The effect of long-term thyroxine on bone mineral density and serum cholesterol

ABSTRACT—The effect of thyrotrophin suppression on bone mineral density (BMD) and serum cholesterol concentration was assessed in 31 treated hypothyroid women. Measurements of the BMD of the lumbar spine and femoral neck were repeated in seven of those with the lowest value after an average period of 22.7 months. Final cholesterol concentrations were compared with values before thyroxine was started. The dose of thyroxine was based on clinical assessment, serum triiodothyronine concentrations kept within the normal range, and thyrotrophin values within the normal range or suppressed. The patients had taken thyroxine replacement for a mean of 12.7 years. Two-thirds (21 subjects) had suppressed thyrotrophin concentrations, and it was normal in one-third (10). Fifteen subjects had a past history of thyrotoxicosis. BMD and cholesterol concentrations were compared between those with suppressed and normal thyrotrophin concentrations and between those with and without a past history of thyrotoxicosis.

No patient had a pathological fracture. One had a Z value for the femoral neck of –1.6, denoting early but definite osteoporosis, and five had borderline osteoporosis with Z values for one or other site between –1.1 and –1.5. None of the seven with the lowest BMDs had any significant change when measurements were repeated. The difference in Z values between subjects with suppressed and normal thyrotrophin concentrations was not significant for either the lumbar spine ($p = 0.68$) or the femoral neck ($p = 0.28$). A past history of thyrotoxicosis had a greater effect on BMD for both sites than thyrotrophin suppression, but again the difference between those with and without a past history of thyrotoxicosis was significant neither for the lumbar spine ($p = 0.18$) nor for the femoral neck ($p = 0.34$). The combination of thyrotrophin suppression and a past history of thyrotoxicosis also failed significantly to reduce the BMD of the lumbar spine ($p = 0.38$) or femoral neck ($p = 0.30$) in comparison with those who had neither thyrotrophin suppression nor a past history of thyrotoxicosis. The mean fall in serum cholesterol concentration was 2.1 mmol/l (SD 1.78) ($p = 0.001$) in those with a suppressed thyrotrophin concentration taking a mean daily dose of thyroxine of 171 μg (SD: 34.7), compared with a fall of 0.89 mmol/l (SD: 1.04) ($p = 0.065$) in those whose thyrotrophin concentration was not suppressed on a mean daily thyroxine dose of 140 μg (SD: 50).

No patient had atrial fibrillation or cardiographic evidence of coronary artery disease (CAD).

The serum cholesterol concentration should play at least as important a part in influencing the dose of thyroxine as a fear of osteoporosis. Fractures are not a feature in the natural history of treated hypothyroidism, whereas CAD is a common cause of death in these patients.

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Hyperthyroidism is a cause of osteoporosis, and it is a reasonable supposition that more than adequate thyroxine replacement in subjects with impaired thyroid function might also cause osteoporosis. Many detailed studies have been made of bone mineral density (BMD) in subjects taking replacement thyroxine [1, 2]. Some workers have found changes suggestive of osteoporosis in the lumbar spine but not in the femoral neck [3]; others have found changes in the femoral neck but not in the lumbar spine [4]. There was no evidence of bone degradation in patients treated with thyroxine for subclinical hypothyroidism [5], nor in a large group of subjects on long-term high-dose thyroxine following thyroidectomy for thyroid cancer [6]. More recent studies of pre and postmenopausal New Zealand women treated with thyroxine suppressing thyrotrophin concentrations found no loss of BMD [7], but a conflicting result was found in a study of Chinese women who all showed bone loss [8]. A meta-analysis suggests that prolonged thyrotrophin suppression affects bone mass in post- but not pre-menopausal women [9].

For many decades before accurate measurement of thyroid function was possible, thyroxine 400 μg daily was a common replacement dose, but osteoporotic fractures were not a feature of hypothyroidism treated with what would now be considered excessive replacement therapy. Simplistic conventional wisdom suggests that the replacement dose of thyroxine should keep the serum thyroxine concentration within the reference range for normal subjects. Normal thyroid glands secrete both thyroxine and triiodothyronine, while in myxoedema, exogenous thyroxine replaces both hormones. A serum thyroxine concentration above the reference range confirms only that the patient is compliant; serum thyrotrophin concentration above the reference range denotes inadequate

replacement. There is dispute about whether a suppressed serum thyrotrophin concentration during thyroxine therapy necessarily or invariably denotes overdosage. Those who believe thyrotrophin suppression denotes subclinical hyperthyroidism and may cause osteoporosis will keep the serum thyrotrophin concentrations within the reference range.

The aim of the study was to assess the influence of thyrotrophin suppressive and non-suppressive doses of thyroxine and a past history of thyrotoxicosis on BMD and cholesterol concentrations. Impaired thyroid function was shown 25 years ago to be associated with hyperlipidaemia [10]. Some authors deny the association of hyperlipidaemia with impaired thyroid function [11], but in a screening study of apparently healthy individuals, 12% of those with plasma cholesterol concentrations above 8 mmol/l had impaired thyroid function compared with none of 80 matched controls with plasma cholesterol concentrations of less than 4 mmol/l [12]. Impaired thyroid function is also associated with coronary artery disease (CAD) [13, 14].

It is important to know whether thyroxine dosage should be influenced more by the fear of cholesterol-related CAD or by the unverified presumption of osteoporosis.

Patients

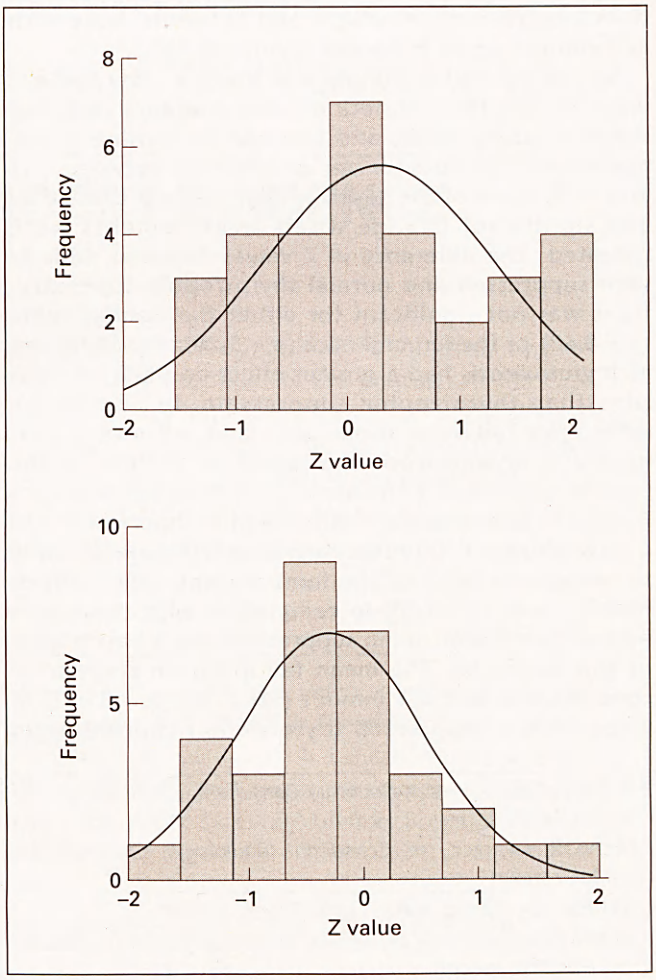
Thirty-one women with hypothyroidism on replacement thyroxine were consecutively studied for a mean of 12.7 years (range 3–41). All gave informed consent. Six were premenopausal and 25 postmenopausal. Six women had taken thyroxine for more than 20 years; hormone assays not being available, protein-bound iodine estimations or radio-iodine studies were done on these subjects. Fifteen patients had a previous history of hyperthyroidism, nine of whom had been treated with radioactive iodine, three with carbimazole only and three by thyroidectomy. The dose of thyroxine for each patient was gradually increased to bring the thyrotrophin value into or below the normal range. Most of the women had been on a constant dose of thyroxine for many years after the initial maintenance dose had been achieved.

The serum free thyroxine concentration confirmed compliance and was often above the reference range. For all subjects, the serum triiodothyronine concentration was kept in the normal range. No patient was clinically hyperthyroid. During the initial stage of stabilisation, patients often felt better on a dose of thyroxine that suppressed the thyrotrophin concentration than on a dose that kept it within the normal range. The dose of thyroxine was also influenced by the serum cholesterol concentration during the initial period of stabilisation. No patient had received corticosteroid therapy or other drugs that might reduce BMD, one had non insulin-dependent diabetes, and none had atrial fibrillation.

Methods

Bone mineral densitometry measurements were done on all subjects. In seven women whose values were low enough to suggest possible osteoporosis, measurements were repeated after an average of 22.7 months (range 14–33). The density of the lumbar spine and femoral neck was measured by dual-energy X-ray absorptiometry, with a dual-photon X-ray system (Norland XR-26, Mark 2, Siel Imagine Equipment Ltd, Aldermaston). The *in vivo* precision was 1.3% for measurements of the femoral neck, and 1.0% for the lumbar spine. A Z score (patient's value minus group value divided by the group SD) was calculated for each bone density measurement from the mean (SD) for the relevant control group. The XR-26 reference data sets were derived from normal Caucasian women with no osteoporosis, bone-affecting drugs or bone-affecting illnesses: 368 for the lumbar spine and 133 for the femoral neck. A Z value of –1.6 or less was considered to denote osteoporosis; between –1.1 and –1.5 it was considered borderline.

Fig 1. *Distribution curve for bone mineral density (Z values);* **(a)** *lumbar spine;* **(b)** *femoral neck*



Chemical analyses were performed on a Technicon Dax system, using Technicon reagents and procedures. Haematology analyses were undertaken on a Bayer haematology analyser using Bayer reagents and procedures. Free serum thyroxine concentrations and thyrotrophin were measured using an Abbott IMX system with Abbott reagents. (The Abbott system is a fully automated enzyme immunoassay system). The reference ranges, based on a group of patients with no thyroid abnormalities were:

- serum thyroxine: 9.4–24 pmol/l
- thyrotrophin: 03–3.5 mU/l.

Triiodothyronine was measured using a Ciba Corning ACS systems with Ciba Corning reagents. (The system is a fully automated chemiluminescence system.) The reference range from a group of patients with no thyroid abnormalities was 0.8–2.7 nmol/l. The variability found was:

- free thyroxine at 18.0 pmol/l: 4.5%
- thyrotrophin at 5.0 mU/l: 8.2%
- triiodothyronine at 2.2 nmol/l: 4.8%
- cholesterol at 3.1 mmol/l: 1.4%.

For data which could be considered to be approximately normally distributed, comparisons of means were made using Student's *t*-test; for non-normally distributed data, comparisons of medians were made using the Mann-Whitney rank-sum test.

Electrocardiograms were done on all subjects.

Results

None of the 31 patients had suffered osteoporotic fractures. One had a Z value for the femoral neck of –1.6, denoting early but definite osteoporosis, and five had borderline osteoporosis with Z values for one or other site between –1.1 and –1.5. BMDs for the lumbar spine and femoral neck were normally distributed among the 31 patients (Fig 1). Twenty-one women had thyrotrophin values below the normal range (group A), and 10 within the normal range (group B). Fifteen women (group C) had previously been hyperthyroid and 16 (group D) had not. Details of all four groups are listed in Table 1. For the thyrotrophin data, the non-parametric Mann Whitney test gives $p < 0.001$ and $p = 0.23$ for the comparison between groups A and B and between groups C and D, respectively. The 21

Table 1. Clinical details and biochemical results (figures in brackets: standard deviations except for thyrotrophin—see text)

	Group A (n = 21)	Group B (n = 10)	Group C (n = 15)	Group D (n = 16)	Total (n = 31)
Age (years)	62.05 (10.19)	53.70 (10.85)	59.93 (8.67)	59.19 (13.05)	59.35 (11.00)
% premenstrual	9.5	40.0	12.5	26.7	19.3
% on OCs	28.6	60.0	26.7	50.0	38.7
% on HRT	28.5	10.0	20.0	25.5	22.6
Body mass index (kg/m)	25.2 (4.3)	24.2 (4.30)	24.8 (3.1)	25.0 (5.2)	24.9 (4.2)
Smoking years	17.9 (17.5)	12.0 (12.1)	22.7 (16.9)	9.8 (12.7)	16.0 (16.0)
Pathological fractures	—	—	—	—	—
Activity score	2.0 (0.55)	1.9 (0.57)	2.0 (0.38)	1.9 (0.68)	2.0 (0.55)
Calcium intake	1.8 (0.41)	2.1 (0.32)	1.8 (0.36)	1.9 (0.68)	1.9 (0.55)
Free thyroxine (pmol/l) NR: 9–27	30.11 (6.07)	21.00 (2.62)	26.93 (6.71)	27.92 (7.51)	27.40 (6.73)
Triiodothyronine (nmol/l) NR: 0.8–2.7	1.87 (0.45)	1.94 (1.90)	2.15 (1.46)	1.64 (0.38)	1.89 (1.07)
Thyrotrophin (mU/l) NR: 0.8–2.7	0.04 (0.04–0.10)	2.20 (0.20–2.80)	0.04 (0.04–2.96)	0.03 (0.04–2.80)	0.63 (1.00) —

Group A: subjects with suppressed thyrotrophin concentration.
Group B: subjects with a normal thyrotrophin concentration.
Group C: subjects with a past history of thyrotoxicosis.
Group D: subjects without a past history of thyrotoxicosis

Free thyroxine (n = 27): difference between groups A and B: $p = 0.05$; groups C and D: $p = 0.19$.

Triiodothyronine (n = 26); difference between groups A and B: $p = 0.89$; groups C and D: $p = 0.24$.

Thyrotrophin (n = 31): difference between groups A and B: $p = 0.0001$; groups C and D: $p = 0.23$.

A value of 0.05 mU/l (assay detection limit) used to calculate the mean for values below the limit.

HRT = hormone replacement therapy NR = normal range OCs = oral contraceptives

subjects (group A) with suppressed thyrotrophin concentrations were on average 8.3 years older than those in group B. The subjects in group A were mainly patients who had been started on replacement therapy before thyrotrophin estimations could be done, at a time when the recognised replacement dose of thyroxine was much higher than has been considered necessary in recent years. Many of the other differences in Table 1 arise from the age difference and higher dose of thyroxine in group A. The other striking difference was in the smoking years. The 15 patients who were originally thyrotoxic (group C) had smoked for twice as long as the 16 subjects in group D who were not initially thyrotoxic. The mean free thyroxine concentrations were at the upper limit of, or above, the normal range in groups A, C and D, and within the normal range only in group B. The triiodothyronine concentrations were well within the normal range. The one patient who had a Z value of –1.6 for the femoral neck, consistent with early osteoporosis, had a value of –1.2 for the lumbar spine. This patient had previously had thyrotoxicosis and had taken thyroxine, 200 µg daily for 26 years with a suppressed thyrotrophin (this was demonstrated when the sensitive IRMA method became available). The seven women with the lowest Z values, two at both sites and

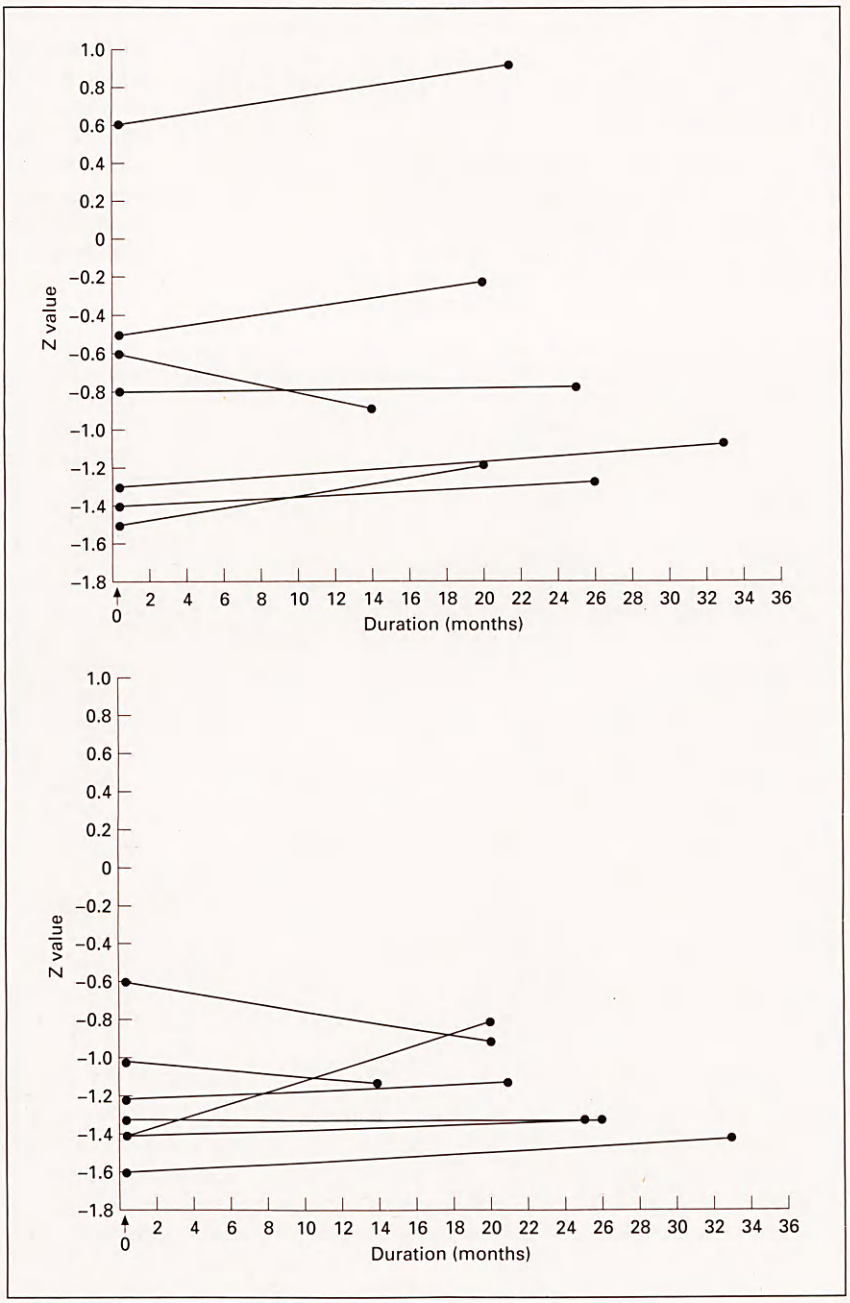


Fig 2. *Change in bone mineral density between first and last measurement in seven women with low initial Z values;* **(a)** *lumbar spine;* **(b)** *femoral neck*

five at one site only, had repeat measurements of BMD on average 22.7 months (range 14–23) from first to last measurement (Fig 2). For lumbar spine, the means were –0.79 (SD: 0.73) and –0.68 (SD: 0.78), an increase of 0.11 (SD: 0.22) from the initial to the later value (p = 0.24 on a paired t-test) (95% confidence interval for the change: 0.09 to 0.31). For femoral neck, the means were –1.21 (SD: 0.33) and –1.13 (SD: 0.22), an increase of 0.08 (SD: 0.28) from the initial to the later value (p = 0.45 on a paired t-test) (95% confidence interval for the change: 0.17 to 0.34).

Four of the seven women with the lowest Z scores had both suppressed serum thyrotrophin concentrations and a history of hyperthyroidism. The Z value difference for women with suppressed and unsuppressed serum thyrotrophin concentrations was associated with a mean daily thyroxine dosage of 171.4 µg (SD: 34.7) and 140 µg (SD: 50.3), respectively (p = 0.05); the cholesterol differences before and after thyroxine were 2.11 mmol/l (SD: 1.78) (p = 0.002) and 0.89 mmol/l (p = 0.06), respectively. The initial mean cholesterol concentration for 20 subjects was 8.17 mmol/l (SD: 2.15), and the final mean cholesterol concentration was 6.48 (SD: 0.96), a fall of 1.68 mmol/l (p = 0.001) (Table 2). The 13 subjects in group A with suppressed thyrotrophin concentrations had a fall in serum cholesterol of 2.11 mmol/l from 8.94–6.83 mmol/l (p = 0.001). The fall in the seven subjects in group B with unsuppressed thyrotrophin was 0.89 mmol/l from 6.73–5.84 mmol/l (p = 0.06).

Although thyrotrophin suppression was associated with mean Z values which were lower for both lumbar spine and femoral neck than in the subjects who had normal serum thyrotrophin concentrations, the differences were not significant (p = 0.68 for the lumbar spine, p = 0.28 for the femoral neck). The mean Z values were more reduced by a past history of hyperthyroidism, but again the differences were not significant (p = 0.18 for the lumbar spine, p = 0.34 for the femoral neck). Further subgrouping led to numbers too small to separate the effect of thyrotrophin suppression from a past history of hyperthyroidism. However, when both influences were present together, there was a greater reduction in BMD than with either influence alone, the Z value for the lumbar spine being –0.42 (p = 0.18) and for the femoral neck –0.57 (p = 0.30). There was no correlation between Z values and the length of treatment.

No subject had atrial fibrillation or cardiographic evidence of CAD.

Discussion

Among 31 women treated with replacement thyroxine 21 had a suppressed serum thyrotrophin concentration and reduced serum cholesterol but no clinical evidence of hyperthyroidism. Fifteen had been thyrotoxic in the past. It was impossible in this study to separate the effect on BMD of thyrotrophin suppression from that of a past history of hyperthyroidism since such a high proportion of patients had been subjected to both influences. Thyrotrophin suppression alone probably has no significant effect on BMD and, even when combined with a past history of hyper-

Table 2. Bone mineral density (Z values), thyroxine dosage and cholesterol (figures in brackets: standard deviations except for change in cholesterol on thyroxine)

	Group A (n = 21)	Group B (n = 10)	p value for difference between A & B	Group C (n = 15)	Group D (n = 16)	p value for difference between C & D	Total (n = 31)
Lumbar spine	0.25	0.42	0.68	0.05	0.55	0.18	0.31
Z values	(0.94)	(1.26)	—	(1.01)	(1.04)	—	(1.04)
Femoral neck	–0.39	–0.06	0.28	–0.43	0.15	0.34	0.28
Z values	(0.78)	(0.80)	—	(0.95)	(0.61)	—	(0.79)
Thyroxine dose	171.40	140.00	0.05	171.70	151.60	0.19	161.30
(µg)	(34.7)	(50.3)	—	(37.6)	(45.20)	—	(42.2)
Cholesterol before	(n = 13)	(n = 7)	0.02	(n = 10)	(n = 10)	0.19	(n = 20)
thyroxine (mmol/l)	8.94	6.73	—	8.81	7.52	—	8.17
	(2.18)	(1.15)	—	(2.71)	(1.20)	—	(2.15)
Final cholesterol	(n = 13)	(n = 7)	0.21	(n = 10)	(n = 10)	0.48	(n = 20)
(mmol/l)	6.83	5.84	—	6.31	6.66	—	6.48
	(1.06)	(0.83)	—	(1.18)	(0.99)	—	(1.07)
*Change in	2.11	0.89	—	2.51	0.86	—	1.68
cholesterol on	(0.001)	(0.06)	—	(0.001)	(0.03)	—	(0.0002)
thyroxine (mmol/l)							

* p values (in brackets) from paired t-test.
See Table 1 for description of groups.

thyroidism, rarely leads to a reduction in BMD likely to produce osteoporosis with its clinical effects, such as spontaneous fractures. The dose and duration of thyroxine treatment did not influence BMD. In the seven subjects who had repeated BMD studies, it is possible to be 95% certain that the mean BMD for the lumbar spine would not have deteriorated by more than 0.09 or increased by more than 0.31 and, for the femoral neck, by not more than 0.17 or increased by more than 0.34.

The dose of thyroxine that suppressed the serum thyrotrophin concentration also reduced the mean serum cholesterol concentration from 8.94 mmol/l, a level associated with a high risk of CAD, to 6.83 mmol/l, a level associated with a lower risk. Subclinical hypothyroidism has been considered to be a risk factor for CAD [13,14]. Some believe that the association between autoimmune thyroiditis and CAD is a genetic link and is not associated with hypercholesterolaemia [15], but numerous studies have shown a raised cholesterol level in subclinical hypothyroidism [12, 16]. An increase in high-density lipoprotein cholesterol, with no change in total cholesterol, has occurred in thyroxine replacement therapy without thyrotrophin suppression [17]. While there are conflicting reports on cholesterol changes due to thyroxine, in our study only the group whose thyrotrophin levels were suppressed had a profound fall in cholesterol levels. Thyrotrophin concentrations within the normal range may have a statistically significant effect on lipid levels in women with ischaemic heart disease [18] and peripheral arterial disease [19]. Treatment with thyroxine of patients with definite subclinical hypothyroidism, especially those in whom thyrotrophin levels fell [20] or whose initial thyrotrophin concentration was over 10 mmol/l [21], resulted in beneficial lipid changes.

This study suggests that long-term replacement treatment of impaired thyroid function with thyroxine should be influenced more by the very real risk of cholesterol-related CAD than by a possible slight effect on bone mass.

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