP = 34.2$

- b. $PINP \ 40 = 100\%$
 $24.4 = \frac{100 \times 24.4}{40} = 61\%$
- c. $CTx \ 0.434 - NMID = 16.2$
 $CTx \ 0.31 - NMID = \frac{16.2 \times 0.31}{0.434} = 8.0$
- d. $NMID \ 15 = 100\%$
 $8.0 = \frac{100 \times 8.0}{15} = 53\%$
- e. $CTx \ 0.31 = 100\%$
 $0.434 = \frac{100 \times 0.434}{0.31} = 140\%$

Conclusion

Bone Resorption is = $140\% - 61\% = 79\%$ more than bone formation and more than resorption of osteocalcin = $140\% - 53\% = 87\%$.

One month after the treatment

Post treatment BMK are - CTx 0.29
 - PINP 36.5
 - NMID 138

Calculation
 A. at $CTx \ 0.29 - PINP = 36.5$
 $0.31 \ PINP = \frac{36.5 \times 0.31}{0.29} = 39$

B. -PINP 40 = 100%

$$39 = \frac{100 \times 39}{40} = 97\%$$

C. CTx 0.29

NMID = 13.8

$$\text{NMID} = \frac{13.8 \times 0.29}{0.31} = 14.7$$

D.

NMID 15 = 100 %

$$14.7 = \frac{100 \times 14.7}{15} = 98\%$$

E. CTx 0.31

= 100%

$$0.29 = \frac{100 \times 0.29}{0.31} = 93\%$$

The BMK results after treatment in one month are;

1. Bone formation is more than bone resorption = 97% - 93% = 4% which is in balance.
2. Resorption of osteocalcin is more than bone resorption = 98% - 93% = 5% which is also in balance.

The use of BMK to adjust the dose of Bisphosphonates for the treatment of osteoporosis [2]

From the study of BMK blood test result to evaluate osteoporosis treatment especially for bone resorption control among 708 patients within 12 years (2005 – 2017), 397 patients have taken Bisphosphonates [5]. The result has turn out, astonishingly, opponent for patients, costing a lot as well even though both doctors and patients have been confident treatment was in the right direction. Consequently, there is in depth analysis of 397 patients using Bisphosphonates as shown in the followings.

Result of one month administration of Bisphosphonates [3].

One month course of all bisphosphonates have so effective:-

196 patients with Ibandronate 150 mg per month can reduce the average CTx from 181.8% to 49.8%

148 patients with Alendronate 70 mg per week can reduce the average CTx from 140.3% to 31.9%

26 patients with Alendronate 10 mg per day can reduce the average CTx from 157.3% to 37.1%

15 patients with Risedronate 35 mg per week can reduce the average CTx from 158% to 62.5%

12 patients with Risedronate 150 mg per month can reduce the average CTx from 154% to 47.4%

If there had not been BMK blood test and dosage had been given to patients continuously, CTx would have been reduced to the point that the bone will have no bone resorption. So, there would have been only old bone cells, prone to degeneration and necrosis. Only light or minor injury, bones are easily broken. For example, when a tooth is extracted, mandible is also broken.

It was found that the time of CTx returning to normal (70% - 100%) following one month of treatment with bisphosphonate:-

1 tablet per month of Ibandronate 150 mg: 196 cases have average CTx of 4.1 months returning to normal

1 tablet per week of Alendronate 70 mg: 148 cases have average CTx of 3.5 months returning to normal

1 tablet/day of Alendronate 10 mg: 26 cases has average CTx of 6 months returning to normal

1 tablet/week of Risedronate 35 mg: 15 cases have average CTx of 4 months returning to normal

1 tablet/month of Risedronate 150 mg: 12 cases have average CTx of 2.8 months returning to normal

No matter which medicines given in a month according to the manufacture, similar results will come out. When stopping the use of those medicines, it will take 3-4 months to resume CTx to 70% - 100%. The results for all medicines are similar. Effectiveness length of time of medicine prescription for each patient can be different depending on patient's conditions whether to resist or accept dosage, their illness conditions, their other treatments, as well as fruits they eat. We can see that all mentions including some herbs or supplements will affect CTx, increasing 100+% of which data has been collected.

Average length of time of CTx resume normal after discontinuation of each medicine following continuation of bisphosphonate treatment of 2-3 years:

- Ibandronate 150 mg: 27 patients had an average of 25.18% CTx only, waiting for 13.3 months to resume to normal.
- Alendronate 70 mg: 16 patients had an average of 21.2% CTx only, waiting for 16.8 months to resume to normal.
- Alendronate 10 mg: 12 patients had an average of 25% CTx only, waiting for 13.3 months to resume to normal.
- Risedronate 35 mg: 5 patients had an average of 10.8% CTx only, waiting for 10.1 months to resume to normal.
- Risedronate 150 mg: 2 patients had 0% of CTx without resuming to normal.

So, Bisphosphonate given to patients for years can turn out disadvantages due to low rate of bone resorption and high cost of treatment until they require long time to resume to normal. Especially for those 2 patients who had no recovery at all.

It is important to control CTx value in 70% -100% besides what was mentioned in 1, Bone life cycle range is considered safe. If CTx is higher than 100%, bone resorption will be more than normal, or bone age will be shorter. Micro fracture can easily happen. It can remarkably decrease bone structure, causing bone fractures more easily. Therefore, CTx or Bone resorpting needs to be 70% - 100%, and if this is controlled, a little longer bone life cycle means Micro fracture prevention.

How many BMK test should be done

Blood test for BMK is needed before treatment, then is compared to that of post-one month treatment so that

1. Bone antiresorption a dosage is appropriate, considering CTx or Betacrosslaps, for example.

If pretreatment CTx = 0.625% or 201%

One month posttreatment CTx = 0.26% or 83%

It shows that treatment dosage is appropriate and bone antiresorption dosage can be the same.

If before treatment CTx = 0.625% or 201% and after treatment = 0.12% or 38%, it shows too much dosage of bone antiresorption which needs to be adjusted; 1 tablet per month change to 1 tablet per 2 months, or 1 tablet a week change to 1 tablet per 2 weeks or 1 tablet a day change to 1 tablet per 2 days. After adjustment for a month have another BMK blood test until getting value of 0.22 – 0.31 or 70% – 100% so that period of bone antiresorpting tablet effectiveness (months, weeks or days) till be measured after that 2 – 3 BMK tests adjustment be performed for sure of accurate dosage.

2. Bone formation adjustment Consider percentage of PINP compared to percentage of CTx; for example, result of PINP = 60% and result of CTx = 80% It shows that Calcium or Vitamin D or K2 must be increased.
3. Vitamin K2 adjustment Consider percentage of NMID compared to percentage of normal CTx; for example, NMID 85% CTx 106%.

It shows insufficient transformation of undercarboxylated osteocalcin (UCOC) to carboxylated osteocalcin (COC) and K2 must be increased.

4. In senior group with long bone life cycle, it could sometimes be shorts automatically. So, BMK blood test is sometimes suggested. If CTx value is not much high (eg. 0.39% or 106%), no needs for bone antiboneresorptive drug needed and wait for another month to check CTx value. If CTx is higher, anti-bone resorptive drug is

needed when BMK blood test is performed a month later, it is normally found that CTx decreases by itself.

5. In case of too much anti bone resorpting drug, CTx is very low (eg. 20% = long bone life cycle). 80% of bone cell lives very long and 20% dies. So, there is less area for new bone cell to fill in the bone. Though BMD is normal, its quality of bone is poor. Bone cell necrosis can happen.

On the other hand, if bone formation is more than Bone resorption, there will be urinary stones or calcium deposit in aorta, or in aortic valve, and extra osseous calcification.

In case that both CTx and PINP values need to be adjusted CTx should be done first until CTx is in between 70% – 100%, and at that point if PINP is not in balance, then PINP would be adjusted later.

Result of Osteoporosis treatment by measuring BMD change via BMK blood test [5]

127 patients used BMK to control the treatment in 2 years.

Tscore Result of Spines at 2 year treatment

No change 19 patients = 15.9%

Decrease 36 patients = 28.3%

Increase 72 patients = 56.7%

So, Tscore of no change + Tscore of increase = 67%

And Tscore of decrease = 28.3% only.

Tscore result of hip bones with 2 year treatment: -

No change 21 patients = 15.9%

Decrease 56 patients = 44.1%

Increase 50 patients = 39.3%

So, Tscore of no change + Tscore of increase = 15.9% + 39.2% = 55.1% and Tscore is decrease = 44.1%.

PR value of spines change after 2 years treatment:-

No change (not above $\pm 2\%$) 62 patients = 48.8%

Decrease 19 patients = 15.0%

Increase 46 patients = 36.2%

So, PR value no change + PR value increasing = 85% which is much more than decreased one (15%).

PR value of hip bones has change after 2 years treatment:-

No change 76 patients = 60.6%



Decrease 33 patients = 25.2%

Increase 18 patients = 14.2%

So, PR value without change + PR value increasing = 60.6% + 14.2% = 74.8%.

And PR has decreased for only 25.2%.

For this patient, osteoporosis treatment dosage has been adjusted by Biochemical Bone Marker for 2 years showing better direction change of BMD value. Also, Bone life cycle has been a little longer than normal. Moreover, it is important that balance of Bone formation and Bone resorption is in control.

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