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Evaluation and Management of Bone Health in Patients with Thyroid Diseases: A Position Statement of the Korean Thyroid Association

A Ram Hong, Ho-Cheol Kang

Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea

Thyroid hormones play an important physiological role in maintaining adult bone structure and strength. Consequently, thyroid dysfunction is related to skeletal outcomes. Overt hyperthyroidism is an established cause of high bone turnover with accelerated bone loss, leading to osteoporosis and increased fracture risk. Hyperthyroidism induced by thyroid-stimulating hormone-suppressive therapy in patients with differentiated thyroid cancer is a cause of secondary osteoporosis. In contrast, there is a lack of evidence on the negative impact of hypothyroidism on bone health. Considering the clinical updates on the importance of bone health in thyroid dysfunction, the Task Force from the Clinical Practice Guidelines Development Committee of the Korean Thyroid Association recently developed a position statement on the evaluation and management of bone health of patients with thyroid diseases, particularly focused on endogenous hyperthyroidism and thyroid-stimulating hormone-suppressive therapy-associated hyperthyroidism in patients with differentiated thyroid cancer. Herein, we review the Korean Thyroid Association's position statement on the evaluation and management of bone health associated with thyroid diseases.

Keywords: Hyperthyroidism; Thyroid hormones; Thyroid neoplasms; Osteoporosis; Bone density

SUMMARY

I. Hypothyroidism

There is insufficient evidence that hypothyroidism increases the risk of osteoporosis and fractures. Therefore, the bone health of patients with hypothyroidism should be evaluated and managed according to general osteoporosis guidelines (E).

II. Hyperthyroidism

1.0. Indications for bone health evaluation

1.1. The bone health of postmenopausal women should be evaluated using central bone (lumbar spine and hip) dual-energy X-ray absorptiometry (DXA) at diagnosis (A). Quantitative ultrasonography and peripheral bone densitometry (non-central bone; wrist, ankle, and heel) are more convenient than DXA. However, the T-scores obtained using these tests tend to be lower and less precise than those obtained using DXA. Therefore, central bone DXA is recommended for evaluating the bone health of patients with thyroid diseases (E).

1.2. Since hyperthyroidism in premenopausal women and men younger than 70 can lead to osteoporosis, bone health as-

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Corresponding author: Ho-Cheol Kang
Department of Internal Medicine, Chonnam National University Medical School, 160 Baekseo-ro, Dong-gu, Gwangju 61469, Korea
Tel: +82-61-379-7620, **Fax:** +82-61-379-7628, **E-mail:** drkang@chonnam.ac.kr

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sessment using DXA can be considered in this population (E). In men aged 70 years and older, bone health should be assessed using DXA at diagnosis according to general osteoporosis guidelines (E).

1.3. The interval for follow-up DXA examinations should be determined according to general osteoporosis guidelines (E).

2.0. Evaluation of bone health using assessment tools other than DXA

2.1. Bone health evaluation using bone turnover markers (BTMs) is generally not recommended. However, for patients diagnosed with osteoporosis, measuring BTMs is recommended at diagnosis and during follow-up to assess the response to anti-osteoporosis treatment (E).

2.2. Imaging methods for assessing bone quality, including the trabecular bone score (TBS), femoral geometry, and high-resolution quantitative computed tomography (HR-QCT), are not recommended instead of DXA, but can be used as an adjunct to DXA (E).

3.0. Calcium and vitamin D supplementation

3.1. Calcium and vitamin D supplementation should be considered for postmenopausal women and men older than 50 years and is particularly recommended for patients with osteopenia or osteoporosis confirmed by DXA (E).

3.2. There is no evidence of benefits or risks of calcium and vitamin D supplementation for premenopausal women and men younger than 50 years with normal bone mineral density (BMD) (E). Calcium and vitamin D supplementation is recommended in premenopausal women and men younger than 50 years of age whose BMD Z-score is below the expected range for age (E).

4.0. Anti-osteoporosis drugs

4.1. Anti-osteoporosis drugs are recommended for postmenopausal women and men over 50 years of age who have osteoporosis according to DXA or are at high risk for osteoporotic fractures (C).

4.2. In premenopausal women and men younger than 50 years of age with BMD Z-scores below the expected range for age according to DXA, hyperthyroidism can be treated first, and BMD improvement can be re-evaluated (E). However, for patients at high risk for fracture, anti-osteoporosis drugs can be considered immediately after the diagnosis of hyperthyroidism.

4.3. Anti-resorptive agents, including bisphosphonates, are generally recommended for the treatment of osteoporosis, and anabolic agents may be considered for patients at high risk for fragility fractures (E).

5.0. Special circumstance: subclinical hyperthyroidism

5.1. Bone health should be assessed using DXA according to general osteoporosis guidelines in postmenopausal women and men aged 70 years or older (E). Although there is insufficient evidence that subclinical hyperthyroidism *per se* causes osteoporosis in premenopausal women and men younger than 70 years, bone health assessment using DXA can be considered if the thyroid-stimulating hormone (TSH) level is <0.1 mU/L (E).

5.2. Calcium and vitamin D supplementation is recommended for patients diagnosed with osteopenia and osteoporosis by DXA (E).

5.3. Anti-osteoporosis drugs may be considered for patients diagnosed with osteoporosis and osteopenia by DXA (E).

III. Hyperthyroidism induced by TSH-suppressive therapy in patients with differentiated thyroid cancer

1.0. Indications for bone health evaluation

1.1. Bone health evaluation using DXA is recommended when initiating TSH-suppressive therapy in postmenopausal women (A).

1.2. For premenopausal women and men younger than 70 years who are at high risk for osteoporotic fractures, bone health evaluation using DXA can be considered when initiating TSH-suppressive therapy. The bone health of men aged 70 years or older should be assessed using DXA at the start of treatment based on general osteoporosis guidelines (E).

1.3. Bone health evaluation using DXA should be considered for premenopausal women at the time of menopause and men aged over 70 years during follow-up (E).

1.4. The interval for follow-up DXA should be determined according to general osteoporosis guidelines (E).

2.0. Evaluation of bone health using assessment tools other than DXA

2.1. Bone health evaluation based on BTMs is generally not recommended. However, for patients diagnosed with osteoporosis, measuring BTMs is recommended at diagnosis and at follow-up to assess the response to anti-osteoporosis treatment (E).

2.2. Imaging methods for assessing bone quality, including TBS, femoral geometry, and HR-QCT, are not recommended in-

stead of DXA, but can be used as an adjunct to DXA (E).

3.0. Calcium and vitamin D supplementation

3.1. Calcium and vitamin D supplementation should be considered for postmenopausal women and men older than 50 years, particularly for patients with osteopenia or osteoporosis confirmed by DXA (E).

3.2. There is no evidence of benefits or risks of calcium and vitamin D supplementation for premenopausal women and men younger than 50 years of age with normal BMD (E). Calcium and vitamin D supplementation is recommended for premenopausal women and men younger than 50 years whose BMD Z-score is below the expected range for age (E).

4.0. Anti-osteoporosis drugs

4.1. Anti-resorptive agents, including bisphosphonates, are recommended for treating osteoporosis in patients diagnosed with osteoporosis by DXA (B).

4.2. Anabolic agents may be considered for patients at high risk for osteoporotic fractures (E).

4.3. Anti-osteoporosis drugs should be considered for patients at high risk for osteoporotic fractures even if they do not have osteoporosis confirmed by DXA (E).

5.0. Special circumstance: postsurgical hypoparathyroidism

5.1. Bone health management of patients with postsurgical hypoparathyroidism should adhere to the general principles of treatment for postsurgical hypoparathyroidism (B).

5.2. Adequate calcium and vitamin D supplementation is recommended to avoid hypocalcemia or hypercalcemia and its related complications and preserve bone health (B).

INTRODUCTION

Thyroid hormones are related to bone growth, development, and remodeling [1]. Thyroid hormones act via the thyroid hormone receptor α in osteoblasts and stimulate osteoclastic bone resorption through osteoblast-mediated cytokine signaling [2,3]. Thyroid hormones also play an important physiological role in maintaining bone structure and strength in adults. Therefore, thyroid dysfunction is inevitably associated with skeletal consequences to various degrees. However, the cellular and molecular mechanisms underlying the action of thyroid hormones on bone remain a matter of debate and are incompletely understood.

Overt hyperthyroidism is an established cause of high bone turnover with accelerated bone loss, resulting in osteoporosis and an increased risk of fractures [4]. Subclinical hyperthyroidism, either endogenous or induced by TSH suppression-related to excessive levothyroxine treatment for hypothyroidism, also has a deleterious effect on bone health. According to some studies, TSH-suppressive levothyroxine therapy reportedly leads to bone loss in postmenopausal women [5] that is greater in the cortical bone than in the trabecular bone [6].

Furthermore, there are increasing concerns about osteoporosis and fragility fractures in patients with thyroid cancer receiving TSH-suppressive therapy. Patients with differentiated thyroid cancer (DTC) who undergo total thyroidectomy often require high-dose levothyroxine replacement for TSH suppression. TSH-suppressive therapy has been a mainstay of treatment for reducing disease recurrence in DTC patients with high-risk features. However, subsequent hyperthyroid status is associated with an increased risk of osteoporosis, particularly in postmenopausal women [7]. TSH-suppressive levothyroxine replacement is linked to an increased risk of bone resorption through stimulated osteoblast and osteoclast activity in patients with DTC [8], but studies on the therapeutic efficacy of anti-osteoporosis drugs in these patients are scarce. Osteoporosis and fragility fractures have potentially harmful effects on the quality of life and life expectancy of DTC patients [8,9]. Therefore, skeletal health has emerged as an important decision-making factor for TSH suppression in patients with DTC according to the latest 2016 American Thyroid Association guidelines [10].

The Korean Thyroid Association (KTA) recently published a position statement on the evaluation and management of bone health in patients with thyroid diseases in Korea [11]. This position statement focused on patients with hypothyroidism, endogenous hyperthyroidism, and DTC receiving TSH-suppressive therapy. In this review, we summarize the key aspects of the KTA's position statement on the evaluation and management of bone health in patients with thyroid diseases and outline the clinical implications from an endocrinologist's point of view.

METHODS

Development of evidence-based recommendations

This guideline was developed by the Task Force from the Clinical Practice Guidelines Development Committee of the KTA. The guideline contains the most up-to-date evidence-based recommendations for the evaluation and management of bone health in patients with thyroid diseases, with a particular focus on endogenous hyperthyroidism and TSH suppression-related hyperthyroidism in DTC patients. Endogenous hyperthyroidism

Table 1. Definition of Recommendation Levels

Recommendation level	Definition
A	When there is a clear rationale for the recommendations: When manifold randomized controlled trials that can be generalized because they have sufficient test or meta-analysis results support a recommendation.
B	When there is a reliable basis for the recommendations: When reasonable grounds support this through well-performed cohort studies or patient—control group studies.
C	When there is a possible basis for the recommendations: When relevant grounds are seen through randomized clinical studies or case reports and observational studies carried out in a small institution, despite their inherent unreliability.
E	Expert recommendations: There is no basis to support the recommendations, but they are supported by expert opinion or expert clinical experience.

and TSH suppression-related hyperthyroidism in patients with DTC affect the bone differently. When endogenous hyperthyroidism is treated with anti-thyroid drugs, bone loss could be reversed by the recovery of normal thyroid function. In contrast, TSH-suppressive therapy in DTC patients can have a stronger effect on bones because the hyperthyroid status persists for a certain period for the purpose of tumor suppression. Therefore, this guideline distinguishes between endogenous hyperthyroidism and TSH-suppressive therapy-related hyperthyroidism in DTC and establishes recommendations for each.

The grading system included the following types of evidence: well-designed randomized controlled trials, meta-analysis results, cohort studies, patient-control studies, and expert opinions on clinical experiences. The guideline committee used the grading levels of A, B, C, and E to grade the evidence supporting each recommendation, as described in previous publications (Table 1) [12,13].

HYPOTHYROIDISM

In patients with hypothyroidism, both bone formation by osteoblasts and bone resorption mediated by osteoclasts decrease, resulting in a low rate of bone turnover [14]. As a result, the bone remodeling cycle is delayed, resulting in a net increase in bone mineralization and bone density without a change in bone volume. However, it is difficult to demonstrate a significant correlation between hypothyroidism and BMD or fractures owing to the small number of studies and disparate results of clinical studies published to date. Although levothyroxine treatment has been associated with an increase in fractures in some studies, there have been no long-term prospective follow-up studies of patients with untreated hypothyroidism [4,15,16]. Therefore, the bone health of patients with hypothyroidism should be evaluated and managed according to general osteoporosis guidelines.

HYPERTHYROIDISM

Indications for bone health evaluation

Endogenous hyperthyroidism mainly includes Graves' disease, toxic multinodular goiter, and toxic adenoma. Overt hyperthyroidism is associated with accelerated bone remodeling and net bone loss [17,18]; therefore, it is a well-known risk factor for secondary osteoporosis [19]. Extensive evidence supports that postmenopausal women with overt hyperthyroidism have a lower BMD and a three- to four-fold increased risk of fracture [4,20-22]. In some studies, a prior history of hyperthyroidism was related to an increased risk of fracture in the elderly [23,24]. A meta-analysis of 25 studies by Vestergaard and Mosekilde [25] showed that the risk of hip fracture was higher in patients with hyperthyroidism than in normal controls, especially at ages 50 and above. A cohort study conducted in the United States reported that among patients aged ≥65 years, serum TSH levels below 0.1 mU/L were related to a three-fold increased risk of hip fracture and a four-fold increased risk of vertebral fracture [21]. A longitudinal study reported that bone loss was reversed by treatment of hyperthyroidism [26].

DXA is considered a standard measurement tool for the diagnosis of osteoporosis that can effectively predict the fracture risk [27,28]. Thus, in most guidelines for the management of osteoporosis, including those of the Korean Society for Bone and Mineral Research (KSBMR) [29-31], DXA is recommended for postmenopausal women who are ≥65 years old. In addition, even for postmenopausal women younger than 65 years, DXA is recommended if they have a risk factor for secondary osteoporosis such as hyperthyroidism. Therefore, the use of DXA to evaluate the bone status of postmenopausal women

with overt hyperthyroidism seems to be justified.

Compared to DXA, peripheral bone densitometry (non-central bones; wrists, ankles, and heels), including quantitative ultrasonography, has the advantage of being easier to perform and less expensive than DXA. However, since the T-score obtained with peripheral bone densitometry tends to be lower than that obtained with DXA, there is a risk of over-diagnosing osteoporosis with the former. In addition, most peripheral bone densitometry data cannot be used for follow-up owing to low precision. Therefore, central bone DXA is recommended when evaluating the bone health of patients with hyperthyroidism.

Some studies have shown that premenopausal women and men with hyperthyroidism had decreased BMD and an increased risk of fracture [32-34]. A cross-sectional study with a small sample size showed that premenopausal women with hyperthyroidism had lower BMD than those without hyperthyroidism [35]. Based on the research results so far, it is difficult to conclude that hyperthyroidism has a detrimental effect on bone health in premenopausal women and men, but it may be possible to some extent. Thus, bone health evaluation using DXA can be considered for premenopausal women and men under the age of 70 with hyperthyroidism. Bone health evaluation of men aged 70 years or older with hyperthyroidism through DXA is necessary because of the high risk of osteoporosis and fractures.

Although bone loss due to overt hyperthyroidism is evident, there is insufficient evidence to warrant frequent BMD evaluation in this patient population. Therefore, for patients diagnosed with overt hyperthyroidism and under follow-up, DXA should be performed according to the generally recommended osteoporosis guidelines.

Evaluation of bone health using assessment tools other than DXA

Several studies have evaluated BTMs in patients with overt hyperthyroidism [36-43]. In one study that compared patients with hyperthyroidism and age-matched controls, it was found that both bone formation and resorption markers were increased in the former, and the changes in resorption markers were more prominent than those in formation markers [36]. Thus, bone resorption markers, rather than formation markers, were reported to be sensitive markers of bone turnover status in patients with hyperthyroidism [36,40]. One study that focused on men with hyperthyroidism found an increase in BTMs [43]. Some BTMs, especially resorption markers, are correlated with serum free triiodothyronine (T3) levels [36,39]. Recovery of BTMs can be achieved after treating hyperthyroidism [36,39,41], and in such cases, bone resorption markers show a more rapid decrease than formation markers [39]. However, neither absolute levels of BTMs nor changes in BTMs after treatment of hyperthyroidism seem to reflect bone status better than DXA. Therefore, evaluating bone health using BTMs is not recommended unless hyperthyroidism is accompanied by osteoporosis. However, if osteoporosis is diagnosed in patients with hyperthyroidism, BTMs can be useful for evaluating the treatment response after the initiation of anti-osteoporosis drugs.

DXA is an excellent tool for predicting fracture risk by assessing bone density. However, DXA cannot capture alterations in bone microarchitecture or femur geometry, which are also important contributing factors to bone strength. Therefore, several bone quality assessment tools have recently emerged in bone research, including the TBS, hip geometry, and HR-QCT.

There has been insufficient research on the use of these bone quality assessment tools for estimating the bone status of patients with hyperthyroidism. Although low TBSs in subjects with hyperthyroidism and recovery of the TBSs after anti-thyroid drug therapy were observed in some studies [34,44], the results are limited by small study populations restricted to premenopausal women and men with hyperthyroidism. A recent study using HR-QCT showed that women with hyperthyroidism had lower volumetric BMD and bone strength than healthy controls, as well as compromised cortical microarchitecture in the radius. Significant improvements in these parameters were observed after the attainment of euthyroid status [45]. To our knowledge, no study has examined the hip geometry of patients with hyperthyroidism. Therefore, although there is still insufficient evidence that bone quality analysis is superior to DXA for assessing bone health in patients with hyperthyroidism, it can be used as an adjunct bone health assessment method.

Calcium and vitamin D supplementation

To our knowledge, there are no studies on the direct effects of calcium and vitamin D supplementation on BMD and fracture risk in patients with hyperthyroidism. However, several large-scale studies have demonstrated that calcium and vitamin D supplementation prevents fractures and reduces bone loss in the general population with osteoporosis or osteopenia [46-49]. Therefore, for patients with hyperthyroidism, especially postmenopausal women and men aged 50 years or older with osteopenia or osteoporosis confirmed by DXA, calcium and vitamin D supplementation is recommended [29-31]. Even for postmenopausal women and men over 50 years of age with normal

bone density, calcium and vitamin D supplementation can be considered since the population in South Korea generally has a low average dietary intake of calcium and vitamin D [50,51]. Calcium and vitamin D supplementation is recommended for premenopausal women and men younger than 50 years whose BMD is below the expected range for age according to DXA. However, there is no evidence of any benefits or disadvantages of calcium and vitamin D supplementation for premenopausal women and men younger than 50 years with normal BMD.

Anti-osteoporosis drugs

Only a few observational studies with very small sample sizes have demonstrated the effect of anti-osteoporosis treatment on the increase in BMD in patients with hyperthyroidism. Alendronate treatment for 12 months increased BMD in women with both hyperthyroidism and osteoporosis regardless of menopausal status (n=40) [52]. The combination of alendronate and anti-thyroid drugs appeared to be more efficacious than anti-thyroid drugs only for increasing BMD after 12 months in 26 elderly men with both hyperthyroidism and osteoporosis [53]. In a Japanese study including 27 men with both Graves' disease and osteopenia/osteoporosis, 14 men treated with risedronate and an anti-thyroid drug showed a greater increase in BMD and a decrease in BTMs than 13 men treated with an anti-thyroid drug alone [54]. However, to our knowledge, no study has investigated the effect of anti-osteoporosis treatment on the risk of fracture among patients with hyperthyroidism.

Considering the findings of previous studies and general guidelines for osteoporosis treatment, anti-osteoporosis drugs should be prescribed to postmenopausal women and men aged 50 years or older diagnosed with osteoporosis by DXA or at high risk for fractures according to FRAX [29-31,55]. Premenopausal women and men younger than 50 years generally do not have a high risk of fracture, so hyperthyroidism can be treated first, and BMD can be re-evaluated for improvement; however, if the risk of fracture is high, anti-osteoporosis treatment can be considered immediately once the diagnosis of hyperthyroidism is confirmed.

Anti-resorptive agents, including bisphosphonates, are generally recommended to reduce bone remodeling in patients with hyperthyroidism and osteoporosis. To our knowledge, no study has examined the effect of denosumab, selective estrogen receptor modulators, or anabolic agents on bone health in patients with hyperthyroidism. Denosumab, a monoclonal antibody to the receptor activator of nuclear factor kappa B ligand, is an anti-resorptive agent recommended as a first-line drug for groups at high risk for fractures in the recently published osteoporosis management guidelines of the Endocrine Society and the American Association of Clinical Endocrinologists and American College of Endocrinology [29,30]. Additionally, the guidelines recommend anabolic agents for patients at very high risk for fractures. Therefore, individualized anti-osteoporosis treatment should be offered to patients with hyperthyroidism and osteoporosis.

Special circumstance: subclinical hyperthyroidism

Subclinical hyperthyroidism is defined as a biochemical state where the TSH level decreases below the reference ranges and the levels of thyroid hormones such as free thyroxine (fT4) and T3 remain within the reference ranges. The incidence of subclinical hyperthyroidism increases with age [56]. As mentioned above, overt hyperthyroidism is a well-established cause of secondary osteoporosis, and several studies have confirmed a decrease in bone density and an increased risk of fracture in such patients [19,25,57]. However, studies have reported conflicting findings on the association between subclinical hyperthyroidism and skeletal consequences. The majority of previous studies have consistently shown that BMD is significantly reduced in postmenopausal women [58-61]. Postmenopausal women have significantly low BMD in the femoral neck and radius, predominantly consisting of cortical bone [62]. The association between subclinical hyperthyroidism and bone loss in premenopausal women and men is unclear [63-65]. Most studies involving premenopausal women did not show a significant association between low BMD or fracture risk and subclinical hyperthyroidism [66]. Very few studies have investigated the correlation between subclinical hyperthyroidism and bone health in men, and those studies mainly focused on the risk of hip fractures. In one study, men aged over 65 years with subclinical hyperthyroidism showed a higher risk of hip fracture than postmenopausal women [67]. Therefore, further studies are needed to confirm the association between subclinical hyperthyroidism and bone health in men and premenopausal women.

Regarding BTMs, some studies reported an increase in BTMs in patients with subclinical hyperthyroidism, while others did not [38,42,58]. A meta-analysis showed that subclinical hyperthyroidism was associated with a 1.5-fold higher risk of hip fracture, 1.4-fold higher risk of any fracture, and 1.7-fold higher risk of spine fracture than euthyroidism [68]. In terms of the degree of hyperthyroidism, the fracture risk is increased in subjects with TSH levels below 0.1 mU/L or undetectable TSH [61,68,69].

Considering the results of previous studies and osteoporosis treatment guidelines, bone health should be evaluated using DXA in postmenopausal women and men aged 70 years or older diagnosed with subclinical hyperthyroidism. There is insufficient evidence that subclinical hyperthyroidism *per se* causes osteoporosis in premenopausal women and men younger than 70 years of age. However, if the degree of hyperthyroidism is severe, the risk of fracture increases. Thus, if the TSH level is less than 0.1 mU/L, bone health evaluation using DXA can be considered in premenopausal women and men younger than 70 years of age.

To our knowledge, no study has evaluated the role of calcium and vitamin D supplementation in the bone health of patients with subclinical hyperthyroidism; moreover, no study has reported the definitive efficacy of anti-osteoporosis treatment in subclinical hyperthyroidism. Therefore, it is reasonable to recommend calcium and vitamin D supplementation or anti-osteoporosis drugs according to the general principles of osteoporosis treatment for patients with subclinical hyperthyroidism. Based on the above recommendations, Fig. 1 shows an algorithm for bone health evaluation and treatment in patients diagnosed with hyperthyroidism.

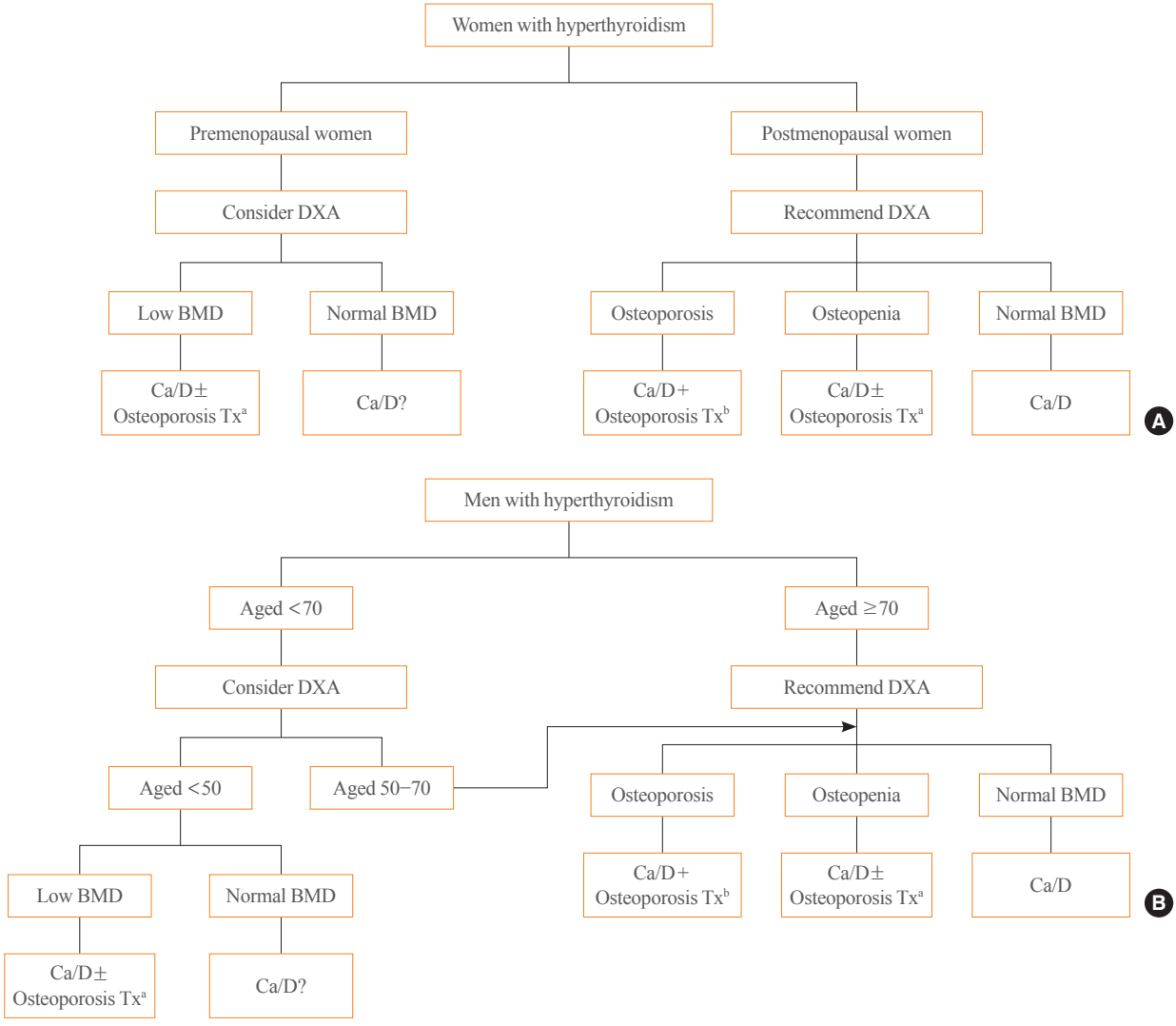

Fig. 1. Evaluation and management of bone health in (A) women and (B) men with hyperthyroidism. Anti-osteoporosis treatment includes therapy with anti-resorptive agents (e.g., bisphosphonates) and anabolic agents. Certain types of bisphosphonates (e.g., ibandronate) are not approved for men. DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; Ca/D, calcium and vitamin D; Tx, therapy. [a]Ca/D ±Osteoporosis Tx: Treatment for osteoporosis can be considered in combination with calcium and vitamin D replacement; [b]Ca/D+Osteoporosis Tx: Treatment for osteoporosis is needed in combination with calcium and vitamin D replacement.

HYPERTHYROIDISM INDUCED BY TSH-SUPPRESSIVE THERAPY IN PATIENTS WITH DTC

Indications for bone health evaluation

Studies on the skeletal effect of TSH-suppressive therapy in patients with DTC have shown heterogeneous results according to the study design, type of patients included (premenopausal women, postmenopausal women, or men), and follow-up duration. Nonetheless, several recently published meta-analyses showed considerable agreement with each other.

According to the results of meta-analyses, TSH-suppressive therapy has a deleterious effect on BMD in postmenopausal women, but not in premenopausal women [7,70-75]. Faber and Galloe [70] reported that annual BMD loss during TSH-suppressive therapy was 1.0% in postmenopausal women and 0.13% in premenopausal women. A recent meta-analysis by Ku et al. [74] revealed that TSH-suppressive therapy obviously decreased BMD at the lumbar spine, femoral neck, and total hip in postmenopausal women. Despite the low number of eligible studies in previous meta-analyses, the effect of TSH-suppressive therapy on BMD seems to be insignificant in men [7,71,73,74].

There have been conflicting results regarding fracture risk among patients with DTC on TSH-suppressive therapy. Out of the five cross-sectional studies with a mean duration of TSH-suppressive therapy of 5 to 12 years, only the study of Mazziotti et al. [76] showed an association of TSH-suppressive therapy with fractures [76-80]; in that study, a higher incidence of vertebral fracture was observed among patients with TSH levels of <0.5 mU/L. In two population-based studies, no significant associations were observed between TSH suppression and the risk of osteoporotic fractures [81,82]. Nevertheless, in a study by Shin et al. [82], levothyroxine doses >170 μg/day were associated with a higher risk of fracture than doses <170 μg/day. To date, the relationship of BMD with the duration or degree of TSH suppression, levothyroxine dose, and serum levels of fT4 or T3 is not clear.

Based on the most up-to-date study results, BMD measurement is recommended in postmenopausal women with DTC when initiating TSH-suppressive therapy. BMD measurement is not generally recommended in premenopausal women, but may be considered when patients are at high risk for osteoporosis and fragility fractures. For men under the age of 70, it is not necessary to perform DXA when initiating TSH-suppressive therapy, but BMD assessment may be considered if the risk of osteoporotic fractures is high. Although there is insufficient evidence of bone loss due to TSH-suppressive therapy in men aged 70 years or older, as in the case of men with hyperthyroidism, the risk of osteoporosis and fracture is usually high because of old age; therefore, bone health evaluation with DXA is necessary when initiating TSH-suppressive therapy.

Menopause is the most important cause of osteoporosis in women due to estrogen deficiency. Therefore, if menopause is confirmed in premenopausal women who continue TSH-suppressive therapy, it is necessary to evaluate bone status using DXA. Among men, age is the main cause of osteoporosis. According to the current national insurance coverage and KSBMR's guidelines for osteoporosis management, BMD evaluation using DXA is required for men aged 70 years or older who are continuing TSH-suppressive therapy [31].

As with endogenous hyperthyroidism, there is a lack of evidence for frequent follow-up BMD assessments of patients with hyperthyroidism induced by TSH-suppressive therapy. Therefore, even for patients receiving TSH-suppressive therapy for DTC, follow-up BMD assessments should be performed according to generally recommended osteoporosis guidelines and national insurance coverage.

Evaluation of bone health using assessment tools other than DXA

Few studies have evaluated the role of BTMs in DTC patients with TSH-suppressive therapy. Some studies showed increased serum levels of bone resorption and/or bone formation markers in patients than in controls, but others did not [78,79,83]. In another study that evaluated BTMs according to TSH and fT4 levels in 94 women with DTC who were receiving TSH-suppressive therapy, the BTMs were not affected by TSH or fT4 levels [84]. Collectively, bone health assessment using BTMs alone is not recommended due to limited evidence of efficacy. However, for patients diagnosed with osteoporosis by DXA, baseline and follow-up BTM measurements are recommended to assess the treatment response after the initiation of anti-osteoporosis therapy.

Long-term TSH suppression could have a negative effect on bone microarchitecture and hip geometry in addition to bone density. In several recent studies using the TBS, patients with DTC who were receiving TSH-suppressive therapy showed significantly lower TBSs than the controls, indicating deteriorated bone microarchitecture [85-87]. Moon et al. [88] showed altered femur geometry in patients with DTC who were receiving TSH-suppressive therapy as opposed to controls. Although few studies have investigated the bone microstructure using HR-QCT in patients with DTC, changes in bone quality due to TSH sup-

pression were also observed in these studies [89,90]. These results suggest that imaging-based bone quality assessment tools are helpful for capturing deteriorated bone strength in patients with DTC who receive TSH-suppressive therapy. Considering cost-effectiveness and accessibility, these modalities can be applicable as an adjunct to bone health assessment.

Calcium and vitamin D supplementation

To our knowledge, there are no randomized controlled studies on calcium and vitamin D supplementation for patients with DTC and without postsurgical hypoparathyroidism receiving TSH-suppressive therapy. Calcium and vitamin D supplementation can be considered for postmenopausal women, high-risk groups for fractures, or patients with comorbidities that can cause secondary osteoporosis if calcium and vitamin D intake through diet is insufficient. TSH-suppressive therapy induces hyperthyroidism, which can cause secondary osteoporosis. Therefore, calcium and vitamin D supplementation is recommended for patients with DTC receiving TSH-suppressive therapy and osteopenia or osteoporosis confirmed by DXA. Calcium and vitamin D supplementation can be considered for postmenopausal women and men older than 50 years of age, as they are at high risk for fractures even if normal BMD is confirmed by DXA. However, as with hyperthyroidism, it is difficult to conclude whether calcium and vitamin D supplementation benefits the bone health of premenopausal women and men under the age of 50 with normal bone density and of patients with DTC receiving TSH-suppressive therapy.

For the prevention and treatment of osteoporosis and fragility fractures, the KSBMR guidelines recommend an average daily intake of 800–1000 mg of calcium and 800 IU of vitamin D for postmenopausal women and men aged above 50 years [31]. Serum 25-hydroxy vitamin D (25[OH]D) levels should be measured at least 3 months after the initiation of calcium and vitamin D supplementation to evaluate treatment efficacy. To prevent osteoporosis, the serum 25(OH)D concentration should be at least 20 ng/mL or higher. Levels exceeding 30 ng/mL may be needed to treat osteoporosis and prevent osteoporotic fractures and falls. Thus, it would be necessary for patients with DTC receiving TSH-suppressive therapy to maintain a serum 25(OH)D level of at least 20 ng/mL after the initiation of calcium and vitamin D supplementation. The need for calcium and vitamin D supplementation among patients with normal thyroid function after the completion of TSH-suppressive therapy should be determined according to each patient's risk of osteoporosis and fractures.

Anti-osteoporosis drugs

Two studies examined the efficacy of an anti-osteoporosis drug, namely a bisphosphonate (alendronate), in patients with thyroid cancer [91,92]. Panebianco et al. [92] showed the efficacy of alendronate in reducing TSH suppression-induced bone loss in patients with thyroid cancer. Panico et al. [91] demonstrated the efficacy of alendronate treatment in 74 patients with DTC without bone metastasis; in that study, 2-year alendronate treatment significantly increased lumbar spine BMD (7.88%) if the duration of TSH suppression was less than 3 years. However, in patients receiving TSH-suppressive therapy for 6 and 9 years, alendronate treatment showed a minor or no increase in lumbar spine BMD (4.63% and 0.86%, respectively). In the control group, a significant increase was observed in lumbar spine BMD (8.2%) after 2 years of alendronate treatment. Total hip BMD also increased by 4.62% and 3.01% if TSH-suppressive therapy was administered for less than 3 and 6 years, respectively. There was no significant change in the total hip BMD (0.95%) of patients on TSH suppression for 9 years. In the control group, a significant increase was observed in total hip BMD (5.27%) after 2 years of alendronate treatment. These results suggest that bisphosphonate treatment is effective in improving BMD when TSH-suppressive therapy has been administered for less than 3 years, but the effect seems to decrease as the duration of TSH suppression increases. To our knowledge, there have been no studies on the efficacy of bisphosphonates other than alendronate or other types of anti-resorptive agents in preventing TSH suppression-induced bone loss. However, based on the latest osteoporosis treatment guidelines, anti-resorptive agents such as denosumab or anabolic agents may be suitable for postmenopausal women or men aged 50 years or older.

As mentioned above, long-term TSH-suppressive therapy can be considered a cause of secondary osteoporosis due to prolonged hyperthyroidism. Hence, anti-osteoporosis treatment should be considered for patients at high risk for osteoporotic fractures even if they do not have osteoporosis confirmed by DXA.

Special circumstance: postsurgical hypoparathyroidism

The incidence of permanent postsurgical hypoparathyroidism is reported to be 0% to 3% [93-95]. Extensive invasive thyroid cancer surgery, total thyroidectomy with cervical lymph node dissection, and surgery for Graves' disease increase the risk of postsurgical hypoparathyroidism [96-98]. Parathyroid hormone (PTH) maintains calcium homeostasis in the body. PTH promotes calcium release from the bones, increases calcium reab-

sorption in the kidney, and stimulates calcitriol synthesis in the kidney to increase calcium absorption in the intestine, thereby increasing blood calcium levels [99]. PTH also affects several bone cells, including the osteocytes, osteoblasts, and osteoclasts, and promotes bone remodeling [100]. Therefore, hypoparathyroidism decreases bone turnover [101] and leads to increased BMD [102]. In previous studies, both premenopausal and postmenopausal women with postsurgical hypoparathyroidism and those receiving TSH-suppressive therapy were found to have lower bone turnover and higher BMD than healthy controls [103-105]. Further, there is insufficient evidence to determine whether the increased bone mass increases bone strength or reduces fracture risk among patients with postsurgical hypoparathyroidism. Therefore, patients with postsurgical hypoparathyroidism should be treated with calcium and vitamin D to maintain serum calcium levels within the asymptomatic range, avoid

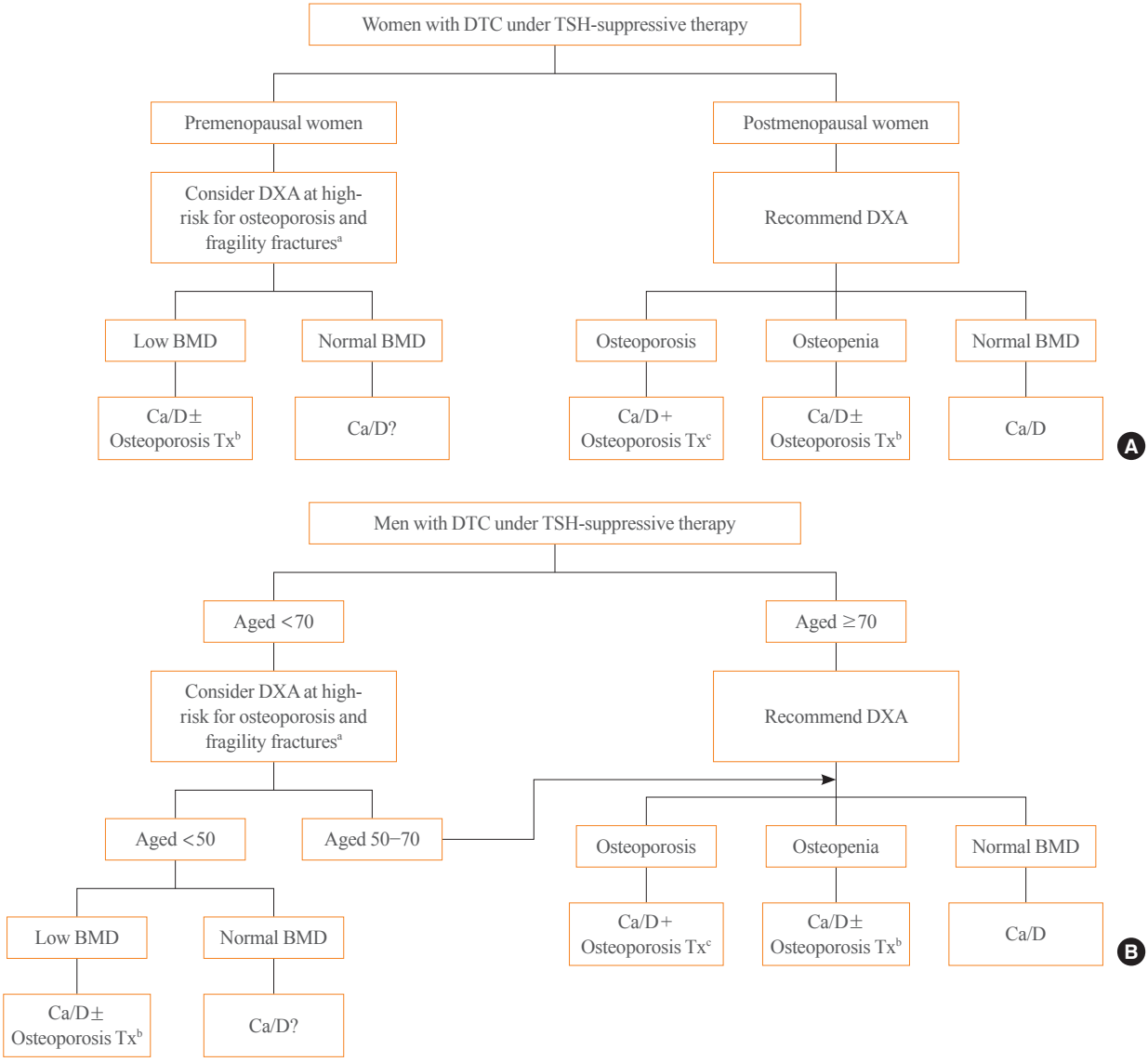

Fig. 2. Evaluation and management of bone health in (A) women and (B) men with differentiated thyroid cancer (DTC) receiving thyroid-stimulating hormone (TSH)-suppressive therapy. Anti-osteoporosis treatment includes therapy with anti-resorptive agents (e.g., bisphosphonates) and anabolic agents. Certain types of bisphosphonates (e.g., ibandronate) are not approved for men. DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; Ca/D, calcium and vitamin D; Tx, therapy. [a]The high-risk group for osteoporosis and fragility fractures had a previous history of fragility fractures, had amenorrhea for more than 1 year (for women), had other medical diseases, and took medications that cause osteoporosis; [b]Ca/D±Osteoporosis Tx: Treatment for osteoporosis can be considered in combination with calcium and vitamin D replacement; [c]Ca/D+Osteoporosis Tx: Treatment for osteoporosis is needed in combination with calcium and vitamin D replacement.

significant hypocalcemia or hypercalcemia and its associated complications, and preserve bone health [106,107].

Based on the above recommendations, Fig. 2 presents an algorithm for the evaluation and management of the bone health of patients who start TSH-suppressive therapy for DTC.

CONCLUSIONS

Although there are increasing concerns about osteoporosis and fragility fractures related to thyroid diseases, the guidelines for the evaluation and management of these conditions are not yet established, mainly because of insufficient clinical evidence. The KTA's position statement summarizes the research findings on endogenous hyperthyroidism and TSH-suppressive therapy-related hyperthyroidism in patients with DTC and suggests a practical evaluation and management strategy mostly based on expert opinion. Further studies are needed to better understand the clinical impact and long-term effects of thyroid diseases on bone health and to shed light on appropriate decision-making protocols.

CONFLICTS OF INTEREST

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

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ORCID

A Ram Hong *https://orcid.org/0000-0002-2494-9902*
Ho-Cheol Kang *https://orcid.org/0000-0002-0448-1345*

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