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Original Article

Use of Bone Turnover Markers in Clinical Practice for the Management of Osteoporosis in Korea: From the Survey on the Prescription Pattern of Bone Turnover Markers

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Background: There has been interest in the clinical potential of bone turnover markers (BTMs) as tools both for assessing fracture risk and for monitoring treatment. However, the practical use of BTMs has been limited by their biological variability and difficulties in the interpretation of results. We investigated the current situation of application of BTMs by clinicians in Korea for the management of osteoporosis through a survey asking the patterns of BTMs prescription in clinical practice. **Methods:** The survey was conducted online using the "google survey" by the BTM committee authorized by the Korean Society for Bone and Mineral Research. **Results:** Total 108 clinicians responded the survey. Most of the respondents prescribed BTMs (80.6%) when they prescribed anti-osteoporotic medications (AOMs). The most frequently prescribed bone resorption and formation markers were serum C-terminal telopeptide of type I collagen (90.7%) and osteocalcin (65.1%), respectively. BTMs were mostly prescribed before starting AOMs (90.8%) and used for the purpose of evaluating treatment response (74.4%). Treatment response and compliance to AOMs were evaluated according to the change of absolute value of BTMs (55.1%). The respondents complained difficulties in the interpretation of BTMs (33.3%), the choice of proper BTMs (17.2%), and the proper sample preparation and handling (13.8%). **Conclusions:** In Korea, most of clinicians recognized the benefit of BTMs in the management of osteoporosis. However, there are limitations in the broad use of these markers in clinical practice. Therefore, a clear recommendation for BTM in Korea enhances their use in clinical practice.

Key Words: Biomarkers · Bone remodeling · Osteoporosis

INTRODUCTION

Osteoporosis is a major health problem worldwide. The clinical consequence of osteoporosis resides in the fractures, which accounts for the increased health cost in the world of increasing numbers of elderly.[1,2] However, there are still gaps in the management of osteoporosis and osteoporotic fractures. These gaps include the identification of individuals who would really benefit from intervention and the choice of optimal method for monitoring treatment response.

So far, bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) has been regarded as a gold standard method for diagnosing osteoporosis, predicting the risk of osteoporotic fractures, and monitoring treatment response.[3,4] However, it is known that decrease in bone mass dose not solely account for fracture risk.[5,6] Moreover, BMD testing is often performed every 1 to 2 years, thereby, it takes quite long time with BMD to evaluate the efficacy of anti-osteoporotic medications (AOMs).[7]

Therefore, there has been interest in the clinical potential of bone turnover markers (BTMs), as tools both for assessing fracture risk and for monitoring treatment.[8-11] However, the practical use of BTMs has been limited by their biological variability, difficulties in the interpretation of results, thus by the absence of a unified recommendation.[12,13] These limitations prompted several institutions worldwide to make an international reference standard and to provide a clear recommendation.[14] However, in Korea, there is still no recommendation for the use of BTMs in the management of osteoporosis, therefore, many clinicians have difficulties in the application of BTMs in clinical practice.

In this context, the BTM committee authorized by the Korean Society for Bone and Mineral Research (KSBMR) has been constituted in 2018 for making a standard in the use of BTMs in Korea.[15] As one of the working group's activity, we investigated the current situation of application of BTMs by clinicians in Korea for the management of osteoporosis through a survey asking the patterns of BTMs prescription in clinical practice.

METHODS

The survey was conducted on Korean clinicians who may take care of patients with osteoporosis in primary, secondary, or tertiary medical centers regardless of their specialty, using "google survey", which is a service provided by google internet site, by the BTM committee from January to July, 2019. The clinicians were registered as members of the KSBMR. They received e-mail that was invited to the internet site for google's survey and voluntarily responded it. The survey results of the respondents were analyzed. We first asked information on the name, e-mail address, specialty, and the kind of medical center of each clinician. The remaining questions about the patterns of BTMs prescription were as follows;

1. Do you prescribe BTMs when you prescribe AOMs to your patients with osteoporosis?
   - yes
   - no
2. If you prescribe BTMs, what kinds of them do you prescribe? (Multiple responses are available)
   - serum osteocalcin
   - serum bone specific alkaline phosphatase (sBSALP)
   - serum carboxyl-terminal propeptide of type I collagen
   - serum amino-terminal propeptide of type I collagen (sP1NP)
   - serum C-terminal telopeptide of type I collagen (CTX-I)
   - urine CTX
   - serum N-terminal telopeptide of collagen type I (sNTX-1)
   - urine NTX
   - urine free and total pyridinoline
   - urine free and total deoxypyridinoline (uDPD)
3. If you prescribe BTMs, when do you prescribe them? (Multiple responses are available)
   - before starting AOMs
   - within 2 months after starting AOMs
   - between 3 and 6 months after starting AOMs
   - between 7 and 12 months after starting AOMs
4. If you prescribe BTMs, what purpose do you prescribe them for?
   - for diagnosing osteoporosis
   - for predicting the risk of osteoporotic fracture
   - for choosing an AOMs
   - for evaluating treatment response
   - for evaluating compliance to treatment
   - for predicting side effects of AOMs
   - for deciding whether or not to treat the patients
5. If you prescribe BTMs, how do you evaluate the effica-

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cy or compliance of AOMs (anti-resorptive drugs)?
- percent change of BTMs
- change of absolute values of BTMs
- if the value of BTMs reach the target

6. If you prescribe BTMs, what is the difficulty in the prescription of them?
- proper choice of BTMs
- interpretation of BTMs results
- proper sampling of BTMs
- no difficulty

7. If you do not prescribe BTMs, what is the reason?
- It is impossible to prescribe BTMs in our medical center.
- I do not feel the necessity of BTMs, although it is possible to prescribe them in our medical center.
- I have no idea which BTMs to be prescribed, although I feel the necessity of them and it is possible to prescribe these markers in our medical center.

8. What do you think to be supplemented in the clinical utility of BTMs in Korea?

RESULTS

A total of 195 clinicians were asked to participate the survey by e-mail, of which 108 completed the survey. The 13 (12.1%) of the 108 respondents worked in primary, 16 (15.0%) in secondary and 75 (70.1%) in tertiary medical centers. Most of the respondents were endocrinologists (n=58, 54.2%) and orthopedic surgeons were second most (n=23, 21.5%). Many of the respondents prescribed BTMs (n=87, 80.6%) when they prescribed AOMs.

Serum CTX was the most often prescribed BTM (n=79, 90.7%) among bone resorption markers. Among bone formation markers, serum osteocalcin (n=56, 65.1%) and serum BSALP (n=36, 41.9%) were frequently prescribed and 25.5% of the respondents prescribed serum P1NP (n=22) (Fig. 1).

BTMs were mostly prescribed before starting AOMs (n=79, 90.8%). The respondents also prescribed BTMs between 3 and 6 months after starting AOMs (n=50, 57.5%) and between 7 and 12 months after starting AOMs (n=27, 31.0%) (Fig. 2).

The respondents who prescribed BTMs used those markers for the purpose of evaluating treatment response (n=64, 73.5%) or compliance (n=7, 8.0%) of AOMs. Other reasons were for determining AOMs (n=5, 5.7%), predicting the risk of fracture (n=3, 3.4%), or diagnosing osteoporosis (n=3, 3.4%) (Table 1). Treatment response and compliance to AOMs, especially to anti-resorptive agents, were evaluated according to the change of absolute value of BTMs (n=43, 55.1%) or to the percent change of BTMs from base-

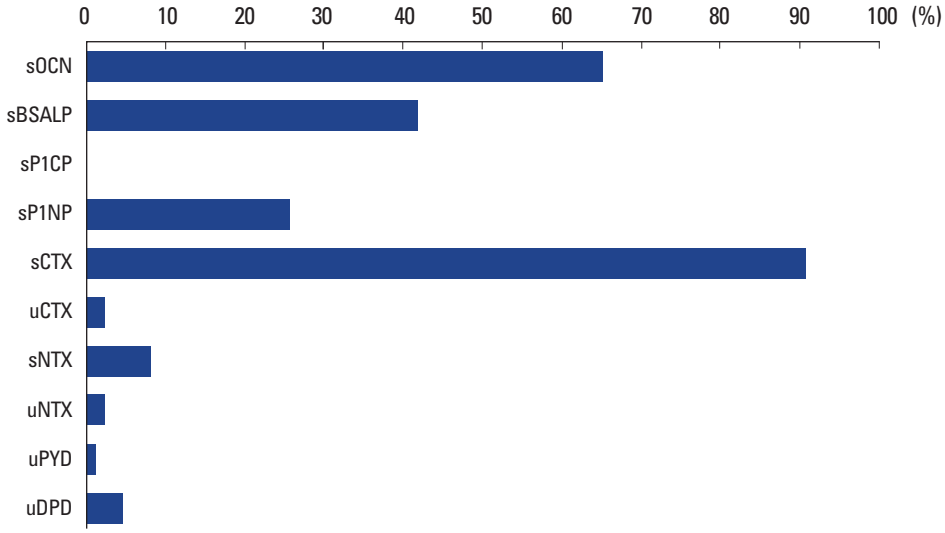

Fig. 1. Bone turnover markers (BTMs) usually prescribed by 87 Korean clinicians who prescribed BTMs in clinical practice. sOCN, serum osteocalcin; sBSALP, serum bone specific alkaline phosphatase; sP1CP, serum carboxyl-terminal propeptide of type 1 collagen; sP1NP, serum amino-terminal propeptide of type I procollagen; sCTX, serum C-terminal telopeptide of type I collagen; uCTX, urine C-terminal telopeptide of type I collagen; sNTX, serum N-terminal telopeptide of collagen type I; uNTX, urine N-terminal telopeptide of collagen type I; uPYD, urine free and total pyridinoline; uDPD, urine deoxypyridinoline.

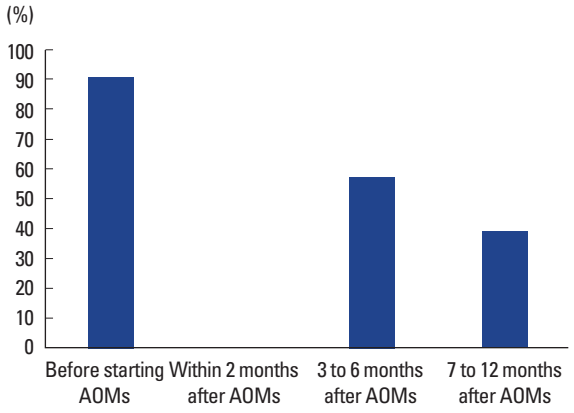

Fig. 2. The time point when 87 Korean clinicians who prescribed bone turnover markers in clinical practice. AOMs, anti-osteoporotic medications.

Table 1. Reasons for prescribing bone turnover markers

Reason	Total (n=87)
For evaluating treatment response	64 (73.6%)
For evaluating compliance to treatment	7 (8.0%)
For choosing an AOM	5 (5.7%)
For diagnosing osteoporosis	3 (3.4%)
For predicting the risk of osteoporotic fracture	3 (3.4%)
For deciding whether or not to treat the patients	2 (2.3%)
For predicting side effects of AOMs	1 (1.1%)
No answer	2 (2.3%)

AOMs, anti-osteoporotic medications.

line (n=31, 39.1%), or whether the followed up BTMs reached the target range (n=4, 5.1%).

On the contrary, some respondents who did not prescribed BTMs when they prescribed AOMs answered that they were not aware of the necessity of BTMs in clinical practice (n=7, 33.3%) even though they could use those markers in their hospitals. Others answered that they had no ideas which BTMs have to be chosen in clinical practice (n=5, 23.8%) even though they were aware of the necessity of prescribing those markers. Moreover, the respondents who usually prescribed BTMs complained difficulties in the interpretation of BTMs (n=29, 33.3%), the choice of proper BTMs (n=15, 17.2%), and the proper sample preparation and handling (n=12, 13.8%) (Fig. 3).

Lastly, clinicians who participated in this survey proposed that the extension of health insurance coverage for BTMs is needed in Korea for more broad application of these markers for the management of osteoporosis. They also suggested the necessity of standard BTMs not only for bone resorption, but also bone formation, standard methods for the preparation of samples for measuring BTMs, and reference ranges for each BTM in Korea.

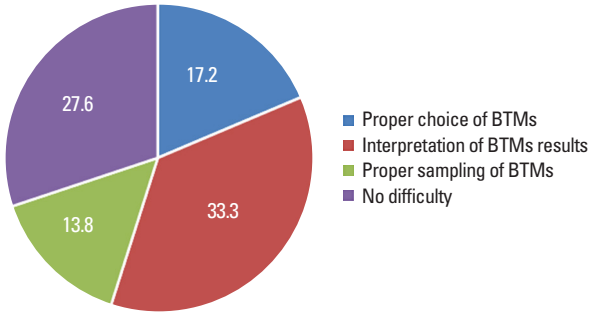

Fig. 3. Difficulties in the prescription of bone turnover markers (BTMs) in 87 clinicians who prescribed BTMs in clinical practice.

DISCUSSION

This study investigated and analyzed the patterns of BTM prescription among Korean clinicians through a survey for the first time. As a result, osteocalcin as bone formation marker and CTX as bone resorption marker have been mostly prescribed. And serum samples were preferred to urine samples. The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have recommended P1NP and CTX as reference bone formation and resorption markers, respectively because those are relatively less variable and well-automated.[14] While osteocalcin might be predominantly prescribed in Korea, because P1NP was not covered by insurance. However, insurance regulation changed that P1NP can be covered by insurance since September, 2019. Therefore, P1NP prescriptions are expected to increase rapidly in Korea. Serum samples are preferred to urine samples because of their stability and convenience. The second urine in the morning should be used for analysis.

According to the survey analysis, the BTMs measurement interval was different among the respondents who prescribed BTMs. This may also have been affected by the Korean insurance regulation on the measurement interval for BTMs. In the past, the BTMs measurement was covered by insurance twice in Korea as follows: (1) once before osteoporosis medication; and (2) osteoporosis drug treatment 3 to 6 months later for drug effect assessment. But the insurance regulations have also eased since August, 2019 as fol-

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lows: (1) once before osteoporosis medication; and (2) less than twice a year to determine the efficacy of drugs after osteoporosis medication. Therefore, it is expected to be able to follow up BTMs in a more consistent pattern.

Most of the respondents used BTMs for evaluating treatment response to AOMs. AOMs are divided by 2 groups such as anabolic drugs and anti-resorptive drugs. Anti-resorptive drugs inhibit bone resorption and consequently decrease bone resorption markers. The anabolic drugs promote bone formation and consequently increase bone resorption markers. Therefore, drug response could be predicted according to the degree of change in the BTMs after AOMs administration.

Korean clinicians used the change of absolute value of BTMs the most to evaluate the efficacy or compliance of AOMs. The percent change of BTMs from baseline was used secondly. The guidelines for the use of BTMs by IOF and Japan Osteoporosis Society recommend that significant change of BTMs should exceed the least significant change (LSC). LSC is defined as 2.77×intra-individual coefficient of variation (CV).[14,16] Because intra-individual CV is different according to BTM types and assay methods, it would be difficult to calculate the percent change of BTMs from baseline in clinical practice. If standardized and automated unified BTMs are available, it will be possible to use BTMs widely in clinical practice.

Some respondents complained that there were difficulties in the exact sample preparation and handling. National Bone Health Alliance made a recommendation for sample handling and patient preparation methods to reduce pre-analytical variability.[17] Patient sample collection procedure standardization is a task that needs to be established in Korea.

Due to the limitation of BMD by DXA as a tool for predicting the risk of osteoporotic fracture and for monitoring treatment response, BTMs have received great attentions recently.[8-11] Actually, BTMs have attractive features such as easy and noninvasive sample collection from blood or urine and a variety of available assays.[14,18] Moreover, some evidences have supported the clinical utility of BTMs for monitoring anti-osteoporosis therapeutic efficacy and compliance [19-22] and for predicting bone loss and osteoporotic fracture risk.[23,24]

However, the clinical utility of BTMs in the management of osteoporosis is still suboptimal due to multiple reasons. These include inadequate quality control, biological and analytical variabilities, lack of normative reference population databases, and limited data comparing the impact of bone turnover changes with treatment over time. In our study, it was found that clinicians did not prescribe BTMs because they did not know the needs of prescription or which BTMs to choose. Several guidelines for the management of osteoporosis have not shown an accordance for the use of BTMs, that is some advocated their routine use, while others were more cautious, and did not recommend their routine use.[14,25]

The prescription rate of BTMs in this study was higher compared to other study, in which the prescription rate of BTMs was reported from 19% to 55%.[26] It suggests that most of clinicians recognized the additional benefit of BTMs independent of BMD in the management of osteoporosis in Korea. However, many respondents still complained that there were difficulties in the proper choice of these markers and the interpretation of BTMs. If there is a clear recommendation, such as which BTMs can be used as reference BTMs, how often we have to check BTMs, what purpose we have to use BTMs for, what is the reference interval of BTMs in Korea, and what the standardized preparation and handling methods of samples are, we can more efficaciously applicate them in clinical practice. The BTM working group authorized by the KSBMR has been recently established [15] and is preparing a position statement for BTMs use in clinical practice in Korea.

There are some limitations in this study. First, because the sample sized was small, the results of this study are difficult to represent Korean society. Second, the participation rate of tertiary medical center was higher than primary and secondary medical centers. Because the prescription rate of BTMs may be lower in primary and secondary medical centers, the prescription rate of BTMs might be overestimated. However, because the insurance regulation of BTMs has been recently eased, the BTMs can be prescribed a lot in the future if the guidelines for clinical use of the BTMs are presented.

In conclusion, survey analysis of current BTM prescription and recognition among Korean clinicians could give directions how to exactly and properly applicate BTMs in the management of Korean patients with osteoporosis.

DECLARATIONS

Ethics approval and consent to participate

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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