

ORIGINAL ARTICLES

Latent thyroid dysfunction in elderly patients with persistent nonvalvular atrial fibrillation

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Abstract: Purpose – The objective of this study was to evaluate the prevalence of subclinical thyroid dysfunction in patients(pts) aged over 60 admitted to a cardiology department for persistent atrial fibrillation (AF). **Methods** – Inclusion criteria were: age over 60, persistent nonvalvular AF, hospitalized within 6 months, beta blocker therapy at maximum dose. Exclusion criteria were: acute coronary syndromes, known thyroid disease, treatment with amiodarone, thyroid changes on ultrasound, congestive heart failure class III/IV, left ventricular ejection fraction (LVEF)<40%, severe comorbidities. In all patients cardiovascular history was noted, TSH, freeT4 (FT4) were determined and thyroid ultrasound was performed. Patients with TSH and FT4 within normal ranges were considered euthyroid, those with TSH below 0.1 mU/L and normal FT4 were diagnosed with clinically latent hyperthyroidism and those with TSH over 6.5 mU/L and normal FT4 with clinically latent hypothyroidism. **Results** – 290 patients were included, 52.2% men, mean age 72.14±12, mean LVEF 48.4±4%. 274 patients were euthyroid, 6(2%) had subclinical hypothyroidism and 10(3.44%) subclinical hyperthyroidism, with mean resting heart rate (HR) 10 beats/min more than euthyroid pts. **Conclusions** – Clinically latent hyperthyroidism was found in 3.4% of patients with persistent AF aged over 60, with higher prevalence than in the general population and higher rest HR than in euthyroid patients. Latent hypothyroidism was found in 2% of patients with persistent AF, to a lesser extent than in the general population.

Keywords: subclinical hyperthyroidism, subclinical hypothyroidism, atrial fibrillation, heart failure

Rezumat: Obiectivul lucrării – a fost evaluarea prevalenței disfuncției tiroidiene subclinice la pacienții cu vârsta de peste 60 de ani internați într-o secție de cardiologie pentru fibrilație atrială (FA) persistentă. **Metodă** – Criteriile de includere au fost: vârsta peste 60 de ani, FA persistentă nonvalvulară, internare în ultimele 6 luni, tratament beta blocant în doză maximă. Criteriile de excludere au fost: sindroamele coronariene acute, istoric de patologii tiroidiene, tratament cu amiodaronă în ultimele 6 luni, modificări ecografice tiroidiene, insuficiență cardiacă clasa III/IV, fracția de ejeție a ventriculului stâng (LVEF) <40%, comorbidități severe. S-au notat antecedentele cardiovasculare, s-au determinat TSH, freeT4 (FT4) și s-a efectuat ecografie tiroidiană. Pacienții cu TSH și FT4 normale au fost considerați eutiroidieni, cei cu TSH sub 0,1 mU/l și FT4 normal cu hipertiroidism latent clinic și cei cu TSH peste 6,5 mU/l și FT4 normal, cu hipotiroidism latent clinic. **Rezultate** – Au fost incluși 290 de pacienți, 52,2% bărbați, vârsta medie 72,14±12, LVEF medie 48,4±4%. 274 de pacienți au fost eutiroidieni. 6(2%) au prezentat hipotiroidism subclinic iar 10(3,44%) hipertiroidism subclinic, cu frecvența cardiacă (FC) medie de repaus cu 10 bătăi/min mai mare decât pacienții eutiroidieni. **Concluzii** – Hipertiroidismul latent clinic a fost prezent la 3,4% bolnavi cu vârsta peste 60 de ani și FA persistentă, cu prevalență mai mare decât în populația generală și cu FC mai mare decât la eutiroidieni. Hipotiroidismul latent a fost prezent la 2% dintre bolnavii cu FA persistentă, în proporție mai mică decât în populația generală.

Cuvinte cheie: hipertiroidism subclinic, hipotiroidism subclinic, fibrilație atrială, insuficiență cardiacă

BACKGROUND

Subclinical thyroid dysfunction is defined as asymptomatic thyroid tests abnormalities in people with no history of thyroid disease or treatment with thyroid hormones.

Subclinical hypothyroidism is defined by increased TSH levels over 6.5 mU/l concurrently with normal T4 and/or T3. Subclinical hyperthyroidism is defined by low TSH levels, generally below 0.1 mU/l, with normal T4 and/or T3¹. TSH determination as a screening test in the general population has low positive predictive

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value I and test interpretation is influenced by concomitant diseases that alter thyroid function. Subclinical hyperthyroidism is associated with atrial fibrillation, dementia, osteoporosis but not with progression towards overt hyperthyroidism¹. The association of subclinical hypothyroidism with faster development of atherosclerosis in adults is not clearly established¹.

In the general population the prevalence of subclinical hypothyroidism is of 5% in women and 3% in men, increasing with age, whilst the prevalence of subclinical hyperthyroidism is of 1% in men and 1.5% in women over 60 years¹.

Atrial fibrillation is the most common arrhythmia in the general population, with a prevalence of 1.5-2%, which increases with age². In the US, 12% of pts with atrial fibrillation are between 75 and 84 years old. Over 30% of pts with atrial fibrillation are over 80 years old³. Myocardial ischemia, atrial dilation, heart failure, overt hyperthyroidism are important factors involved in the occurrence of atrial fibrillation. It is possible that thyroid dysfunction may intervene in the occurrence of atrial fibrillation. Revealing subclinical thyroid dysfunction could have therapeutic consequences.

AIM

The objective of this study was to evaluate the prevalence of subclinical thyroid dysfunction in pts aged over 60 admitted to a cardiology department for persistent atrial fibrillation.

METHODS

Inclusion criteria were: age over 60 years, persistent nonvalvular atrial fibrillation- defined by atrial fibrillation lasting for more than 7 days, hospitalized within 6 months, beta blocker therapy for ventricular rate control. Exclusion criteria were atrial fibrillation in acute coronary syndromes, personal history of thyroid disease or thyroid hormone therapy, treatment with Amiodarone during the last six months, thyroid changes on ultrasound examination (appearance of thyroiditis, thyroid nodules over 2 cm), congestive heart failure class III and IV, left ventricular ejection fraction (LVEF) below 40%, severe comorbidities. We noted: demographics, history of arterial hypertension (AH), stable coronary artery disease (CAD), old myocardial infarction (OMI), diabetes mellitus (DM), echocardiographic data: left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI)- normal values less than 115 g/m² in men and less than 95 g/m² in women, serum cholesterol, ventricular rate (HR) at discharge

and also the drug therapy. In all pts TSH, free T4 (FT4) were determined and thyroid ultrasound was performed. Normal laboratory values were between 0.34-5.6 mU/ml for TSH and between 0.58-1.64 ng/dL for FT4. Patients with TSH and FT4 within normal ranges were considered euthyroid, those with TSH below 0.1 mU/L and normal FT4 were diagnosed with clinically latent hyperthyroidism and those with TSH over 6.5 mU/L and normal FT4 with clinically latent hypothyroidism.

Patients were divided into 3 groups according to TSH levels: G1, euthyroid (EuT), G2 clinically latent hypothyroidism (HipoT), G3 clinically latent hyperthyroidism (HiperT). The 3 groups were compared in terms of resting ventricular rate, of beta blockers doses needed to control ventricular rate, of LVEF. Statistical analysis was performed using Statistica⁸.

RESULTS

290 consecutive pts admitted within 6 month to the cardiology department for persistent nonvalvular atrial fibrillation were included in the study. Demographic data are shown in Table 1. 152 of the 290 pts (52.2%) were men. The mean age of pts was 72.14 ± 12 years, with no significant differences between women and men. 95.17% of pts had AH, 82.75% HF, 14.48% OMI, 89.65% CAD, 10.34% DM, 34.13% CKD. There were no significant differences between men and women regarding the age and history of AH, CAD. Male pts had significantly more often HF (59.21% in men versus 49.27% in woman, p<0.05), OMI (73.68% in men versus 26.8% in women, p<0.05), peripheral artery disease (PAD) (1.7% in men versus 0.6% in women, p<0.05), DM (71.7% in men versus 45% in women, p<0.05), CKD (55.9% in men versus 44.2% in women, p<0.05). Pts had increased LVMI. The mean resting heart rate at discharge was 78 ± 17/min, with no significant differences between men and women. Total serum cholesterol level was 254 ± 68 mg% ml, with no significant differences between men and women. All pts received treatment with beta blockers (metoprolol succinate, bisoprolol), ACEI or ARBs, statins and anticoagulants (Table 2). 95% of pts reached the maximum dose of the beta blocker therapy: metoprolol succinate 200 mg/day, bisoprolol 10 mg / day. 3.4% of pts received also digoxin for ventricular rate control.

Group 1 (EuT), included 274 pts. Group 2 (HipoT) consisted of 6 pts. Group 3 (HiperT) consisted of 10 pts. Patients with HipoT represent 2% of all pts and those with HiperT, 3.44%. Demographic data of the 3 groups are in Table 3. There were no significant diffe-

rences between the 3 groups regarding demographic data and medical history of cardiovascular disease. A higher proportion of pts in group G2 (HipoT), but not statistically significant, had DM and CKD. Serum cholesterol level was not statistically different between the 3 groups. LVEF was similar between the 3 groups. LVMI was increased in all 3 groups. Left atrial area was 21 ± 3 cm² in G1, 22 ± 2 cm² in G2 and $21,5 \pm 4$ cm² in G3 (p=ns). Pts in G3 had a mean resting HR of 10 beats/min higher than pts in G1 pts, on maximum doses of beta blockers (Figure 1).

DISCUSSION

Cardiovascular effects of thyroid hormones acting through genomic and non-genomic changes are well known⁴. Thyroid gland synthesizes thyroxine (tetraiodothyronine -T₄), which is transformed into triiodothyronine (T₃), the active form, within the peripheral cells by deiodination with 5 deiodinase. Cardiac myocytes cannot perform this conversion but T₃ can enter the myocyte as it enters other cells. Genomic effects are achieved by activation of transcription or by repression of genes encoding structural and functi-

Table 1. Demographic data of the pts included in the study

Pts	Total number (%)	Men(%)	Women (%)	p
No pts	290	152 (52.5)	138 (47.5)	ns
Mean age	72.14 (60-86) years	70.71 (60-85) years	73.56 (61-88) years	ns
Arterial hypertension (AH)	276 (95.17)	80 (52.6)	68 (49.27)	ns
Heart failure (HF) NYHA II	240 (82.75)	90(59.21)	66 (47.8)	< 0.05
Stable coronary artery disease(CAD)	260 (89.65)	79 (51.97)	67 (48.55)	ns
Old myocardial infarction (OMI)	42 (14.48)	112 (73.68)	37 (26.8)	< 0.05
Diabetes mellitus (DM)	30 (10.34)	109 (71.7)	62(45)	< 0.05
Chronic kidney disease (CKD)	99 (34.13)	85 (55.9)	61 (44.2)	<0.05
Peripheral artery disease (PAD)	5 (1.7)	17 (1,7)	1(0.6)	< 0.05
LVEF (%)	48.5±4	44±4	46±5	ns
LVMI (g/m ²)	122±15	130±20	115±20	na
Left Atria Area	21 +/- 3	22 +/- 2	21.5 +/- 4	ns
Resting cardiac rate (HR) /min	78±17	76±17	80±15	ns
Cholesterol (mg%ml)	254±68	260±55	250±50	ns

ns=nonsignificant

Table 2. Drugs used for rate control in pts over 60 years old with persistent atrial fibrillation

Pts	Total number and %	Man(%)	Woman (%)	p
No pts	290	152 (52.5)	138 (47.5)	ns
Metoprolol succinat	280 (96.55)	140 (92.1)	126 (91.3)	ns
Bisoprolol	10 (3.4)	12 (7.89)	12 (8.6)	ns

ns=nonsignificant

Table 3. Demographic data of pts in the 3 groups: G1-euthyroid; G2-hypothyroidism; G3-hyperthyroidism

	G1 (EuT)	G2 (HipoT)	G3 (HiperT)
total	274	6	10
%	94.48	2	3.44
Men (%)	145 (52.9)	2 (33.3)	5 (50)
Women (%)	128 (46.71)	4 (66.6)	5 (50)
Age	71.5 (60-88)	72.8 (61-83)	70.17 (60-84)
CAD (%)	247 (90.14)	5 (83)	8 (80)
HF (%)	227 (82.84)	5 (83)	8 (80)
OMI (%)	38 (13.86)	0	4 (40)
HTA (%)	268 (97.81)	3 (50)	5 (50)
Resting HR	78	76	88
LVEF	48.5±4	51.25	48.5
LVMI (g/m ²)	124±15	122±10	128±12
DM (%)	28 (10.2)	1 (16.6)	1 (10)
CKD (%)	95 (34.67)	2 (33)	2 (20)
Cholesterol(mg/dl)	254±68	225±70	234±66

CAD-coronary artery disease, stable; HF-heart failure; OMI-old myocardial infarction; AH- arterial hypertension; resting HR-resting heart rate, LVEF- left ventricular ejection fraction, CKD-chronic kidney disease

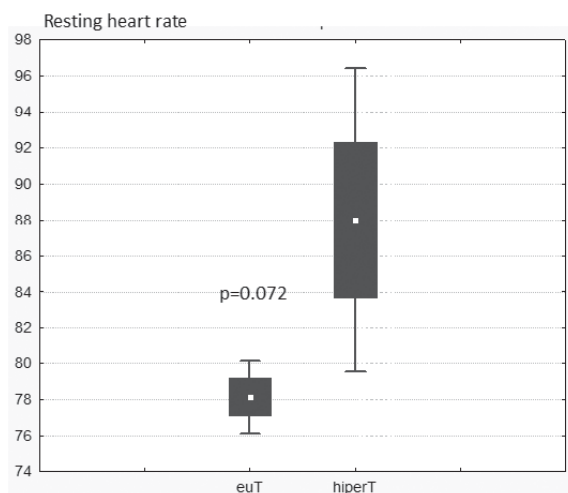


Figure 1. Resting heart rate compared in G1 (euT) and G3 (HiperT).

onal proteins. T3 enters the myocardial cells through specific membrane transporters, enters the nucleus, acting on nuclear receptor $\alpha 1$ (activator) and $\alpha 2$ (repressor). T3 - receptor complex engages or disengages from certain sequences of DNA. Expression of myosin heavy chains, sarcoplasmic reticulum protein involved in the regulation of intracellular calcium handling and phospholamban, its inhibitor are modified^{5,6}. There is an increase of the transcription of the myosin heavy chain (MHC) α gene and a decrease of the transcription of the MHC β gene. There is an increased synthesis of myosin VI isoform consisting of two α MHC having enhanced ATPase activity. There is a decrease in the synthesis of myosin V3 isoform consisting of two β MHC with low ATPase activity⁶. Calcium (Ca^{2+}) reuptake within the smooth endoplasmic reticulum is faster. T3 accelerates the speed of myocardial fiber contraction and relaxation and increase the consumption of ATP within the heart⁶. Nongenomic mechanisms are responsible for the faster actions of T3. They induce rapid phosphorylation of phospholamban and prevent its inhibitory action on sarcoplasmic reticulum ATPase activated by Ca^{2+} . This is done by intracellular kinases system, also involved in adrenergic activity, which explain the similarity of thyroid hormone effects with those of the adrenergic system⁴.

Evaluation of subclinical thyroid dysfunction is difficult because old age, stress, alcohol consumption, chronic inflammatory diseases, heart failure reduce T4 conversion to T3. Non-thyroid severe disease can cause false positivity for TSH tests¹. It was also found that TSH level in the elderly with subclinical hypothyroidism or hyperthyroidism is normalized by itself in a

few months^{1,7}, without being clear whether there are pathological implications. However, studies have shown that subclinical persistent changes of thyroid function induced myocardial pathological changes⁴. Subclinical hyperthyroidism is associated most commonly with the appearance of atrial fibrillation and left ventricular hypertrophy^{1,4}. Subclinical hypothyroidism is associated with dyslipidemia, atherosclerosis acceleration, slight increase in long-term myocardial infarction but statistically insignificant⁸. However, some studies have shown that in women with subclinical hypothyroidism serum levels of cholesterol are lower than in the euthyroid, which would imply the existence of other risk factors in a rapidly evolution of atherosclerosis, such as lipoprotein a (Lp (a)), homocysteine⁸.

We studied the prevalence of subclinical thyroid dysfunction, defined by TSH changes concurrently with normal FT4 in pts aged over 60 years and persistent atrial fibrillation. All pts had personal history of cardiovascular disease that may be associated with atrial fibrillation but we searched if there was any impact of possible thyroid dysfunction. We excluded pts with severe comorbidities, NYHA class III and IV heart failure, acute coronary syndromes, situations in which unexpected changes in TSH may arise. Most pts were euthyroid.

3.4% of pts over 60 years old with persistent atrial fibrillation had subclinical hyperthyroidism. This prevalence exceeds the prevalence of latent hyperthyroidism in the general population aged over 60, which is 1.5% in women and 1% in men¹. This is explained by selecting the population with atrial fibrillation. It was also noticed that latent hyperthyroidism was present both in women and in men. There were no demographic differences between the 3 groups of pts. Patients with latent hyperthyroidism had a mean resting heart rate of 10 beats/min higher than euthyroid pts, with the same doses of beta blockers. LVMI was increased, but with no differences between pts with different thyroid functional status. This is contrary to literature data⁸ describing the increase of the left ventricle muscle mass in pts with latent hyperthyroidism. One explanation could be the small number of pts with latent hyperthyroidism and also the associated cardiovascular diseases that induce left ventricular hypertrophy independent of thyroid function. Clinically latent hypothyroidism was present in 2% of pts with atrial fibrillation. The prevalence is lower than that of the general population but the small number of pts does not allow us to interpret this observation. Moderately elevated cho-

lesterol values were similar in the 3 groups, influenced by statin therapy.

There is no consensus in the literature whether clinically latent thyroid dysfunction should be treated.

CONCLUSIONS

Clinically latent hyperthyroidism was present in 3.4% pts over 60 years old with persistent atrial fibrillation. Its prevalence in pts with atrial fibrillation is greater than in the general population. Ventricular rate at rest was higher in the group with latent hyperthyroidism than in euthyroid pts, at the same doses of beta blockers. Latent hypothyroidism was present in 2% of pts with persistent atrial fibrillation, to a lesser extent than in the general population.

THE LIMITS OF THE STUDY

The low prevalence of subclinical thyroid dysfunction in our group of 290 pts makes interpretation of data difficult and we could not determine the appropriateness of initiating the hormonal treatment. We did not perform echographic assessment of the left atrial strain and of the left atrial functions (conduit, reservoir and pump).

Conflict of interest: none declared.

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