

## The Effect of Thyroid Hormone on Skeletal Integrity

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**Background:** Thyroid disease and osteoporosis are common problems often managed by primary care physicians. Despite many studies, confusion still exists about the effect of thyroid hormone on skeletal health.

**Purpose:** To review evidence on the effect of thyroid hormone (from hyperthyroidism, exogenous or endogenous suppression of thyroid-stimulating hormone [TSH], and thyroid hormone replacement therapy) on skeletal integrity.

**Data Sources:** A MEDLINE search of papers published between 1966 and 1997.

**Data Selection:** Cross-sectional studies, longitudinal studies, and meta-analyses that had appropriate control groups (patients matched for age, sex, and menopausal status), made comparisons with established databases, or defined thyroid state by TSH level or thyroid hormone dose were reviewed.

**Data Extraction and Synthesis:** Data synthesis was not straightforward because of changes in doses and types of thyroid hormone preparations; changes in definitions of thyroid hormone replacement therapy and suppressive therapies; problems with study design; differences in skeletal sites assessed (hip, spine, forearm, or heel) and techniques used to measure bone mineral density; and inclusion of heterogeneous and changing thyroid disease states. Overall, hyperthyroidism and use of thyroid hormone to suppress TSH because of thyroid cancer, goiters, or nodules seem to have an adverse effect on bone, especially in postmenopausal women; the largest effect is on cortical bone. Thyroid hormone replacement seems to have a minimal clinical effect on bone.

**Conclusion:** Women with a history of hyperthyroidism or TSH suppression by thyroid hormone should have skeletal status assessed by bone mineral densitometry, preferably at a site containing cortical bone, such as the hip or forearm.

Thyroid disease is one of the most common endocrine problems managed by primary care physicians. In fact, in the United States, 10% of women older than 65 years of age receive thyroid hormone replacement therapy (1). Limited access to subspecialists in managed care settings and the ease with which thyroid abnormalities can be detected will increase the role played by primary care providers in the evaluation and management of thyroid status. Concomitantly, osteoporosis affects almost one in two U.S. women older than 50 years of age, and the number of women affected is expected to increase with the aging of the U.S. population (2). The prevalence of these two medical problems makes it critical for physicians to understand the effects of thyroid hormone on bone.

The relation between thyroid hormone and bone was first recognized in the 1890s, when von Recklinghausen reported on a patient with hyperthyroidism and multiple fractures (3). However, over the next 100 years, clinicians often overtreated hypothyroid patients with thyroid hormone therapy. Hyperthyroidism accelerates bone turnover (4) and shortens the normal bone remodeling cycle (5). Thyroid hormone seems to be more detrimental to cortical bone (found in the hip and forearm) than to trabecular bone (found in the spine) (6).

The development of noninvasive techniques for diagnosing bone loss and the availability of second- and third-generation assays for thyroid-stimulating hormone (TSH) led to a better understanding of the consequences of thyroid hormone overtreatment with respect to bone loss. However, the consequences of overtreatment were not fully appreciated until the late 1980s, when Ross and colleagues (7) reported significant reductions in radial bone mineral density in premenopausal women receiving suppressive doses of L-thyroxine. The past decade has witnessed almost 100 studies attempting to explain the effect of thyroid hormone on skeletal integrity. Regardless, more confusion than clarity currently exists.

The purpose of this review is to summarize the available data on thyroid hormone and skeletal integrity and to help the primary care physician understand the reasons for confusion on this topic. We examine three general thyroid conditions—hyperthyroidism, exogenous or endogenous TSH suppression, and receipt of thyroid hormone replacement

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therapy—and highlight relevant studies on bone health with practical guidelines for the management of skeletal integrity.

## Methods

We performed a MEDLINE search for papers published between 1966 and June 1997 under the following headings: *thyroid hormone, thyroxine, hyperthyroidism, bone density, and osteoporosis*. Two studies then in press (8, 9) were brought to our attention by the primary authors. We included cross-sectional studies, longitudinal studies, and meta-analyses that had appropriate control groups (patients matched for age, sex, and menopausal status), made comparisons with established databases, or defined thyroid status by TSH level or thyroid hormone dose. Thyroid conditions were grouped into three categories: hyperthyroidism, endogenous or exogenous TSH suppression, and receipt of thyroid hormone replacement therapy.

## Thyroid Conditions Affecting Skeletal Health

### Hyperthyroidism

The main causes of endogenous hyperthyroidism are Graves disease, toxic multinodular goiter, and toxic thyroid nodule. The overall prevalence of hyperthyroidism is 2.7% in women (10), but the prevalence increases with age (11). Most (12–18) but not all (19, 20) studies have shown decreases in bone mineral density in hyperthyroid persons. One prospective study (21) showed an increased risk for hip fracture with a history of hyperthyroidism (relative risk, 1.8), and a case-control study (22) pointed to an increased risk for hip fracture in patients with previous or current hyperthyroidism (odds ratio, 2.5). With the development of third-generation TSH assays and the increased frequency of screening today, hyperthyroidism is generally identified earlier. Therefore, the consequences of thyrotoxicosis on bone may be less in future studies. Several studies (18, 23, 24) have shown that bone mineral density improves in both men and women after treatment moves patients from a hyperthyroid to a euthyroid state.

Current management for patients with hyperthyroidism includes treatment of thyroid disease to achieve a euthyroid state, as defined by results in the normal range on a third-generation TSH assay. On the basis of the nine studies showing that hyperthyroidism has a detrimental effect on bone mass or is associated with fractures, it is reasonable to measure bone mineral density, especially in postmenopausal women, to determine whether treatment for osteopenia or osteoporosis is required.

## Exogenous or Endogenous Suppression of Thyroid-Stimulating Hormone

Exogenous administration of L-thyroxine to fully suppress TSH is widely used to inhibit progression or recurrence of papillary or follicular thyroid cancer (25). Complete TSH suppression is usually defined as a TSH level less than 0.1  $\mu\text{U/mL}$  on a third-generation assay (26); however, some physicians define complete TSH suppression as a TSH level less than 0.01  $\mu\text{U/mL}$ . The dose of L-thyroxine usually required to maintain this degree of suppression is about 2.2  $\mu\text{g/kg}$  of body weight per day (27). Partial TSH suppression by thyroid hormone treatment, also known as *exogenous subclinical hyperthyroidism*, has been used to inhibit the growth of benign thyroid nodules and goiters, although this practice is controversial (28–31). For this purpose, a dose of L-thyroxine is adjusted to bring the TSH level to just below normal (between 0.2 and 0.5  $\mu\text{U/mL}$ ). Partial TSH suppression caused by endogenous subclinical hyperthyroidism (normal free thyroxine and triiodothyronine levels and partially suppressed TSH levels [32]) can result from a functioning nodule or nodules, nodular goiter, early Graves disease, or spontaneously resolving hyperthyroidism resulting from subacute thyroiditis. Although patients with these three conditions—full exogenous TSH suppression, partial exogenous TSH suppression, and partial endogenous TSH suppression—represent a spectrum of TSH suppression, many studies have combined these patients.

Studies examining the effect of thyroid hormone suppression on premenopausal women are controversial (**Table 1**). Cross-sectional studies have shown either no significant negative effect (33–41) or decreased bone mineral density (7, 42–46). Similar controversy exists with respect to prospective studies (8, 34, 47, 48), but it seems that higher doses of L-thyroxine are associated with greater bone loss (39, 47, 48). Two meta-analyses (56, 57) did not find a significant reduction in bone mineral density.

Several cross-sectional studies in postmenopausal women receiving suppressive doses of thyroid hormone suggest an overall adverse effect on bone (**Table 1**) (37, 42, 43, 49, 50), but other investigators report no significant adverse effect (16, 33–36, 40, 52, 53). A meta-analysis (56) showed a pooled effect of losses of 5% to 9% at multiple sites. Another meta-analysis (57) reported bone loss of 0.91% per year in postmenopausal women with reduced serum TSH levels. A longitudinal study of postmenopausal women receiving suppressive doses of L-thyroxine who received calcium, calcitonin, or placebo found a decrease in bone mineral density of the spine and hip in the placebo group only (54). In another group of heterogeneous patients, bone mineral den-

**Table 1. Effect of Suppression of Thyroid-Stimulating Hormone or Bone\***

Study (Reference)	Patient Characteristics	Controls	Study Design	Mean Duration of Treatment, y	BMD Measurement Technique	Menopausal Status	Patients, n	Site Tested	Change in BMD
Ross et al. (7)	Hashimoto hypo- thyroidism, goiter, nodule, thyroid cancer	Yes	Cross-sectional	>5 >10	SPA	Premenopausal	28 12	Forearm	-4%
Forearm								-9%	
Rosen et al. (8)	Thyroid cancer	Yes	Longitudinal	2	DXA	Premenopausal Postmenopausal	17 2	Forearm	NS†
Spine								NS†	
Hip								NS†	
Total body								NS†	
Bauer et al. (9)	Previous hyperthyroidism or hypothyroidism‡	Yes	Longitudinal	5.7 3.5	SPA DXA	Postmenopausal	41	Calcaneus	NS
Femoral neck								NS	
Trochanter								NS	
Total hip								NS	
Spine								NS	
Adlin et al. (16)	Hashimoto hypo- thyroidism, goiter, nodule§	Yes	Cross-sectional	15.1	DPA	Postmenopausal	11	Femoral neck	NS
Trochanter								NS	
Ward triangle								NS	
Spine								NS	
Femoral neck								NS	
Florkowski et al. (33)	Thyroid cancer	No	Cross-sectional	9	DXA	Premenopausal	20	Spine	NS
Femoral neck								NS	
Postmenopausal						18	Spine	NS	
Femoral neck							NS		
Muller et al. (34)	Thyroid cancer, goiter	Yes	Cross-sectional¶	11	DXA	Premenopausal	23	Spine	NS
Femoral neck								NS	
Postmenopausal						27	Spine	NS	
Femoral neck							NS		
Franklyn et al. (35)	Thyroid cancer	Yes	Cross-sectional	8	DXA	Premenopausal	18	Femoral neck	NS
Spine								NS	
Lateral spine								NS	
Femoral neck								NS	
Trochanter								NS	
Postmenopausal						26	Ward triangle	NS	
Spine							NS		
Lateral spine							NS		
Femoral neck							NS		
Trochanter							NS		
Giannini et al. (36)	Thyroid cancer	Yes	Cross-sectional	8 9	DXA	Premenopausal	12	Spine	NS
Postmenopausal						13	Spine	NS	
Lehmke et al. (37)	Thyroid cancer	Yes	Cross-sectional	5	SPA QCT	Premenopausal	25	Forearm	NS
Calcaneus								NS	
Postmenopausal					16	Spine	+12.4%		
Forearm						-15%			
Marcocci et al. (38)	Thyroid cancer, goiter	Yes	Cross-sectional	10	DXA	Premenopausal	47	Calcaneus	-22%
Spine								NS	
Hip								NS	
Garton et al. (39)	Autoimmune thyroiditis	Yes	Cross-sectional	4	DXA	Premenopausal	20	Total body	NS
Spine								NS	
Femoral neck								NS	
Trochanter								NS	
Ward triangle								NS	
Gorres et al. (40)	Thyroid cancer	No	Cross-sectional	6	DXA	Premenopausal	15	Spine	NS
Total hip								NS	
Femoral neck								NS	
11				DXA	Postmenopausal	32	Trochanter	NS	
Spine							NS		
Total hip							NS		
De Rosa et al. (41)	Goiter**	Yes	Cross-sectional	1.1	DXA	Premenopausal	25	Femoral neck	NS
Trochanter								NS	
Ward triangle								NS	
3.5				DXA	Postmenopausal	25	Spine	NS	
Femoral neck							NS		
Trochanter							NS		
Diamond et al. (42)	Thyroid cancer	Yes	Cross-sectional	11	SPA DPA	Premenopausal	14	Forearm	NS
Spine								NS	
Femoral neck								-11%	
6				SPA DPA	Postmenopausal	10	Forearm	-11%	
Spine							-16%		
Femoral neck							-23%		
Taelman et al. (43)	Goiter††	Yes	Cross-sectional	5.8 10	SPA	Premenopausal	36	Forearm	-5%
Postmenopausal						24	Forearm	-20%	
Mudde et al. (44)	Goiter	Yes	Cross-sectional	-‡‡	SPA	Premenopausal	16	Forearm	Decreased
Postmenopausal						17	Forearm	Decreased	

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**Table 1—Continued**

Study (Reference)	Patient Characteristics	Controls	Study Design	Mean Duration of Treatment, y	BMD Measurement Technique	Menopausal Status	Patients, n	Site Tested	Change in BMD
Foldes et al. (45)	Subclinical hyperthyroidism§§	Yes	Cross-sectional	—##	DXA DXA SPA	Premenopausal	13	Spine	NS
								Femoral neck	NS
								Forearm	NS
	Toxic nodule	Yes	Cross-sectional	—##	DXA DXA SPA	Postmenopausal	24	Spine	Decreased
								Femoral neck	Decreased
								Forearm	Decreased
Paul et al. (46)	Previous hypothyroidism or hyperthyroidism, thyroid cancer, goiter¶¶¶	Yes	Cross-sectional	9.6	DXA DXA SPA	Premenopausal	6	Spine	Decreased
								Femoral neck	Decreased
								Forearm	Decreased
	Goiter, thyroid cancer	Yes	Longitudinal	1–3	DXA DXA SPA	Postmenopausal	16	Spine	Decreased
								Femoral neck	Decreased
								Forearm	Decreased
Pioli et al. (47)	Thyroid cancer, goiter, nodules	Yes***	Longitudinal	2.9–5.4	DPA	Premenopausal	24	Forearm	Decrease†
								Spine	Decrease†
McDermott et al. (48)	Previous hyperthyroidism or hypothyroidism, unknown diagnosis†††	Yes	Cross-sectional	20.4	SPA DXA	Postmenopausal	120	Femoral neck	Decrease†
Schneider et al. (49)	Thyroid cancer	Yes	Cross-sectional	12.2	DXA	Postmenopausal	34	Forearm	–7.1% to –7.6%
								Hip	–7.8%
								Spine	–5.4%
								Spine	–18.3%
								Femoral neck	–12.1%
								Trochanter	–13.1%
Kung et al. (50)	Thyroid cancer	Yes	Cross-sectional	12.2	DXA	Postmenopausal	34	Ward triangle	–12.1%
								Spine	NS
Hawkins et al. (51)	Thyroid cancer	Yes	Cross-sectional	6.2	DXA	Postmenopausal	21	Spine	NS
Grant et al. (52)	Hypothyroidism	Yes	Cross-sectional	12.6	SPA	Postmenopausal	44	Forearm	NS
Ribot et al. (53)	Thyroid cancer	No	Cross-sectional	6	DPA	Postmenopausal	28	Spine	NS
Kung and Yeung (54)	Thyroid cancer	No	Longitudinal	2	DXA	Postmenopausal	15	Spine	–5%
								Femoral neck	–6.7%
								Trochanter	–4.7%
								Ward triangle	–8.8%
								Spine	–2.9%
Stall et al. (55)	Hashimoto hypothyroidism, Graves disease	Yes	Longitudinal	2	DPA	Postmenopausal	10	Femoral neck	NS
								Forearm	NS

\* BMD = bone mineral density; DPA = dual-photon absorptiometry; DXA = dual-energy x-ray absorptiometry; NS = not significant; QCT = quantitative computed tomography; SPA = single-photon absorptiometry.  
 † Premenopausal and postmenopausal patients included in results.  
 ‡ Included some women receiving estrogen and some patients not receiving thyroid hormone.  
 § Patients with hyperthyroidism (Graves disease) removed from analysis.  
 || Manufacturer reference database used as control.  
 ¶¶ Longitudinal follow-up in 21 patients for 1.5 years; no change in bone mineral density.  
 \*\*\* Subnormal thyroid-stimulating hormone values.  
 †† Triiodothyronine used in most patients.  
 ## No thyroid hormone treatment.  
 §§ Subclinical hyperthyroidism: subnormal thyroid-stimulating hormone levels; normal thyroxine and triiodothyronine levels.  
 ||| Suppression of thyroid-stimulating hormone.  
 ¶¶¶ 55% had suppression of thyroid-stimulating hormone.  
 \*\*\* Controls not completely matched for menopausal status.  
 ††† Thyroid-stimulating hormone levels not measured.

sity response was mixed (55). A recent prospective study (9), confounded by the inclusion of patients with a heterogenous group of thyroid disorders, suggested that postmenopausal women with low TSH levels (most of which were due to therapy) did not have low bone mineral density or accelerated bone loss. Other studies have suggested that estrogen replacement therapy improves bone mineral density in postmenopausal women receiving thyroid hormone suppression (24, 49).

The effects of exogenous partial TSH suppression on bone vary. Some studies have suggested that this suppression adversely affects bone mineral density,

predominantly in postmenopausal women (44, 45), but one investigation reported no adverse effect (41). The variation may be due to differences in duration and intensity of the relative hyperthyroxinemia.

To summarize, in premenopausal women, six cross-sectional studies and two longitudinal studies have shown a negative effect on bone resulting from partial or complete TSH suppression; in postmenopausal women, seven cross-sectional and three longitudinal studies have demonstrated such an effect. Although a roughly equal number of studies has shown that TSH suppression has no effect on bone,

our interpretation of these studies suggests that physicians should assess bone mass in both premenopausal and postmenopausal women who are not receiving hormone replacement therapy and have been receiving thyroid hormone replacement therapy with full TSH suppression. However, in the absence of a large, well-monitored, randomized trial with careful inclusion and exclusion criteria, we do not know whether thyroid hormone suppression poses a risk to skeletal integrity. Because the meta-analyses published to date have included many small and heterogeneous studies, they provide limited information. Data are less clear in patients with partial TSH suppression, but we recommend that bone mass be assessed in postmenopausal women.

Because of the tendency toward thyroid hormone-induced cortical bone loss, we recommend testing bone mineral density at a cortical site if only one site can be tested at a particular center. However, because national reimbursement guidelines are by visit and technology rather than by number of sites assessed (58), many centers routinely measure bone mass of both the hip and the spine for the same cost. No studies have specifically addressed the appropriate timing of follow-up bone mineral density in this patient population with TSH suppression. Standard guidelines for the prevention of osteoporosis suggest that follow-up be done in 1 to 2 years (58, 59). Estrogen replacement or bisphosphonates should be considered along with calcium, vitamin D, and exercise in postmenopausal women. Calcitonin has not been shown to be of benefit (54).

### Thyroid Hormone Replacement

Thyroid hormone replacement therapy is usually defined as a dose of L-thyroxine that will maintain a normal TSH level of 0.5 to 5.0  $\mu\text{U/mL}$ , as measured by a TSH assay sensitive to 0.1  $\mu\text{U/mL}$  or less. The recommended dose of L-thyroxine is 1.7  $\mu\text{g/kg}$  of body weight per day for young adults and 1.0  $\mu\text{g/kg}$  per day for elderly persons (60).

In premenopausal women, some (14, 15, 61) but not all (39, 62, 63) studies suggest that thyroid hormone replacement therapy has no deleterious effect on bone (**Table 2**). A meta-analysis (56) has suggested a decrease in bone mineral density at the hip and spine; however, it included several older studies involving patients who were probably "over-replaced" (43, 46). It further suggested that bone loss is greater at the hip than at the spine. One study done in adolescent girls receiving thyroid hormone replacement therapy for autoimmune thyroiditis indicated that this therapy had no negative effect on the attainment of peak bone mass (65).

In postmenopausal women, most cross-sectional studies have shown no major effect of thyroid hormone replacement therapy on bone mineral density

(**Table 2**) (15, 49, 51–53, 61, 62). However, some investigators have reported decreased bone mineral density (14) but have included patients who were previously hyperthyroid. A prospective study by Ross (64) showed no major effect on bone mineral density in postmenopausal women who were truly "thyroid hormone replaced." However, the most important outcome concerns hip fracture, and prospective studies have shown that thyroid hormone replacement does not contribute to hip fracture in elderly women (21, 22, 66). Estrogen replacement therapy has been associated with higher bone mineral density in patients receiving thyroid hormone replacement therapy (49). Although bone loss has been noted over the first year of thyroid hormone therapy for overt hypothyroidism (18) (the remodeling cycle decreases from 700 to 200 days with this condition), overt hypothyroidism is rare today because TSH screening is common, particularly in elderly persons.

In the absence of a large, carefully designed clinical trial, we still do not know the effect of thyroid hormone replacement therapy on skeletal health. Our interpretation of the available data, along with the study by Ross (64), suggests that this therapy does not have a clinically significant negative effect on bone and that patients receiving this therapy should be treated like members of the general population. Local standards of care or the guidelines of the National Osteoporosis Foundation (59) or other agencies (58) should be followed.

### Men

The influence of thyroid hormone therapy on bone is less impressive in men than in women. Studies suggest that bone mineral density is not decreased in men as a result of TSH suppression of thyroid hormone status or thyroid hormone replacement therapy (40, 67–70). One case-control study (71) suggested a twofold increased risk for hip fracture in men with a history of hyperthyroidism. However, because thyroid disease is significantly less common in men than in women, fewer studies have been conducted in men and less information is available.

### Areas of Confusion or Controversy

Older studies were unable to clarify the effects of thyroid hormone suppression and replacement on skeletal integrity for many reasons, but these reasons can be grouped into four categories: thyroid hormone dosage, study design, bone mineral density assessment, and changes in thyroid status for individual patients.

## Thyroid Hormone Dosage

The dosages of L-thyroxine used for both replacement and suppression have decreased substantially in the past 15 years (72, 73). Before 1984, the dosage of thyroid hormone used in replacement therapy ranged from 50 to 300  $\mu\text{g}/\text{d}$  (72). The current range is 50 to 150  $\mu\text{g}/\text{d}$  (74). Similarly, the dosage used for suppression was often double that

used today (73, 74). Improved standardization of the hormone content of thyroxine tablets and the availability of sensitive TSH assays have both contributed to the general reduction in thyroid dosages. Before 1984, U.S. Pharmacopoeia (USP) thyroid preparations were standardized only by iodine content, and their hormone content varied widely. In 1984, the USP required all manufacturers of USP

**Table 2. Effect of Thyroid Hormone Replacement Therapy on Bone\***

Study (Reference)	Patient Characteristics	Controls	Study Design	Mean Duration of Treatment, y	BMD Measurement Technique	Menopausal Status	Patients, n	Site Tested	Change in BMD
Campos-Pastor et al. (14)	Thyroid cancer, previous hyperthyroidism or hypothyroidism, goiter†	Yes	Cross-sectional	0.7–15	DXA	Premenopausal	15	Spine	NS
						Postmenopausal	9	Ward triangle	NS
Duncan et al. (15)	Hashimoto hypothyroidism, previous hyperthyroidism, nodule, thyroid cancer‡	No§	Cross-sectional	9	DPA	Premenopausal	195	Femoral neck	NS
						Postmenopausal		64	Spine
Garton et al. (39)	Autoimmune thyroiditis	Yes	Cross-sectional¶	4	DXA	Premenopausal	20	Ward triangle	Decreased
						Postmenopausal		64	Femoral neck
Schneider et al. (49)	Previous hyperthyroidism or hypothyroidism, unknown diagnosis†	Yes	Cross-sectional	20.4	DXA	Premenopausal	74	Trochanter	NS
						Postmenopausal		74	Forearm
Hawkins et al. (51)	Thyroiditis	Yes	Cross-sectional	9	DXA	Postmenopausal	10	Hip	NS
Grant et al. (52)	Hypothyroidism	Yes	Cross-sectional	10.3	SPA	Postmenopausal	34	Spine	NS
Ribot et al. (53)	Goiter nodule	No§	Cross-sectional	5.5	DPA	Postmenopausal	21	Forearm	NS
Franklyn et al. (61)	Previous hyperthyroidism	Yes	Cross-sectional	5.8	DXA	Premenopausal	27	Spine	NS
						Postmenopausal		27	Lateral spine
Greenspan et al. (62)	Previous hyperthyroidism	Yes	Cross-sectional	9.8	DXA	Premenopausal	60	Femoral neck	NS
						Postmenopausal		60	Trochanter
Kung and Pun (63)	Previous hypothyroidism	Yes	Cross-sectional	5.9	DXA	Premenopausal	22	Ward triangle	NS
						Postmenopausal		22	Spine
Ross (64)	Hypothyroidism	Yes	Longitudinal	1.2	SPA DXA	Premenopausal	17	Lateral spine	NS
						Postmenopausal		17	Femoral neck

\* BMD = bone mineral density; DPA = dual-photon absorptiometry; DXA = dual-energy x-ray absorptiometry; NS = not significant; QCT = quantitative computed tomography; SPA = single-photon absorptiometry.

† Included patients with changing thyroid status.

‡ Included some patients receiving estrogen.

§ Manufacturer's reference database used as control.

¶ Premenopausal and postmenopausal women included in analysis.

|| Longitudinal follow-up in 24 patients (>1 year) found no significant change in BMD.

\*\* When patients with previous hyperthyroidism were omitted, the decrease in BMD at the hip was nonsignificant.

**Table 3. Summary of Recommendations\***

Condition	Cause	Thyroid Management	Skeletal Management†
Hyperthyroidism	Graves disease, toxic nodule, toxic multinodular goiter	Treat to achieve euthyroidism	Measure BMD, preferably at the hip, in premenopausal and postmenopausal women
Exogenous or endogenous TSH suppression			
Full TSH suppression with thyroid hormone therapy	Thyroxine therapy for high-risk thyroid cancer	Suppress TSH level to <0.1 $\mu\text{U}/\text{mL}$	Measure BMD, preferably at the hip, in premenopausal and postmenopausal women
Exogenous subclinical hyperthyroidism	Thyroxine therapy for multinodular goiters or solitary nodules	Decrease TSH level to 0.2–0.5 $\mu\text{U}/\text{mL}$	Measure BMD, preferably at the hip, in postmenopausal women
Endogenous subclinical hyperthyroidism	Subacute thyroiditis, multinodular goiters, or solitary nodules	Restore to euthyroidism, if possible	Measure BMD, preferably at the hip, in postmenopausal women
Receipt of thyroid hormone replacement therapy	Hypothyroidism	Treat to achieve euthyroidism	Follow guidelines (58, 59, 80, 81) or standard of care for premenopausal and postmenopausal women with normal thyroid status

\* BMD = bone mineral density; TSH = thyroid-stimulating hormone.

† Skeletal management includes use of appropriate calcium, vitamin D, and exercise in all patients (59). Bone mineral densitometry should include assessment of cortical bone (at the hip or forearm) and, if available, trabecular bone (at the spine) (58). Antiresorptive therapy should be considered when indicated by BMD measurements or occurrence of fractures (59).

L-thyroxine to monitor the L-thyroxine content of their tablets with high-pressure liquid chromatography; thus, current potency is generally reliable (75). Although the methods used to determine the bioequivalence of thyroxine preparations have been controversial (76), recent studies have clearly shown that some brand name and generic preparations are interchangeable (75, 77). Until a decade ago, desiccated thyroid or mixtures of triiodothyronine and thyroxine were common in the treatment of thyroid disease. The amount of triiodothyronine in desiccated thyroid preparations can vary, and triiodothyronine can substantially increase bone resorption (78).

### Study Design

Differences in study design have led to conflicting findings. Many cross-sectional investigations are small and thus lack the power to show true negative results. Cross-sectional studies cannot account for all of the biases that can occur if case-patients and controls are not appropriately matched. Furthermore, the inclusion of both men and women or both premenopausal and postmenopausal women in the same study is also a source of confusion. Finally, even meta-analyses, which have larger numbers of patients, can still provide faulty results because they do not account for changing doses, types of therapy, or changing status in individual patients. Despite the larger numbers, the conclusions can be misleading because they are based on analyses of earlier, possibly misleading studies.

### Bone Mineral Density Assessment

Bone mineral density is another issue that makes between-study comparison of results difficult. As bone densitometry techniques were developed, studies measured various skeletal sites by using different

techniques that often produced incomparable results (79–81). Many early studies, for example, measured the radius by using single-photon absorptiometry. The next wave of studies used dual-photon absorptiometry and quantitative computed tomography. More recently, dual-energy x-ray absorptiometry has been used to measure the lumbar spine, hip, and radius. However, because thyroid hormone has a greater effect on cortical than on trabecular bone, studies examining sites rich in cortical bone (such as the forearm and femoral neck) may show a greater effect than investigations measuring only sites containing trabecular bone (such as the spine). Moreover, the newer techniques, including dual-energy x-ray absorptiometry, have better precision and reproducibility and can document differences better than the older techniques can (79–81).

### Changes in Thyroid Status

One of the most difficult problems is the inclusion of patients with heterogenous thyroid diseases in a single study. For example, a single study sample might contain patients with Hashimoto hypothyroidism receiving thyroid hormone replacement therapy, previously thyrotoxic patients with Graves disease currently receiving thyroid hormone replacement therapy, and euthyroid patients requiring thyroid hormone replacement after surgical removal of a nodular or multinodular goiter. In addition, the status of patients with thyroid disease often changes. Some investigations have included patients who were originally overtreated with thyroid hormone but were later treated to attain a more physiologic euthyroid state or patients with Graves disease who had been hyperthyroid, euthyroid, and hypothyroid at various times. The variety of changing thyroid conditions may provide misleading information.

## Conclusions

Although the effect of thyroid hormone on the skeleton is not difficult to assess, the interpretation of clinical studies is complex. The complexity results from changes in types of therapy, changes in definitions of "suppression" and "replacement," problems with study design, variety in the techniques used to assess bone mass, inclusion of heterogeneous patient populations, and problems inherent to the changeability of thyroid disease.

Despite these drawbacks in the interpretation of previous studies, it is clear that hyperthyroidism can adversely affect bone and is associated with hip fracture. Assessment of bone mass is recommended for all hyperthyroid patients. Thyroid hormone suppression of TSH for thyroid cancer, goiter, or nodules seems to have an adverse effect on bone, and this effect seems to be greater in postmenopausal women (Table 3). It also seems to be greater in cortical than in trabecular bone; assessment of bone mass is recommended. Thyroid hormone replacement therapy resulting in normal serum TSH levels seems to have minimal or no effect on bone, and bone mass in this setting should be assessed according to the community's standard of care or national guidelines for skeletal health (58, 59).

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