Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Cardiac and metabolic effects in patients who present with a multinodular goitre

A. Berghout[1*], J. van de Wetering[1], P. Klootwijk[2]

[1]Department of Internal Medicine, Medical Centre Rijnmond-Zuid, location Zuider, Groene Hilledijk 315, 3075 EA Rotterdam, the Netherlands, e-mail: berghouta@mcrz.nl,
[2]Department of Cardiology Dijkzigt, University Hospital, Rotterdam, the Netherlands,
[*] corresponding author

ABSTRACT

Twenty-six consecutive patients who presented with clinically euthyroid multinodular goitre were studied for an overnight fasting serum lipid profile and 24h Holter monitoring. Mean serum TSH was 0.6 ± 0.4 *vs* 2.4 ± 1.3 mU/l (p<0.0001) and mean TT3 2.4 ± 0.4 *vs* 2.0 ± 0.5 nmol/l (p=0.009) in patients *vs* controls (n=15) while mean FT4 was not different from controls. Total serum HDL, LDL cholesterol and triglycerides were lower in patients but creatinine, ferritin and SHBG levels did not differ between patients and controls. The 24-hour ambulatory continuous ECG recordings did not demonstrate significant differences in mean, minimal and maximal heart rate between the study and the control group. Nocturnal heart rate, measured between 23.00 and 06.00 hours, also showed no differences between the two groups. Atrial fibrillation was absent in both the study and the control group. Premature atrial and ventricular complexes occurred equally frequently in both groups. Comparison of patients with a serum TSH below 0.4 mU/l (n=11) and patients with a TSH above 0.4 mU/l revealed no differences.

In conclusion, in consecutive patients who present with multinodular goitre, effects were found on the lipid profile, but not on the heart. It is argued that in this type of patients, cardiac effects depend on the degree of subclinical hyperthyroidism.

INTRODUCTION

Sporadic nontoxic goitre is one of the most common thyroid disorders, with a prevalence of 5 to 10% in the general population.[1,2] It is defined as a benign enlargement of the thyroid, with normal thyroid function in subjects not living in an endemic area.[1] Its aetiology is multifactorial.[3] The natural course of multinodular goitre is characterised by a gradually increasing size with concomitant rising plasma thyroid hormone levels and lowering thyroid-stimulating hormone (TSH) levels.[4,5] Ultimately a multinodular goitre can cause overt hyperthyroidism often complicated by cardiac rhythm disturbances, in particular atrial fibrillation.[6] Recently, in a population-based study, cardiovascular mortality was found to be increased in elderly people with a low serum TSH.[7] In the last decade, publications focused on the cardiac effects in patients with a low TSH. One study published findings of an increased heart rate, an increased left ventricular mass and impaired diastolic function in patients on T4 suppressive therapy ('subclinical thyrotoxicosis').[8] These findings, however, were not confirmed by others.[9] Very recently abnormalities in heart rate and function, similar to the patients with subclinical thyrotoxicosis due to T4 treatment, were also found in patients with 'endogenous' subclinical hyperthyroidism i.e. caused by a multinodular goitre or an autonomously functioning thyroid nodule.[10] In the patients of that study mean values of both T4 and T3 were in the upper normal range, suggesting an advanced state of subclinical hyperthyroidism compared with patients with subclinical hyperthyroidism in whom only mean serum T3 is increased. In that study only patients were included with a low or suppressed TSH level.[10] However, in most multinodular goitre patients plasma TSH levels often vary between the minimal detection limit of the assay and the lower normal limit, while plasma T3 and T4 levels are

still within the normal range. The clinical significance of these different TSH levels is not known. The aim of this study was, therefore, to study heart rate, the incidence of cardiac arrhythmias and metabolic effects in consecutive patients who presented with clinically euthyroid multinodular goitre.

SUBJECTS AND METHODS

All consecutive patients who presented with clinically euthyroid multinodular goitre at the medical clinics of our hospital between June 1997 and October 1999 were eligible. Those patients taking medication influencing cardiac or thyroid function, lipid metabolism and/or with a history of cardiac diseases, hypertension or diabetes mellitus were excluded. Most complaints were of a compressive nature or patients wanted to have information about the nature of the disease. There were no spontaneous complaints of cardiac palpitations. All patients were clinically euthyroid and had thyroid hormone levels within the normal range. A group of 15 healthy females matched for age served as controls. In all participants an overnight fasting serum lipid profile and 24h Holter monitoring were performed.

Assays

Serum TSH was determined using a chemiluminometric (sandwich) immunoassay, normal range from 0.4 to 4.2 mU/l (interassay variation 4.5-10%). Serum FT4 and TT3 were determined using a competitive immunoassay, normal ranges 10.0 to 22.0 pmol/l (interassay variation 4-6.5%) and 1.25 to 2.80 nmol/l (interassay variation 4.5-7%), respectively. Serum lipids were measured using an enzymatic colorimetric assay. Plasma creatinine was measured by a kinetic assay according to Jaffe, and ferritin and sex hormone binding globulin (SHBG) by an immunoluminescent assay.

Electrocardiography

A standard 12-lead electrocardiogram (ECG) was performed at the time of inclusion. All ECGs were screened for frequency, rhythm, conduction and depolarisation abnormalities and for evidence of left ventricular mass hypertrophy. A 24-hour ambulatory continuous recording was performed in each subject at the time of inclusion for measurement of heart rate and to detect any rhythm disturbances.

Statistical analysis

Student's test was used for comparison of results between patients and controls. Results are given as the mean ± standard deviation (SD). All p values are based on two-tailed analysis.

RESULTS

Fifty-eight patients were evaluated. Thirty-two patients were excluded for single or multiple reasons: cardiac history (n=10), hypertension (n=8), medication (n=6), diabetes mellitus (n=4), toxic goitre (n=6), other reasons (n=7). Twenty-four females and two males were in the patient group and 15 healthy females served as controls (*table 1*). The patients were divided in two subgroups, with a serum TSH above or below 0.4 mU/l. Mean serum TSH

Table 1
Characteristics of the multinodular goitre patients (mean ± SD)

	PATIENTS TSH >0.4 MU/L	PATIENTS TSH <0.4 MU/L	ALL PATIENTS	CONTROLS	P VALUE
Number	15	11	26	15	
Females	14	10	22	15	
Mean age (years)	53 ± 10	55 ± 11	54 ± 10	59 ± 10	NS
TSH (mU/l)	0.2 ± 0.2	0.9 ± 0.2	0.6 ± 0.4	2.4 ± 1.3	0.0001
FT4 (pmol/l)	13.4 ± 1.3	14.8 ± 3.0	14.0 ± 2.2	13.7 ± 2.1	NS
TT3 (nmol/l)	2.4 ± 0.4	2.4 ± 0.3	2.4 ± 0.4	2.0 ± 0.5	0.009
Creatinine (µmol/l)	58 ± 10	61 ± 9	61 ± 9	64 ± 9	NS
Ferritin (µg/l)	52 ± 40	85 ± 45	72 ± 52	116 ± 93	NS
Total cholesterol (mmol/l)	5.3 ± 1.0	5.4 ± 1.0	5.4 ± 1.0	6.2 ± 1.1	0.02
HDL cholesterol (mmol/l)	1.4 ± 0.2	1.3 ± 0.2	1.4 ± 0.3	1.6 ± 0.4	0.02
LDL cholesterol (mmol/l)	3.7 ± 0.9	3.6 ± 0.7	3.7 ± 0.8	4.4 ± 1.1	0.04
Triglycerides (mmol/l)	0.9 ± 0.4	0.8 ± 0.6	0.8 ± 0.5	1.3 ± 0.4	0.009
Sex hormone-binding globulin (nmol/l)	62.1 ± 32.4	54.1 ± 30.1	61.1 ± 37.7	52.9 ± 28.6	NS

P values: statistic tests between all patients and controls. TT3 = total trijodothyronine, TSH = thyroid-stimulating hormone.

and TT3 levels were lower and higher in both patient groups compared with the control group, respectively. Mean serum FT4 levels were not different. Mean total, HDL and LDL cholesterol and triglyceride levels were lower in both patient groups. Mean creatinine, ferritin and SHBG levels did not differ between patients and controls (*table 1*).

The 24-hour ambulatory continuous ECG recordings did not demonstrate differences in mean, minimal and maximal heart rate between both patient groups and the control group. Nocturnal heart rate, measured between 23.00 and 06.00 hours also showed no differences between the groups. Atrial fibrillation was absent in both the patients and the controls. Premature atrial and ventricular complexes were observed, but occurred equally frequently in patients and controls (*table 2*). Thyroid hormone levels and 24 hour or nocturnal heart rate were not significantly correlated in patients and controls.

DISCUSSION

Reports on effects of 'endogenous' subclinical hyperthyroidism on heart and lipids are limited. A recent study showed cardiac abnormalities in patients who were on TSH suppressive T4 therapy but with thyroid hormone levels within the normal range. These abnormalities were reflected by a higher mean daytime and nocturnal heart rate, a higher prevalence of atrial or ventricular arrhythmias, an increased cardiac mass and diastolic dysfunction.[8] These findings could not be confirmed by another group of investigators in a comparable patient group.[9] Interestingly, however, in another study in T4-suppressed patients, an increased left ventricular mass and reduced exercise tolerance was found. If, in these patients, T4 dose was lowered to the minimal amount to keep TSH at 0.1 mU/l, echocardiographic and ergometric parameters normalised.[11] Recently, cardiac abnormalities, this time in patients with subclinical hyperthyroidism due to a multinodular goitre, were published by Biondi *et al.*[10] The authors found an increased basal heart rate and also an abnormal systolic and diastolic function. In the present study we were unable to find cardiac effects. The two studies differ, however, in several aspects. Firstly, our study is a consecutive study whereas Biondi *et al.* presented results of a study of patients selected from a larger number of outpatients with a low TSH. Secondly, the patients in Biondi's study were probably more thyrotoxic than our patients as reflected by the fact that both mean TT3 and FT4 levels were in the upper normal range[10] whereas in our patients only mean TT3 was higher. Thirdly, the patients in Biondi's study – as in most other studies (*table 3*) – were significantly younger than our patients. These differences could very well explain that their patients showed cardiac effects whereas ours did not. Interestingly, in a consecutive study of 102 consecutive multinodular goitre patients performed in the Amsterdam area several years ago, TT3 was also higher but FT4 was not different compared with 50 healthy adults.[4] These data confirm again that in the natural course of multinodular goitre TT3 levels start to rise first, before FT4 levels rise, with a concomitant decrease in plasma TSH levels. Also of interest is the finding in our study that TT3 was in the upper normal range in all patients studied, both in patients with a TSH level below as well as above 0.4 mU/l.

Contrary to the findings in our patients with respect to the heart, there was evidence of an effect on plasma lipids in that serum levels were significantly lower than in controls. However, other metabolic parameters such as SHBG, ferritin or creatinine, known to be affected by thyroid hormone, were not different. Similar changes in circulating lipids have been found in another study in subjects with subclinical hyperthyroidism.[12] In that study, FT4 was also higher compared with controls, but still within normal

Table 2
Heart rate and incidence of arrhythmias in multinodular goitre patients

	PATIENTS TSH >0.4 MU/L	PATIENTS TSH <0.4 MU/L	ALL PATIENTS	CONTROLS	P VALUE
Number	15	11	26	15	
Mean heart rate (bpm)	81 ± 8	81 ± 8	81 ± 8	80 ± 9	NS
Minimal heart rate (bpm)	53 ± 7	54 ± 8	53 ± 7	52 ± 6	NS
Maximal heart rate (bpm)	141 ± 14	151 ± 24	145 ± 19	138 ± 23	NS
Mean nocturnal heart rate	69 ± 9	70 ± 9	70 ± 9	67 ± 6	NS
Minimal nocturnal heart rate	55 ± 7	54 ± 8	54 ± 7	53 ± 6	NS
Maximal nocturnal heart rate	107 ± 13	114 ± 23	110 ± 18	105 ± 11	NS
Premature ventricular complexes >100	3	0	3	3	NS
Premature atrial complexes >100	4	3	7	4	NS

Statistical analysis between all patients and controls. TSH = thyroid-stimulating hormone.

Table 3
Comparison of cardiac and metabolic effects in subclinical thyrotoxicosis due to T4 suppressive therapy and subclinical hyperthyroidism due to multinodular goitre

AUTHOR	YEAR	N	MEAN AGE	FT4*	TT3*	HEART RATE	PREMATURE BEATS	LV MASS	SHBG	LIPIDS
Subclinical thyrotoxicosis in subjects on T4 suppressive therapy										
Bell[15]	1983	7	28	↑	=	↑	nd	nd	nd	nd
Biondi[8]	1993	20	39	↑	=	↑	↑	↑	↑	nd
Ching[16]	1996	11	45	↑	=	=	nd	↑	nd	nd
Shapiro[9]	1997	17	45	↑	=	=	=	↑	nd	nd
Subclinical hyperthyroidism in patients with multinodular goitre										
Biondi[10]	2000	23	43	↑	↑	↑	=	↑	nd	nd
Faber[17]	2001	6	64	↑	↑	↑	nd	nd	nd	nd
Berghout	2003	11	55	=	↑	=	=	nd	=	↓

*LV = left ventricular, SHBG = sex hormone-binding globulin, nd = not done. * Levels within the normal range, ↑ elevated as compared with controls, ↓ decreased as compared with controls, = not different as compared with controls.*

limits.[12] In a study of 44 patients with clinically euthyroid goitre plasma levels of bone gla protein and SHBG were found to be higher compared with controls in those patients who had a lowered TSH.[13] A study of 27 consecutive multinodular goitre patients reported elevated levels of serum osteocalcin, which correlated with FT4 levels.[14] TSH was lower and FT4 was higher, but still within the normal range.[14]

From an analysis of all available studies of patients with subclinical hyperthyroidism caused by a multinodular goitre or with thyrotoxicosis caused by T4 suppressive therapy it is apparent that cardiac effects are seen in both groups but not in all studies (*table 3*).[8-10,15-17] It remains debatable whether endogenous subclinical hyperthyroidism in patients with a goitre and subclinical thyrotoxicosis due to exogenous T4 therapy are two different entities. In both situations plasma TSH levels are low or suppressed. In endogenous subclinical hyperthyroidism first TT3 and later both TT3 and FT4 are elevated – within the normal range – while in subclinical thyrotoxicosis due to T4 suppressive treatment only FT4 is elevated.[8] In both situations TSH is suppressed because the pituitary can respond independently to changes in plasma levels of T4 that enter the thyrotroph and is locally converted to T3, and to changes in plasma T3 that is directly taken up by the pituitary.[18] It is also evident that one cannot conclude from these studies whether the human heart is more sensitive to plasma T3 or T4 levels, in contrast to the liver that appears to be sensitive mainly to the plasma T3 concentration. The situation in the human heart is largely unknown. In neonatal rats cardiac uptake was mostly for T3 but not T4.[19] The conversion of T4 into T3 in human cardiac myocytes has thus far only indirectly been demonstrated by the finding of the expression of mRNA of type II deiodinase.[20]

In summary, in consecutive patients with euthyroid multinodular goitre metabolic effects are found. The expression of these effects depends upon the degree of increased thyroid function as occurring in the natural course of 'nontoxic' goitre.

NOTE

Part of the data in this article were presented at the 26th Annual Meeting of the European Thyroid Association in Milan, Italy from 28 August to 1 September 1999.

ACKNOWLEDGEMENTS

The authors thank Ineke Jongste for excellent technical assistance and Inge Glerum for editorial assistance.

REFERENCES

1. Henneman G. Nontoxic Goitre. Clin Endocrinol Metab 1979;8:167-79.
2. Tunbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham Survey. Clin Endocrinol 1977;7;:481-93.
3. Hennemann G. Multinodular Goiter. In: Groot LJ de, Hennemann G (eds). The Thyroid and its diseases. Chapter 17. 2001. www.thyroidmanager.org.
4. Berghout A, Wiersinga WM, Smits NJ, Touber JL. The interrelationships between age, thyroid volume, thyroid nodularity and thyroid function in patient with sporadic nontoxic goiter. Am J Med 1990;89:602-8.
5. Elte JWF, Bussemaker JK, Haak A. The natural history of euthyroid multinodular goitre. Postgrad Med J 1990;66:186-90.
6. 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.

7. 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.
8. Biondi B, Fazio S, Carella C, et al. Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. J Clin Endocrinol Metab 1993;77:334-8.
9. Shapiro LE, Sievert R, Ong L, et al. Minimal cardiac effects in asymptomatic athyreotic patients chronically treated with thyrotropin-suppressive doses of L-thyroxine. J Clin Endocrinol Metab 1997;82:2592-5.
10. Biondi B, Palmieri EA, Fazio F, 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.
11. Mercuro G, Panzuto MG, Bina A, et al. Cardiac function, physical exercise capacity and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring. J Clin Endocrinol Metab 2000;85:154-64.
12. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC. Circulating lipids and minor abnormalities of thyroid function. Clin Endocrinol 1992;37: 411-4.
13. Faber J, Perrild H, Johansen JS. Bone gla protein and sex hormone binding globulin in nontoxic goiter: parameters for metabolic status at the tissue level. J Clin Endocrinol Metab 1990;70:49-55.
14. Mudde AH, Bastiaanse AJ, Jonkers H. Is there a relationship between thyroid function and serum osteocalcin in women with multinodular goitre? A preliminary report. Neth J Med 1990;37:17-20.
15. Bell GM, Sawers JSA, Forfar JC, Doig A, Toft AD. The effect of minor increments in plasma thyroxine on heart rate and urinary sodium excretion. Clin Endocrinol 1983;18:511-6.
16. Ching GW, Franklyn JA, Stallard TJ, Daykin J, Sheppard MC, Gammage MD. Cardiac hypertrophy as a result of long-term thyroxine therapy and thyrotoxicosis. Heart 1996;75:363-8.
17. Faber J, Wiinberg N, Schifter S, Mehlsen J. Haemodynamic changes following treatment of subclinical and overt hyperthyroidism. Europ J Endocrinol 2001;145:391-6.
18. Reed Larsen P. Thyroid-pituitary interaction: feedback regulation of thyrotropin secretion by thyroid hormones. N Engl J Med 1982;306:23-31.
19. Everts ME, Verhoeven FA, Bezstarosti K, et al. Uptake of thyroid hormones in neonatal rat cardiac myocytes. Endocrinology 1996;137:4235-42.
20. Croteau W, Davey JC, Galton VA, St Germain DL. Cloning of the mammalian type II iodothyronine deiodinase. A selenoprotein differentially expressed and regulated in human and rat brain and other tissues. J Clin Invest 1996;98:242-3.