

# Risk of Osteoporotic Fractures after Thyroid-stimulating Hormone Suppression Therapy in Patients with Thyroid Cancer

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Received: January 28, 2019

Revised: February 3, 2019

Accepted: February 7, 2019

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

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**Background:** The effects of subclinical hyperthyroidism on fracture risk induced by thyroid-stimulating hormone (TSH) suppression therapy in patients with thyroid cancer still remains controversial. We performed a meta-analysis and systematic review to evaluate the effects of TSH suppression therapy on osteoporotic fracture in patients with thyroid cancer. **Methods:** We performed a systematic search to identify studies which included osteoporotic fractures (hip fracture and vertebral fracture) in patients on TSH suppression therapy for thyroid cancer. Main outcome measures were occurrence and risk of osteoporotic fractures including hip and vertebral fractures between patients and controls. **Results:** A systematic search yielded a total of 8 studies appropriate for review which included osteoporotic fracture outcome in patients on TSH suppression therapy for thyroid cancer. Studies with larger number of subjects showed the higher risk of osteoporotic fracture in group with TSH suppression therapy, although studies with smaller sample size presented a similar risk of fracture with control group. **Conclusions:** Although studies were limited by small numbers, results suggested possible association between chronic TSH suppression therapy and the increased risk of osteoporotic fractures in patients with thyroid cancer.

**Key Words:** Osteoporotic fractures · Thyroid neoplasms · Thyrotropin

## INTRODUCTION

Thyroid hormones have physiological stimulatory effects on bone remodeling and mineralization, and normal euthyroid status during childhood and adolescence is required for acquisition of peak bone mass.[1] However, elevated level of thyroid hormone can excessively stimulate a bone remodeling, consequent bone loss, decrease of bone mineral density (BMD), and increase of osteoporotic fracture risk.[2,3]

Majority of thyroid cancer is differentiated thyroid cancer (DTC) raised from thyroid follicular epithelial cells. DTC expresses thyroid-stimulating hormone (TSH) receptor on the cell membrane and TSH stimulates cell growth rate.[1] Suppres-

sion of TSH by supraphysiologic doses of L-thyroxine (L-T4) is commonly used to treat patients with DTC with the purpose of decreasing the risk of cancer recurrence after thyroidectomy for thyroid cancer.[4]

On the other hands, this TSH suppression therapy, that is the chronic subclinical hyperthyroidism, may be associated with undesired adverse effects, such as atrial fibrillation, major cardio vascular events, and osteoporosis.[5,6]

Thus, patients who underwent thyroidectomy for thyroid cancer could be subject vulnerable to loss of bone mass and decreased BMD, osteoporosis.[5,7-9]

However, the influence of TSH suppression therapy following thyroidectomy on fracture risk in patients with thyroid cancer has not been adequately addressed.

Therefore, the purpose of this study was to determine whether TSH suppression therapy in patients with thyroid cancer increase a risk of osteoporotic fractures from the literature review.

## METHODS

This study was exempted from Institutional Review Board (IRB) review because it did not involve human subjects.

### 1. Search strategy and selection criteria

Searches of PubMed-Medline, EMBASE, and Cochrane Library were conducted by using key terms (“thyroid cancer or thyroidectomy” and “osteoporosis or osteoporotic fracture”) The last search was conducted on September 26, 2018.

Two authors independently screened the titles and abstracts. They also checked the reference lists of all potentially eligible studies and review papers to find out additional relevant publications. Among the searched publications, we selected studies, which met predefined inclusion criteria. The inclusion criteria were (1) published as an original article in English; (2) included TSH suppression therapy

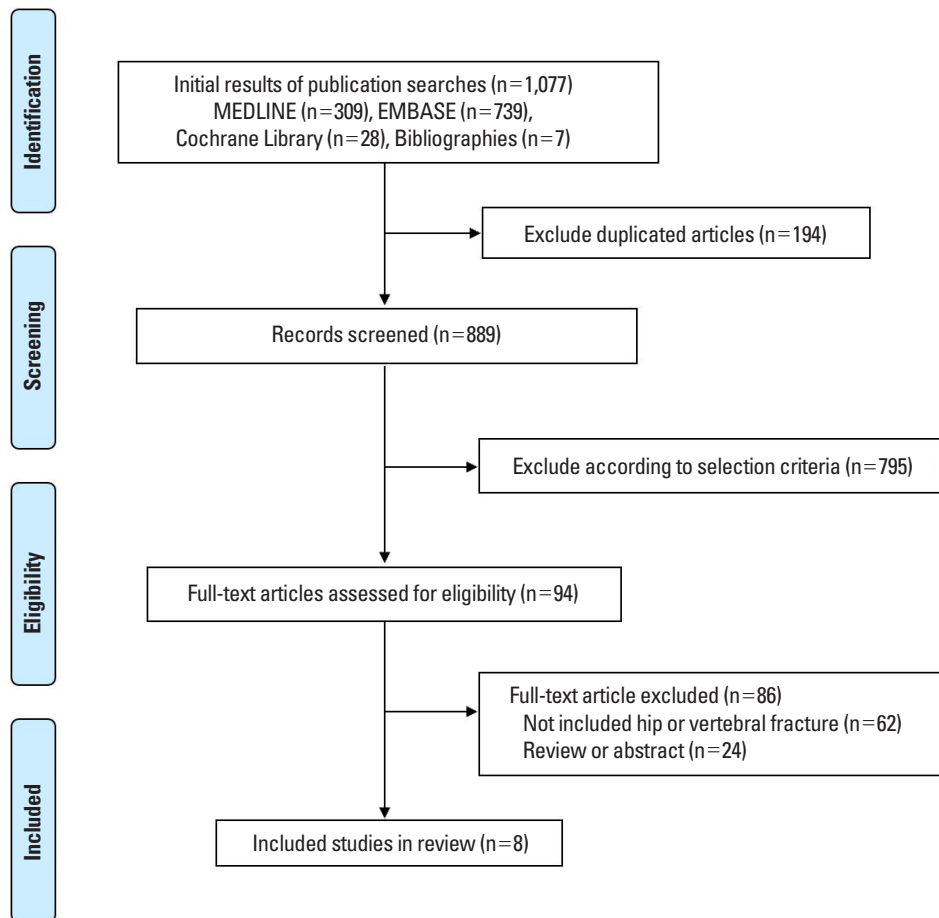


Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analysis flow diagram details the process of relevant study selection.

in patients with thyroid cancer; and (3) evaluated the osteoporotic fractures (vertebral and hip fractures).

Exclusion criteria were (1) not included hip or vertebral fracture as outcomes; and (2) reviews and collection of abstracts for conference meeting.

Two authors (YL and YKL) reviewed the retrieved full manuscripts to determine whether osteoporotic fractures (vertebral and hip fractures) had been reported. Finally, only original studies with osteoporotic fracture fractures in patients with TSH suppression therapy for thyroid cancer were included and reviewed to determine the influence of TSH suppression therapy on the risk of osteoporotic fractures.

## RESULTS

From the PubMed-Medline, EMBASE, and Cochrane Library, a total of 1,077 published articles were searched for osteoporotic fracture in patients with TSH suppression therapy for thyroid cancer (Fig. 1). Of these 1,077 articles, 194 were excluded because of the duplicated articles. Eight hundred seventy seven were excluded because they did not meet our inclusion criteria (Fig. 1).

The remaining 8 studies fulfilling all inclusion criteria were reviewed (Table 1).[10-17] Two was from Rochester, USA, 2

from Italy, 1 from Spain, 1 from Netherland, 1 from Japan, and 1 from Taiwan.

Fujiyama et al.[10] performed a cross-sectional, prospective study to determine whether suppressive doses of thyroxine have any adverse effects on bone in 24 postmenopausal women who underwent total thyroidectomy for DTC. They compared several bone metabolic markers and incidence of vertebral deformity between the suppressed TSH group (TSH < 0.1 mU/L; n = 12) and non-suppressed TSH group (TSH > 0.1 mU/L; n = 12). There was no significant difference of the incidence of vertebral deformity between the suppressed group (0.111 ± 0.06/year/person) and the non-suppressed group (0.146 ± 0.150/year/person). They presented that long-term TSH suppression therapy has no significant adverse effects on risk of vertebral fracture.

Nguyen et al.[11] performed population-based cohort study to assess the risk of fractures among the 136 men who underwent thyroidectomy between 1935 and 1979, comparing with that of age-matched control men from the community (Rochester, MN, USA). With 2,194 person-years of follow-up in each group, the cumulative incidence of any new fracture of the vertebra, proximal humerus, distal forearm, pelvis or proximal femur was similar in both

**Table 1.** Risk of osteoporotic fracture in patients with thyroid-stimulating hormone suppression therapy for thyroid cancer

References	Region	Study design	Subjects	Age	Comparison	Risk of hip fracture	Risk of vertebral fracture
Fujiyama et al.[10]	Japan	Cross-sectional study	24 women	55-80	179 age-matched controls	NA	Similar prevalence with controls
Nguyen et al.[11]	Rochester	Population-based cohort study	136 men	22-77 (median 43)	136 age-matched controls	Higher than controls	Similar with controls
Melton et al.[12]	Rochester	Population-based cohort study	630 women	4-86 (median 42.5)	General population	Higher SIR than expected risk	Higher SIR than expected risk
Heijckmann et al.[13]	Netherlands	Cross-sectional study	40 women 19 men		European reference population	NA	Similar prevalence with controls
Reverter et al.[14]	Spain	Cross-sectional study	33 men	> 18	33 age-, BMI-matched controls	NA	Similar prevalence
Mazziotti et al.[15]	Italy	Cross-sectional study	179 women	42-82 (median 59)	83 patients with TSH < 0.5 mU/L, 50 patients with TSH 0.5 to 1.0 mU/L, 46 patients with TSH > 1.0 mU/L	NA	Higher prevalence than less suppressed group
Lin et al.[16]	Taiwan	Population-based cohort study	9,398	> 20	9,398 propensity-matched controls	Higher risk of osteoporosis	Higher risk of osteoporosis and osteoporotic fracture
Vera et al.[17]	Italy	Case series	74 women	40-80 (51.9 ± 12.0)	120 matched controls	Similar	NA

BMI, body mass index; TSH, thyroid-stimulating hormone; SIR, standardized incidence ratios; NA, not applicable.

groups ( $P=0.23$ ), and the relative risk of any of these fractures in thyroidectomized men was not significantly higher than that of control group (95% confidence interval [CI], 0.7-3.2). Although the observed number of hip fracture was small, the risk of hip fracture (8/136) after thyroidectomy was significantly higher than that (0/136) in control group ( $P<0.001$ ). They suggested that further studies are needed to evaluate the increased risk of hip fractures after thyroidectomy.

Melton et al.[12] performed population-based retrospective cohort study to evaluate the risk of fractures among the 630 Rochester, MN, USA women who underwent thyroidectomy between 1950 and 1974. With 12,804 person-years of follow-up, 261 women sustained 601 different fractures. They calculated standardized incidence ratios (SIR), comparing the number of fractures that were observed at each site to the expected number of fracture in the cohort during their follow-up in the community. There was no increase in overall fracture risk (SIR, 0.9; 95% CI, 0.8-1.00). On the other hands, the risk of vertebral fracture (SIR, 2.8, 95% CI, 2.3-3.3) and hip fracture (SIR, 1.3; 95% CI, 1.01-1.8) were significantly increased, respectively, while there was no increase in SIR of wrist fracture (SIR, 1.1; 95% CI, 0.8-1.4). However, they concluded that the long-term influence of thyroidectomy on overall fracture risk is negligible in women, because fracture risk was associated with advancing age and with the presence of the diseases associated with secondary osteoporosis but not with a history of hyperthyroidism, extent of thyroid surgery, or subsequent use of thyroid replacement therapy.

Heijckmann et al.[13] performed a cross-sectional, retrospective study to compare the prevalence of vertebral fracture in 59 patients, who underwent thyroidectomy for DTC, by using vertebral fracture assessment in dual energy X-ray absorptiometry. The prevalence of vertebral fracture was 7% (4/59), which was not higher than that (12%) of European reference population. They concluded that patients with DTC did not have a higher prevalence of vertebral fracture.

Reverter et al.[14] conducted a cross-sectional, retrospective study to compare the prevalence of vertebral fracture between 33 Caucasian men (mean  $\pm$  standard deviation age,  $56 \pm 14$  years) under treatment for DTC and 33 healthy age- and body mass index-matched male volunteers. Patients were treated for a mean duration of  $15 \pm 5$  years. No

differences were found between patients and controls in bone turnover biomarkers or areal BMD, T-scores or Z-scores in all sites evaluated. No earlier fractures or pain episodes were registered in either group and the incidence of asymptomatic vertebral fractures did not differ significantly between patient (18.8%) and control groups (16.7%), ( $P=0.9$ ). They concluded that long-term TSH suppression treatment with levothyroxine in men with DTC does not appear to exert deleterious effects on BMD or increase the prevalence of vertebral fracture.

Mazziotti et al.[15] performed a cross-sectional study to evaluate the prevalence and associated factors of radiological vertebral fractures in 179 women who receive L-thyroxine therapy following thyroidectomy for DTC. They also compared the prevalence of radiological vertebral fractures and change of BMD according to the level of TSH ( $<0.5$  mU/L, Group 1 [n=83]; 0.5-1.0 mU/L, Group 2 [n=50];  $>1.0$  mU/L, Group 2 [n=46]). Vertebral fractures were found in 51 patients (28.5%), with significantly ( $P<0.001$ ) higher prevalence in Group 1 (44.6%) as compared with Group 2 (24.0%) and Group 3 (4.3%). They presented that older age, osteoporosis in BMD, TSH level  $<1.0$  mU/L, and duration of L-thyroxine therapy were significantly and independently associated with vertebral fracture in the study population. They concluded that the prevalence of vertebral fractures was high in women with DTC who were undergoing long-term, suppressive L-thyroxine therapy.

Lin et al.[16] performed a nationwide retrospective cohort study to compare the risk of osteoporosis among 9,398 thyroid cancer patients with levothyroxine use (n=538), those (n=8,860) without levothyroxine use and propensity-score-matched non-thyroid controls (n=9,398) between 1999 and 2011. In this population-based cohort study, the incidence of osteoporotic fracture in the thyroid cancer cohort (1.15/1,000 person-years) was similar with that in the non-thyroid-cancer cohort (0.95/1,000 person-years), with an adjusted hazard ratio [HR] of 1.32 (95% CI, 0.93-1.87). However, the incidence of osteoporosis in the thyroid cancer cohort (7.54/1,000 person-years) was higher than in the non-thyroid-cancer cohort (5.65/1,000 person-years), with an adjusted HR of 1.4 (95% CI, 1.22-1.61). And, the incidence of osteoporosis and osteoporotic fracture in the thyroid cancer cohort (8.69/1,000 person-years) was higher than that in the non-thyroid-cancer cohort (6.60/1,000 person-years), with an adjusted HR of 1.39 (95% CI, 1.22-

1.58). Thyroid cancer patients with levothyroxine use showed a significantly higher risk of osteoporosis than non-thyroid-cancer patients (adjusted HR, 1.42; 95% CI, 1.24-1.64), while thyroid cancer patients not using levothyroxine did not have significant higher risks than non-thyroid-cancer patients. (adjusted HR, 0.67; 95% CI, 0.39-1.14) After duration-response and dose-response relationships, they demonstrated that long duration of levothyroxine use and high cumulative dose of levothyroxine were significantly associated with an increased risk of osteoporosis in thyroid cancer patients following thyroidectomy. They concluded that thyroid cancer patients receiving levothyroxine have a higher risk of osteoporosis and suggested that close monitoring and primary prevention of osteoporosis are warranted in thyroid cancer patients using levothyroxine.

Vera et al.[17] performed simulation study to compare BMD and fracture risk assessed by fracture risk assessment tool (FRAX) between 74 women with DTC (mean age,  $51.9 \pm 12.0$  years) and 120 euthyroid women, who were matched for age, BMI, and menopausal status, at baseline, 3 years and 5.5 years (median). The risks of major osteoporotic fracture and hip fracture were similar in DTC patients and in controls. They presented that there was no correlation between L-thyroxine dosage, duration of L-thyroxine therapy, free thyroxine level and FRAX in DTC women with well-controlled disease on therapy. They concluded that FRAX increase is a multi-factorial and age-related phenomenon.

## DISCUSSION

Clinical implications of long-term TSH suppression therapy on bone metabolism are critical, because it is associated with the favorable prognosis of thyroid cancer.[18] However, the potential adverse effects of TSH suppression therapy on bone remain controversial. Our purpose was to review the literature on the effects of TSH suppression therapy on fracture risk focusing on reported occurrence of osteoporotic fracture.

Subclinical thyroid dysfunction has been known to be associated with increased risk of hip fracture,[19] but the influence of chronic subclinical hyperthyroidism, TSH suppression therapy, on fracture risk in patients who underwent thyroidectomy for thyroid cancer is unclear.

After review of these four population-based cohort studies, three cross-sectional studies and 1 case series, the ef-

fects of TSH suppression therapy on fracture risk still remain unclear.

Several studies have reported an effect of TSH suppression therapy on BMD in postmenopausal women, although these effects are not clear in men and premenopausal women.[20-22] Menopause, estrogen deprivation in women, is the most important cause of osteoporosis in women. The removal of the physiologic block by sex steroid hormones allows the release and production of receptor activator of nuclear factor- $\kappa$ B ligand, which activates the proliferation of osteoclasts.[23] This effect could be enhanced by the subclinical hyperthyroid state resulting from TSH suppression therapy.[23,24]

There is a lack of studies addressing this issue so that we have systematically categorized studies according to pre-defined criteria in an attempt to reach a clearer conclusion. Although we set to conduct a structural meta-analysis, too small number of the included studies did not allow us to do so. However, through systematic review, we found that some studies with larger number of subjects showed the higher risk of osteoporotic fracture in group with TSH suppression therapy,[12,16] although studies with smaller sample size presented a similar risk of fracture with control group. [10,13,14]

## CONCLUSIONS

Overall, although studies were limited by small numbers, results suggested possible association between chronic TSH suppression therapy and the increased risk of osteoporotic fractures in patients with thyroid cancer. And, it is clear that larger-scale, better-designed studies that report occurrence of osteoporotic fracture after THS suppression therapy are needed in the future to determine the influence of TSH suppression therapy on the risk of osteoporotic fracture in thyroid cancer.

## ACKNOWLEDGMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI18-C0284).

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