J. Endocrinol. Invest. 30: 230-235, 2007

Favorable clinical heart and bone effects of anti-thyroid drug therapy in endogenous subclinical hyperthyroidism

S. Buscemi[1], S. Verga[1], S. Cottone[1], G. Andronico[1], L. D'Orio[2], V. Mannino[3], D. Panzavecchia[4], F. Vitale[5], and G. Cerasola[1]

[1]Department of Internal Medicine, Cardiovascular and Kidney Diseases, Faculty of Medicine, University of Palermo; U.O. of [2]Internal Medicine, [3]Cardiology, [4]Orthopedics, and [5]Clinical Chemistry, Partinico Hospital, AUSL 6, Palermo, Italy

ABSTRACT. Although subclinical hyperthyroidism (SCH) has been associated with increased risk of osteoporosis and cardiac arrhythmias, its treatment is still controversial. This study was designed as a prospective, randomized, intervention, control-study with a 1-year follow-up in order to investigate whether normalization of serum TSH in SCH using methimazole has favorable bone and heart clinical effects. Fourteen patients with endogenous SCH (not Graves' disease) were enrolled, 7 (5 women/2 men; group T) were treated with methimazole (2.5-7.5 mg/day), and 7 (5 women/2 men; group C) were followed without treatment; 10 healthy subjects were also included in the study as controls. Serum free-T_3 (FT_3), free-T_4 (FT_4) and TSH, thyroid echography, bone stiffness index (SI), as measured by heel ultrasonometry, and 24-h electrocardiography monitoring were obtained. SCH patients exhibited higher systolic and diastolic blood pressure than control subjects. They also had a significantly higher number of both ventricular premature beats (VPB) (mean±SEM: 681±238 *vs* 6±2 beats/24 h; *p*<0.02) and atrial premature beats (APB) (mean±SEM: 495±331 *vs* 7±2 beats/24 h; *p*<0.0001), and a lower SI (66±5 *vs* 96±3; *p*<0.001). Twelve months after normalization of TSH with the use of methimazole, the number of VPB decreased significantly (947±443 *vs* 214±109 beats/24 h; *p*<0.05) while it remained unchanged in untreated SCH patients (414±163 *vs* 487±152 beats/24 h; *p*=ns). An insignificant therapy effect was observed as far as APB were concerned (826±660 *vs* 144±75 beats/24 h; *p*=ns), however their number increased significantly in the untreated group (463±49 *vs* 215±46 beats/24 h; *p*<0.05). The SI increased significantly as a result of therapy in group T (64.1±4.8 *vs* 70.0±5.3; *p*<0.02) and was further reduced in group C at the end of the study (69.1±7.3 *vs* 62.9±7.1; *p*<0.001). No adverse effect was observed in group T. In conclusion, anti-thyroid therapy seems to have favorable bone and heart clinical effects in subjects with endogenous SCH.

(J. Endocrinol. Invest. 30: 230-235, 2007)

INTRODUCTION

Subclinical hyperthyroidism (SCH) is characterised by low TSH level and normal levels of circulating thyroid hormones (T_4 and T_3) as a consequence of treatment with levothyroxine (exogenous SCH) or of thyroid diseases such as Graves' disease, multinodular goiter, solitary nodule (endogenous SCH) (1). The clinical significance of SCH relates to some risk factors, such as the progression to overt hyperthyroidism, cardiac (atrial fibrillation and other arrhythmias, cardiac hypertrophy) and skeletal effects (increased bone turnover and reduced mineral density) (2). Furthermore, evidence has recently been gathered that SCH might be involved in dementia (3) and in increased mortality in elderly patients (4). The prevalence of SCH is relatively high and rates between 0.2 and 11.8% have been reported in different groups of subjects (1, 5-7) suggesting that the treatment of this condition might be of great clinical significance. However, no consensus exists regarding the management of SCH, since few clinical trials have investigated this subject, and at times results have been controversial. One recent review (2) has suggested that, in most patients, treatment is unnecessary, while recent clinical guidelines have come to uncertain conclusions (1, 3, 8).

Key-words: Subclinical hyperthyroidism, methimazole, heart, bone, therapy.

Correspondence: S. Buscemi, MD, Divisione di Medicina Interna, Nefrologia ed Ipertensione, Policlinico "P. Giaccone", Via del Vespro 129, I-90127 Palermo, Italy.

E-mail: silbus@tin.it

Accepted October 2, 2006.

This study was therefore designed to investigate if treatment of endogenous SCH has favorable clinical effects on both heart and bone.

MATERIALS AND METHODS

Fourteen (10 women, 4 men) consecutively and newly diagnosed outpatients with endogenous SCH and 10 (7 women, 3 men) healthy control subjects participated in this study. The diagnosis of stable SCH for at least 2 months was based on the finding on two different occasions of low serum TSH values (<0.4 μIU/ml) and free-T_3 (FT_3) and free-T_4 (FT_4) concentrations within the normal range. Patients with Graves' disease and with positive serum antithyroidperoxidase (TPOAb), antithyroglobulin (TGAb) and anti-TSH-receptor (TRAb) antibodies were excluded. No patient had a history of hepatic or renal disorders, alcoholism, or other major medical conditions, including diabetes and hypertension, or had taken any medications that might affect thyroid function or calcium metabolism. Apart from laboratory tests, the diagnosis of endogenous SCH was based on both thyroid ultrasound and uptake of radioactive 99mTc. Therefore, 12 patients proved to be affected by multinodular goiter and 2 patients by autonomously functioning thyroid nodule.

Patients were randomly divided into 2 groups of 7 patients each, a treatment group in which euthyroidism was obtained with methimazole (group T) at variable maintenance dosage of 2.5-7.5 mg/day and an observation group that did not receive thyreostatic treatment and served as the control (group C). Randomization consisted in attributing alternately, one after the other, each patient to group C or T. Patients were informed of the purposes of the study and the substantial uncertainty concerning the consequences of untreated SCH, as well as the benefit of initiating treatment; therefore, each participant in the study was given the possibility of changing his randomly assigned group, but nobody requested it at any time of the study. Table 1 shows the physical characteristics of subjects studied. Serum FT_3, FT_4, and TSH values were performed at 4-week intervals; all subjects of group T achieved the euthyroid state within the next 3 months after starting therapy with methimazole at a dosage of 10 mg/day (subjects with TSH concentrations >0,01 μIU/ml) or 15 mg/day (subjects with TSH concentrations ≤0,01 μIU/ml). The healthy control group was evaluated only at the beginning of the study, while all other subjects were investigated before and 12 months after treatment randomization.

The Ethics Committee of the Institute approved the study protocol and all subjects gave their written voluntary consent according to the Helsinki Declaration.

Calcium and phosphorus were measured in serum and urine by standard laboratory methods. Serum FT_3, FT_4, and TSH were measured with the use of commercially available kits (immunoenzymatic test – Immulite, DPC, Diagnostic Products Corporation, Los Angeles, CA, USA). The normal ranges for hormone blood levels are: FT_3 1.5-4.1 pg/ml; FT_4 0.8-1.9 ng/dl; TSH 0.4-4 μIU/ml; the sensitivity limits of each test are as follows: FT_3 1.0 pg/ml; FT_4 0.15 ng/dl; TSH 0.002 μIU/ml. Thyroid volume (TV) was determined ultrasonographically; each lobe volume was calculated by the Brunn (9) method (length x thickness x width x 0.48 in mm). TV was the sum of both lobes and the istmus was not included. Rhythm disturbance was detected by 24-h electrocardiography monitoring (Holter, Syneflash; ELA medical, France). Bone mineral density was indirectly assessed by heel ultrasonometry (Achilles express; Lunar corp., Madison, WI, USA); briefly, the stiffness index (SI) is obtained by the measurement of two calcaneal ultrasound parameters, the speed of sound (SOS) and the broadband ultrasound attenuation (BUA). The method has a coefficient of variation of 2%. The SI proved to be strongly related to the bone mineral density obtained by dual energy X-ray absorptiometry at the femoral neck or at the vertebral level (10) and it was also related to the risk of hip fracture (11).

All data are expressed as mean±SEM. The t-test for paired and unpaired data were used for comparison of the means of 2 groups. A *p*-value of less than 0.05 was considered as statistically significant. SPSS statistical software (release 6.0; SPSS Inc.; Chicago, Illinois, USA) was utilised to explore differences between groups and relations between variables.

RESULTS

Anthropometric and clinical characteristics of studied groups are reported in Table 1. SCH patients exhibited serum and urinary calcium and phosphorus values not significantly different from control subjects. The SI was significantly lower in the SCH

Table 1 - *Physical and clinical characteristics of controls and subclinical hyperthyroidism (SCH) patients.*

	Controls	SCH	*p*
males/females	3/7	4/10	
Age (yr)	54±4	58±2	ns
Body weight (kg)	72.4±3.2	70.3±3.8	ns
Body mass index (kg/m^2)	27.1±0.7	27.6±0.8	ns
Thyroid volume (ml)	14.8±0.7	27.9±5.6	<0.05
Thyroid main nodule size (mm)	–	22.1±3.9	–
FT_3 (pg/ml)	2.4±0.2	3.3±0.3	<0.005
FT_4 (ng/dl)	1.3±0.1	1.4±0.1	ns
TSH (μIU/ml)	2.3±0.3	0.06±0.01	<0.0001

mean±SEM. FT_3: free-T_3; FT_4: free-T_4.

patients than in controls (66±5 *vs* 96±3; p <0.001). SCH patients exhibited significantly higher systolic and diastolic blood pressure values (respectively: 131±5.0 *vs* 110±2.4 mmHg, p<0.001; 83±3.8 *vs* 66±1.5 mmHg, p<0.005). No difference was observed between control and SCH subjects as far as basal heart rate or 24-h heart rate monitoring are concerned. However, Holter monitoring indicated that SCH subjects had a significantly higher number of both ventricular premature beats (VPB) (681±238 *vs* 6±2 beats/24 h; p<0.02, respectively) and atrial premature beats (APB) (495±331 *vs* 7±2 beats/24 h, p<0.0001, respectively) compared to the control group. All subjects with SCH who were randomly assigned to the treatment group achieved normal serum TSH values, while subjects assigned to the observation group remained in SCH condition after 12 months (Fig. 1). Clinical data, including 24-h electrocardiography monitoring and bone ultrasonometry, are summarized in Table 2 and Figure 1. TV increased

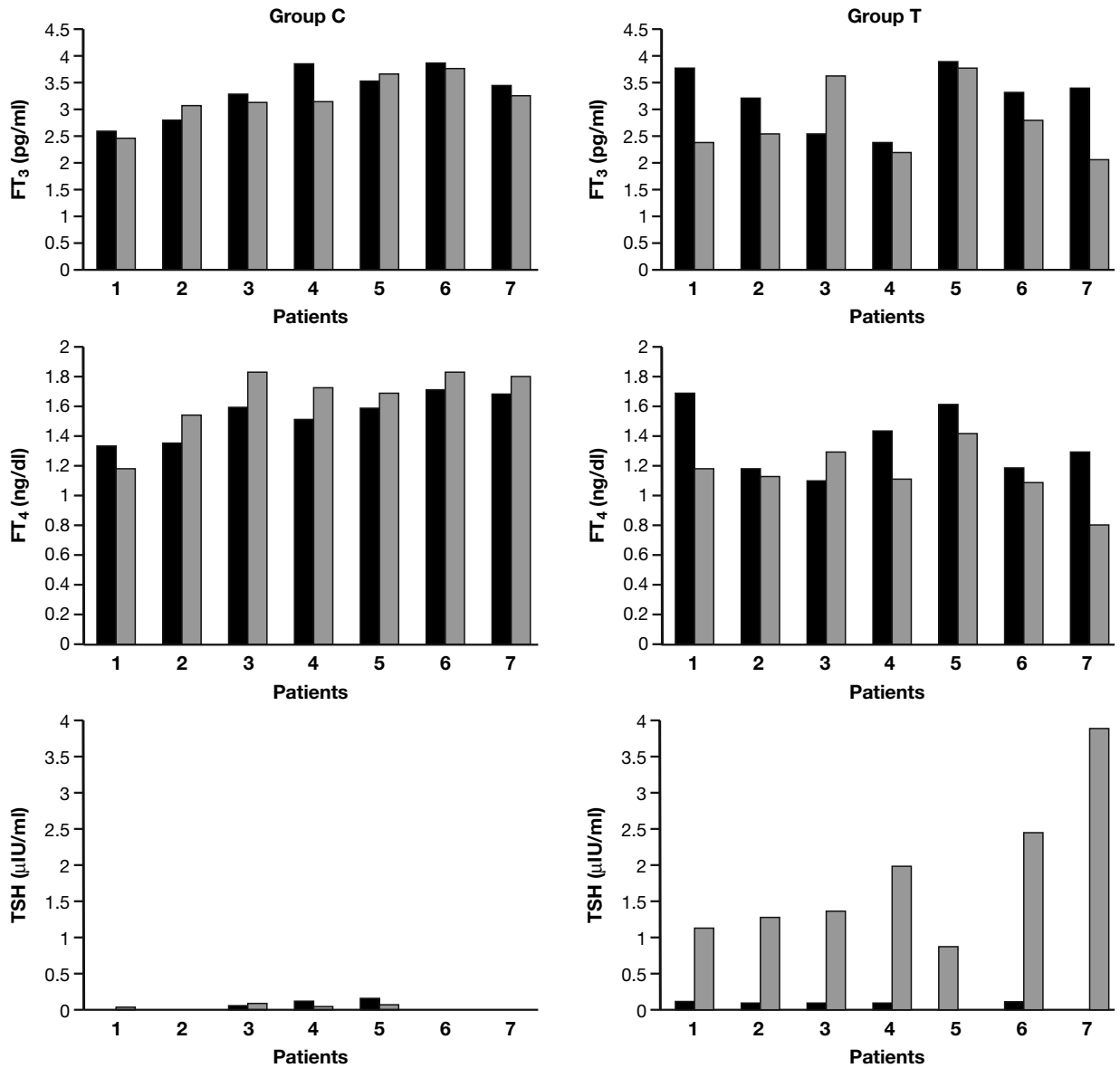

Fig. 1 - *Individual thyroid hormone concentrations in patients with subclinical hyperthyroidism before (T0: solid bars) and 12 months (T12: dotted bars) after starting the study. Group C was not pharmacologically treated; group T received anti-thyroid treatment with methimazole after T0. FT_3: free-T_3; FT_4: free-T_4.*

Table 2 - *Anthropometric, biochemical and hormonal data, bone ultrasonometry and electrocardiography 24-h monitoring before (T0) and 12 months (T12) after starting the study in patients with subclinical hyperthyroidism (SCH) randomly divided in 2 groups, a treatment group (T) that achieved euthyroidism due to anti-thyroid treatment and a control group (C) that was not pharmacologically treated.*

	SCH group C		*p*	SCH group T		*p*
	T 0	T 12		T 0	T 12	
Females/males	5/2	5/2		5/2	5/2	
Age (yr)	57±4			59±3		
Body mass index (kg/m^2)	27.9±1.2	28.1±1.0	ns	27.3±1.3	27.8±1.4	<0.05
FT_3 (pg/ml)	3.4±0.3	3.3±0.2	ns	3.4±0.4	2.8±0.4	ns
FT_4 (ng/dl)	1.6±0.1	1.7±0.1	ns	1.2±0.1	1.1±0.1	ns
TSH (μIU/ml)	0.06±0.02	0.04±0.01	ns	0.06±0.01	1.89±0.43	<0.01
Calcium (mg/dl)	9.8±0.2	9.9±0.2	ns	10.2±0.2	9.5±0.3	<0.005
Phosphorus (mg/dl)	3.4±0.1	3.3±0.1	ns	3.6±0.2	3.6±0.2	ns
Urinary calcium (mg/24 h)	175±30	166±28	ns	161±25	103±17	<0.05
Urinary phosphorus (mg/24 h)	639±51	678±47	ns	585±39	599±45	ns
Stiffness index	69.1±7.4	62.9±7.1	<0.001	64.1±4.8	70.0±5.3	<0.02
Systolic blood pressure (mmHg)	136±8	126±11	ns	139±6	136±4	ns
Diastolic blood pressure (mmHg)	78±3	80±3	ns	79±3	78±3	ns
Basal heart rate (beats/min)	80±3	81±3	ns	82±3	78±5	ns
24-h heart rate (beats/min)	83±4	84±2	ns	81±4	75±5	<0.05
Atrial premature beats (beats/24 h)	163±49	215±46	<0,05	826±660	144±75	ns
Ventricular premature beats (beats/24 h)	414±163	487±152	ns	947±443	214±109	<0.05

mean±SEM. FT_3: free-T_3; FT_4: free-T_4.

at T12 with respect to T0 in both groups C (30.3±4.3 *vs* 27.3±4.1 ml; $p<0.05$) and T (31.9±9.0 *vs* 28.3±9.9 ml; $p<0.05$). Similarly, the diameter of the main nodule increased at T12 with respect to T0 but the difference was not statistically significant in either group of SCH patients (group C: 23.2±9.2 *vs* 22.8±4.5; *p*=ns; group T: 17.7±7.0 *vs* 17.8±8.8; *p*=ns).

DISCUSSION

In the present study, SCH patients showed reduced bone mineral density, as indirectly suggested by a significantly lower SI. Although hyperthyroidism is acknowledged as one of the major causes of secondary osteoporosis (12, 13), few studies have been performed to examine calcium and bone metabolism in SCH, and results have been conflicting (14-17). Thyroid hormones are thought to stimulate osteoclastic bone resorption *via* nuclear receptors (18) and reduce the duration of bone remodelling cycle (19). Furthermore, osteoblasts possess functional TSH receptors (20) and it has therefore been suggested that the presence of thyroid receptor antibodies in Graves' disease could independently exert an influence on bone turnover (21). In our study, it seems reasonable to exclude any immunological influence on bone turnover since only SCH subjects with multinodular goiter or autonomously functioning thyroid nodule negative for serum TPOAb, TGAb or TRAb were included in the study. However, that SCH is associated with reduced mineral density seems to be confirmed by results obtained in our patients after treatment randomization. In fact, 12 months later, normalization of TSH with methimazole therapy (group T) was associated with a significant amelioration of the SI. On the contrary, the SI was further reduced in untreated SCH subjects (group C). Interestingly, group T exhibited a significant reduction of serum and urinary calcium at T12. This result is in agreement with other studies (15) that found increased urinary calcium excretion in SCH subjects as an expression of accelerated bone turnover. Furthermore, it could suggest that SCH subjects treated with thyreostatic drugs must also be treated with calcium supplementation. Despite controversial results in the literature, we have obtained clear evidence

that SCH is associated with reduced bone density, and that thyreostatic treatment is able to reverse this condition. At least two factors could have influenced such results. First, we observed patients for 12 months, a reasonably long time; secondly, the average TSH (0.06 μIU/ml) of our patients was markedly and significantly depressed. In agreement with the above, it has recently been reported (22) that there was a 3-fold increase in hip fracture risk in women with TSH values of less than 0.1 μIU/ml, but not in those with TSH concentrations of 0.1 to 0.5 μIU/ml, whereas, the risk of vertebral fractures was 8.8-fold and 4.4-fold, respectively. It is thus possible that the effects of SCH are clinically evident only in subjects with very low serum TSH (8).

An even more relevant question concerns the possible cardiac effects of SCH. A report on the mortality risk in elderly patients revealed that mortality from all causes and from vascular diseases is higher among patients over 60 yr old with SCH at 5 yr of follow-up (4). According to the Framingham study, SCH is a risk factor (RR 3.1) for the development of atrial fibrillation (23). Furthermore, a low serum thyrotropin concentration has proved to be associated with a >5-fold higher likelihood of the presence of atrial fibrillation with no significant difference between SCH and overt hyperthyroidism (24). Thyroid hormones are thought to induce rhythm disturbances on account of their direct chronotropic effects and in part due to indirect effects on the sympathoadrenergic system (25). A recent report (26) showed that 6 months of anti-thyroid treatment for SCH reduces heart rate, APB and VPB, left ventricular thicknesses and left ventricular mass. In agreement with these reports, our study shows that the number of either the 24-h heart rate and of VPB was significantly reduced in SCH group T at 12 months, while it remained unchanged in SCH group C. Although reduced, APB remained unstatistically changed at T12 in SCH group T; however, they proved significantly increased at T12 in group C. We did not observe atrial fibrillation in either group C or T throughout the 12-month study duration. Therefore, even in this case, treatment of SCH with thyreostatic drugs seems to have favorable clinical effects. This result appears to be relevant, since very few studies have investigated the effects of treatment of endogenous SCH (17, 26). An increase of left ventricular mass was reported in patients with endogenous SCH (27). Hyperthyroidism is able to induce left ventricular hypertrophy as a consequence of both direct transcriptional (28) and indirect non-transcriptional (29) effects (increased cardiac work, contractility or peripheral oxygen consumption); thus the reversal of these mechanisms could probably explain the prevailing reducing effect of anti-thyroid treatment on the number of VPB rather than APB. Taken together with the results of the few other small available trials, our findings are in agreement with the hypothesis that an earlier anti-thyroid therapy might prevent the potential progression to more complex arrhythmias. However, this favorable effect of antithyroid therapy needs to be confirmed by further randomized studies with a higher number of patients.

A possible undesired effect of anti-thyroid therapy in subjects with endogenous SCH due to multinodular goiter or autonomously functioning nodule is a potential increase of goiter or nodule sizes in consequence of the increase in serum TSH concentrations. Our study showed that the size of the main nodule did not increase significantly, as well as in both groups C and T at the end of follow-up; however, both groups C and T exhibited a significantly increased TV at the end of the study. Therefore, the present report seems to exclude such a potential adverse effect of SCH treatment.

The estimated rate of progression from SCH to overt hyperthyroidism in patients with multinodular goiter is 5% each year (2). In agreement with these data was the fact that no subject from group C and T became frankly hyperthyroid during the 12 months of follow-up. TSH levels in some individuals with SCH may spontaneously return to normal values. On the other hand, initiating treatment with anti-thyroid drugs or radioactive iodine in the case of Graves' disease may expose to some risks (i.e. allergic reactions and agranulocytosis or hypothyroidism and exacerbation of exophthalmos, respectively). Until recently (8, 30), it had been affirmed that because of the substantial uncertainty concerning the consequences of untreated SCH, as well as the benefit of initiating treatment, patient preferences were important in deciding on the management of this subclinical condition. Despite randomization, this study is potentially limited by the fact that it was an open study and that the effect of treatment was not compared to the use of placebo. The reason for this was that the study design was mainly required for ethical reasons, since the anti-thyroid treatment of SCH has not yet been clearly established. Nevertheless, the results of this study are mainly based on objective measurements and it seems reasonable to exclude any significant bias due to the investigator influences. Another possible limiting factor is the small number of subjects studied, even though it was comparable to that of other reports (31). However, to our knowledge, this is the first study that considered anti-thyroid treatment *vs* control and with a follow-up of 12 months.

In conclusion, this study suggests that SCH is associated with both reduced bone density and increased

rhythm disturbances, and that anti-thyroid treatment is safe and may have favorable bone and cardiac effects.

ACKNOWLEDGMENTS

The authors are indebted to Nancy W. Birch, BA who edited the English.
This study was supported in part by the Italian Ministry of Education (MURST funds project 2003).

REFERENCES

1. Helfand M. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2004, 140: 128-41.
2. Toft AD. Subclinical hyperthyroidism. N Engl J Med 2001, 345: 512-6.
3. Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA, Breteler MM. Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. Clin Endocrinol 2000, 53: 733-7.
4. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet 2001, 358: 861-5.
5. Vanderpump MPJ, Tunbridge WMG, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995, 43: 55-68.
6. Helfand M, Redfern CC. Clinical guideline, part 2. Screening for thyroid disease: an update. American College of Physicians. Ann Intern Med 1998, 129: 144-58.
7. AACE Thyroid Task Force. American association of clinical endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002, 8: 458-67.
8. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease. Scientific review and guidelines for diagnosis and management. JAMA 2004, 291: 228-38.
9. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC. Volumetric analysis of thyroid lobes by real-time ultrasound. Deutsche Medizinische Wochenschrift 1981, 106: 1338-40.
10. Greenspan SL, Bouxsein ML, Melton ME, et al. Precision and discriminatory ability of calcaneal bone assessment technologies. J Bone Miner Res 1997, 12: 1303-13.
11. Hans D, Dargent-Molina P, Schott AM, et al. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. Lancet 1996, 348: 511-4.
12. Riggs BL, Melton LJ 3rd. Involutional osteoporosis. N Engl J Med 1986, 314: 1676-86.
13. Lee WY, Oh KW, Rhee EJ, et al. Relationship between subclinical thyroid dysfunction and femoral neck bone mineral density in women. Arch Med Res 2006, 37: 511-6.
14. Mudde AH, Houben AJ, Nieuwenhuijzen Kruseman AC. Bone metabolism during anti-thyroid drug treatment of endogenous subclinical hyperthyroidism. Clin Endocrinol (Oxf) 1994, 41: 421-4.
15. Kisakol G, Kaya A, Gonen S, Tunc R. Bone and calcium metabolism in subclinical autoimmune hyperthyroidism and hypothyroidism. Endocr J 2003, 50: 657-61.
16. Gurlek A, Gedik O. Effect of endogenous subclinical hyperthyroidism on bone metabolism and bone mineral density in premenopausal women. Thyroid 1999, 9: 539-43.
17. Yönem O, Dökmetas HS, Aslan SM, Erselcan T. Is antithyroid treatment really relevant for young patients with subclinical hyperthyroidism? Endocr J 2002, 49: 307-14.
18. Britto JM, Fenton AJ, Holloway WR, Nicolson GC. Osteoclast mediate thyroid hormone stimulation of osteoclastic bone resorption. Endocrinology 1994, 134: 169-76.
19. Eriksen EF. Normal and pathological remodeling of human trabecular bone: three dimensional reconstruction of the remodeling sequence in normals and in metabolic bone disease. Endocr Rev 1986, 7: 379-408.
20. Inoue M, Tawata M, Yokomori N, Endo T, Onaya T. Expression of thyrotropin receptor on clonal osteoblast-like rat osteosarcoma cells. Thyroid 1998, 8: 1059-64.
21. Kumeda Y, Inaba M, Tahara H, et al. Persistent increase in bone turnover in Graves' patients with subclinical hyperthyroidism. J Clin Endocrinol Metab 2000, 85: 4157-61.
22. Bauer DC, Ettinger B, Nevitt MC, Stone KL. Risk of fracture in women with low serum levels of thyroid-stimulating hormone. Ann Intern Med 2001, 134: 561-8.
23. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994, 331: 1249-52.
24. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. Am Heart J 2001, 142: 838-42.
25. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001, 344: 501-9.
26. Sgarbi JA, Villaça FG, Garbeline B, Villar HE, Romaldini JH. The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities. J Clin Endocrinol Metab 2003, 88: 1672-7.
27. Biondi B, Palmieri EA, Fazio S, et al. Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. J Clin Endocrinol Metab 2000, 85: 4701-5.
28. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation 1993, 87: 1435-41.
29. Klein I, Hong C. Effects of thyroid hormone on cardiac size and myosin content of the heterotopically transplanted rat heart. J Clin Invest 1986, 77: 1694-8.
30. Col NF, Surks MI, Daniels GH. Subclinical thyroid disease. Clinical applications. JAMA 2004, 291: 239-43.
31. Faber J, Wiinberg N, Schifter S, Mehlsen J. Haemodynamic changes following treatment of subclinical and overt hyperthyroidism. Eur J Endocrinol 2001, 145; 391-6.