THE WESTERN
Journal of Medicine

Refer to: Ettinger B, Wingerd J: Thyroid supplements: Effect on bone mass. West J Med 1982 Jun; 136:473-476

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Thyroid Supplements: Effect on Bone Mass

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Thyrotoxicosis and thyroid replacement therapy can cause osteopenia. The relative effects of such therapy and of aging, body size, menopausal status and smoking on bone mass were compared by measuring the combined cortical thickness (CCT) of the second metacarpal bone in 151 women taking thyroid hormone. Age was the single factor strongly related to CCT, with the mean CCT decreasing by 0.045 mm per year. Women who had taken estrogen replacement medications had a higher CCT measurement, while those who used thyroid hormone in a dose of at least 3 grains a day had a lower CCT. The rate of loss was reduced in those women using estrogen replacement therapy and increased in those women taking 3 grains or more of thyroid hormone. Women taking 3 grains or more of thyroid hormone should be advised that they are at higher risk for osteopenia.

THYROTOXICOSIS CAUSES LOSS of bone mineral.[1-4] Thyroid hormone replacement therapy, often administered in supraphysiologic doses, may also contribute to osteopenia. We have assessed the relative contribution of age, body size, menopausal status, smoking and thyroid hormone therapy to osteopenia by measuring the combined cortical thickness (CCT) of the second metacarpal bone.

Subjects and Methods

White female volunteers, at least 35 years of age, who had regularly used a constant dosage of thyroid hormone supplements for more than five years were self-selected from the Kaiser-Permanente Medical Center, San Francisco, clinic population at the time of their multiphasic health examination.

Criteria for exclusion from the study were the following: chronic alcoholism, malabsorption syndrome, postgastrectomy state, chronic renal failure, hyperparathyroidism, arthritis or other conditions that would affect the bones of the hand and long-term use of phenytoin (Dilantin) or glucocorticoids.

A questionnaire and medical record review provided information regarding each woman's thyroid hormone use, age at menopause, postmenopausal estrogenic hormone use and smoking history, in addition to her usual adult weight and height. The use of 1 grain of desiccated thyroid was considered equivalent to taking 100 μg of levothyroxine. An x-ray film of the nondominant hand was taken with fine-grained, rapid-processing mammography film. Using a scaled magnifier,

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Supported in part by the Community Service Program of Kaiser Foundation Hospitals.

Submitted, revised, December 24, 1981.

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ABBREVIATIONS USED IN TEXT

CCT = combined cortical thickness
FT_4I = free thyroxine index
T_3 = triiodothyronine
T_4 = thyroxine

one of the authors (B.E.) measured within 0.1 mm CCT of the midshaft of the second metacarpal bone according to the method of Garn.[5] Duplicate readings were done without knowledge of the clinical status of the women. Serum thyroxine (T_4) was measured by solid-phase radioimmunoassay (normal range, 4.5 to 11.4 μg per dl) and serum triiodothyronine (T_3) uptake was measured using talc as the adsorber (normal range, 25 percent to 35 percent). Based on an analysis of 2,556 normal women,[6] the product of the T_4 and T_3 uptake, the free thyroxine index (FT_4I), did not exceed 380. Levels above 380 are invariably associated with hyperthyroidism, judged clinically and chemically.

Results

The precision of the CCT measurements was 3.6 percent, and replicate measurements of CCT agreed within 0.3 mm in 85 percent of the cases. The mean CCT measurements obtained in this study were within 1 percent of the values predicted for white women of the same age on the basis of the standards published by Virtama and Helelä and were 2 percent below the standards published by Garn.[5]

Table 1 summarizes the clinical data for 151 women, classified by their thyroid dosage. Desiccated thyroid was used by 73 percent of the groups taking 1 and 2 grains and by 90 percent of the groups taking 3 and 4 grains. A past history of hyperthyroidism existed in 3 percent of the women taking 1 and 2 grains and in 2 percent of the women taking 3 or 4 grains. Hypothyroidism was the reason given for physicians prescribing thyroid hormone in 77 percent of the 1- and 2-grain users and 67 percent of the 3- and 4-grain users. Several of the variables shown in Table 1 proved to be significantly related to CCT. These factors are, however, correlated with each other to varying degrees. Multiple regression analysis was used to measure the independent effects of each variable.

Age and Menopausal Status

Age proved to be the single factor most strongly related to CCT, with the mean CCT decreasing

TABLE 1.—*Clinical Findings Related to Thyroid Hormone Use*

	Grains			
	1	*2*	*3*	*4*
Number of subjects	47	52	39	13
Mean CCT (mm)	4.28	4.64	4.32	4.28
Mean age (yr)	59.3	56.3	56.5	52.8
Mean height (in)	63.9	64.5	64.9	63.5
Mean weight (kg)	61.9	63.0	64.5	57.9
Smokers (%)	13	25	33	31
Postmenopausal (%)	79	79	72	54
Mean age at menopause (yr)	47.6	47.2	47.0	43.1
Women using estrogen (%)*	34	33	28	31
Mean duration thyroid therapy (yr)	19.2	19.3	20.5	19.2
FT_4I	242	289	293	340

Abbreviations: CCT = combined cortical thickness; FT_4I = free thyroxine index.

*Postmenopausal women only.

0.045 mm per year. In part this decrease was accounted for by two other closely related variables: (1) the number of years since menopause was inversely related to CCT, and (2) the number of years taking estrogen-replacement therapy was directly related. A highly significant ($P<.001$) correlation was found between CCT and the difference of these two variables (that is, years beyond menopause without estrogen replacement).

Height and Weight

The CCT increased significantly with height; for a given height, however, the CCT increased only moderately with increasing weight. The Quetelet index (weight divided by height squared) was much less effective as a predictor of CCT than height and weight combined, or even height alone.

Thyroid Dosage and FT_4I

After adjustment for age, years beyond menopause without estrogen replacement, height and weight, the mean CCT of the users of 3 and 4 grains was 0.24 mm lower than that of the groups using 1 and 2 grains ($P<.01$). The FT_4I was also inversely related to CCT ($P<.01$), but this relation was not linear. Below 400, CCT and FT_4I were not related, but the CCT of women with FT_4I's greater than 400 was 0.27 mm below the mean.

Taken together, the factors of age, years beyond menopause without estrogen replacement, height, weight, thyroid dosage and FT_4I accounted for 51 percent of the total variance in CCT. Stepwise multiple regression analysis of these factors yielded regression coefficients that are summarized in

TABLE 2.—*Regression Analysis of Significant Independent Variables**

Variable	*Regression Coefficient (R^2)*	*Partial R^2*	*Student's t-Value*	*Level of Significance*
Age	−0.038 mm/yr	−0.461	6.2	$P<.0001$
Years postmenopausal without estrogen	−0.025 mm/yr	−0.285	3.6	$P<.001$
Height	+0.024 mm/cm	+0.260	3.0	$P<.001$
Thyroid dose				
3 grains	−0.240 mm	−0.162	1.9	$P<.02$
3 and 4 grains	−0.240 mm	−0.160	2.0	$P<.02$
Free thyroxine index (FT_4I)	−0.001 mm/FT_4I	−0.146	1.8	$P<.02$
Weight	+0.011 mm/kg	+0.177	2.2	$P<.01$

*Combined cortical thickness (CCT) is a dependent variable.

Table 2. The variance in CCT accounted for by age alone is reduced slightly when age is considered together with the other significant variables (0.045 mm per year to 0.038 mm per year). A 3-grain dosage of thyroid showed an identical regression coefficient to 4 grains, but the number of 4-grain users was too small to give statistical significance when examined alone. Therefore we pooled the 3- and 4-grain users in our analysis. Except for women aged 70 or older, an unexpected result was that CCT tended to increase with duration of thyroid use. After regression adjustment for the other variables, this increase was not significant ($P<.10$) and may have been due to chance.

Smoking

Smoking history was not a significant variable.

Discussion

Ample evidence indicates an increased rate of bone loss in patients suffering from thyrotoxicosis.[1-4] Restoration of bone loss may follow correction of this metabolic disorder.[3] Three or more grains of desiccated thyroid daily may produce a mild form of thyrotoxicosis, inasmuch as physiologic suppression of thyroid-stimulating hormone in hypothyroid subjects is achieved with the equivalent of 2 grains.[7]

Among our study subjects, 81 percent used desiccated thyroid. Disagreement exists regarding the relative potency of desiccated thyroid and levothyroxine. Several studies[8-11] and standard endocrine texts have stated that 1 grain of desiccated thyroid is equivalent to 100 μg of levothyroxine sodium. Sawin and co-workers[12] suggested that 1½ grains of desiccated thyroid was equivalent to 100 μg of levothyroxine. In our initial experimental design, we chose to use the 1 grain-per-100-μg equivalence. When we analyzed our data using a 1½-grain-per-100-μg equivalence, the derived regression coefficients were only slightly reduced and the recalculated t and P values were essentially unchanged.

Daniell[13] showed that women who used 2 or 3 grains of thyroid hormone had a lower bone mass value than postmenopausal women who did not take thyroid. We stratified our subjects by their replacement dosage and their FT_4I and included a 1-grain thyroid group. Our data show that use of 3 or 4 grains of thyroid is associated with a lower CCT than is found with usage of 1 or 2 grains. We were unable to show a linear correlation between CCT and FT_4I, but a pronounced decrease in CCT occurred in subjects with higher than normal FT_4I (>400).

Numerous studies have shown that estrogen replacement therapy prevents loss of bone mineral in postmenopausal women.[14-16] Our data agree, showing a highly significant relation between the loss of CCT and the number of years since menopause without estrogen replacement. Our regression equation predicts a loss of 0.38 mm (8.6 percent) of CCT per decade in women using estrogen and a loss of 0.63 mm (14.3 percent) of CCT per decade in postmenopausal women who do not use estrogen. The generally accepted rate of bone loss in untreated postmenopausal women is 10 percent per decade.[14-16]

In 97 women aged 60 to 69 years, Daniell[17] showed that smoking was associated with less bone mineral unless a woman's weight exceeded 10 percent of ideal. He also confirmed the presence of more bone mass in long-term estrogen users but found that smokers did not derive this benefit. He found that height was not related to bone mass and neither was weight except in those women whose weight exceeded 10 percent of ideal. Lindsay[18] reported that women who smoke have reduced skeletal mass but do not lose bone more rapidly as they age. We found that height was more strongly associated with CCT than weight and

were unable to show that smoking adversely affected the CCT of any subset of women.

Women who take the equivalent of 3 or more grains of desiccated thyroid a day should be advised that this therapy is associated with a higher incidence of osteopenia. FT_4I values exceeding 400 indicate a high likelihood of bone loss, but many women taking 3 grains and some taking 4 grains do not have an elevated FT_4I. We suspect that isolated T_3 thyrotoxicosis associated with desiccated thyroid hormone use[19] accounted for the osteopenia found in these patients.

We can derive from Table 2 the combined effects of short stature (10 cm below the mean), low weight (10.0 kg below the mean) and nonuse of estrogen replacement therapy for 20 postmenopausal years with a 3- or 4-grain dosage of thyroid supplements resulting in an FT_4I of 400. These factors combined result in a CCT 38 percent lower than in women who were not exposed to these risk factors.

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