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Cent. Eur. J. Med. • 8(6) • 2013 • 742-748
DOI: 10.2478/s11536-013-0235-9

Central European Journal of **Medicine**

Thyroid dysfunction and cardiovascular risk factors in Bulgarian adults

Research Article

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Received 6 September 2012; Accepted 27 May 2013

Abstract: The aim of this study was to determine the prevalence of thyroid dysfunction and its association with cardiovascular risk factors in an adult Bulgarian population. 2402 subjects were studied, 1347 female, 20-94y (median: 48.0y) and 1055 male, 20-91y (median: 45.5y). Body weight, height, waist circumference, arterial blood pressure, TSH, FT4 and lipids were measured. Known hypothyroidism was reported by 53 subjects (2.2%) and hyperthyroidism by 20 (0.8%). New hypothyroidism was found in 98 (4.1%), [subclinical (3.2%), overt (0.9%)]. New hyperthyroidism was found in 68 (2.9%), [subclinical (2.5%), overt (0.4%)]. New diagnosis of hypothyroidism and hyperthyroidism was entered in 84% and 87% in male subjects and 60% and 65% in the females respectively. Arterial hypertension was present in 40% of the women and in 47% of the men ($p<0.001$) and was more prevalent in hypothyroidism. Abdominal obesity and dyslipidemia were more prevalent in males and hypothyroid subjects. Arterial hypertension depended on age, gender and lipid status but not on thyroid function. CHD history depended on thyroid function and age. Conclusion: Most cases of thyroid dysfunction were undiagnosed, especially in the males. CV risk factors were more prevalent in the males with thyroid dysfunction a major determinant of CHD, but not hypertension.

Keywords: *Thyroid dysfunction • Hypothyroidism • Cardiovascular disease risk factors • Hypertension*

1. Introduction

Thyroid dysfunction is among the most common endocrine disorders. The prevalence of hypothyroidism varies between 2.98% [1] and 21.8% [2] depending on age and gender of the studied population. All authors report higher prevalence in females and the female to male ratio varies in wide ranges. Mayer et al. [3] found hypothyroidism in 13.8% of the females and 6.8% of the males. In their study in Quebec, Gagnon F. et al. report 10.8% in the females and 2.9% in the males [2], while lower ratios were observed in the Colorado Study (4% and 3% respectively for the younger group and 21% and 16% in the elderly) [4].

Both subclinical and overt thyroid dysfunction are known to be associated with an increased cardiovascular (CV) risk [5,6]. The effect is probably age-dependent. It is observed in both genders and could add in certain age groups to the global cardiovascular risk, contributing to the CV morbidity and mortality. It is well known that male gender is linked to higher CV risk. The difference between men and women decreases after the menopause in the latter but it nevertheless remains a major factor for the shorter life expectancy in men.

The aim of the current paper was to study the prevalence of thyroid dysfunction and its gender distribution in an adult Bulgarian population with a stress on the undiagnosed disease. The link of thyroid dysfunction to co-existing CV risk factors as arterial hypertension and abdominal obesity was sought.

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2. Materials and methods

The participants in the study were recruited in two major Bulgarian cities with predominantly urban population and four smaller towns with the adjacent villages with mixed urban and rural population in January/February 2006. The total number of participants and their gender and age distribution were planned according to the most recent population data, published by the National Statistical Institute [7]. The numbers of participants in each location were similar with the exception of Sofia, where a larger number was allocated due to the higher population density. The local endocrine practices were involved in the subject recruitment. They sent invitations to the staff of the local municipalities, schools, police, fire brigade, larger factories and the retired subjects' organizations, ensuring participation from a great variety of social, economic and cultural backgrounds.

The study was performed by the same team at all locations within a two-month period, ensuring a standardized workflow, thus decreasing methodological errors. The study team included three physicians, three study nurses and technical assistants from the University Hospital of Endocrinology to the Medical University of Sofia. Each participant signed an informed consent form, approved by the local Ethics Committee.

All studied subjects filled a structured interview form including data on current disorders and medication use, personal and family medical history, smoking and reproductive history in the females. Separate questions were included especially on current or past thyroid disorders and medication influencing the thyroid (thyroid hormone preparations, antithyroid drugs, amiodarone, lithium) as well as cardiovascular disorders, medication and CV risk factors.

Body height, body weight and waist circumference (WC) were measured and body mass index (BMI) was calculated using the standard formula. Arterial blood pressure was measured by a mercury sphygmomanometer in a seated position after a 10-minute rest.

Increased WC as a measurement of abdominal obesity was defined according to International Diabetes Foundation (IDF) criteria – equal or above 80 cm for women (A) and equal or above 94 cm for men.

Arterial hypertension (AH) was determined as systolic arterial blood pressure above 140 mmHg and diastolic pressure above 90 mmHg and/or current antihypertensive medication. A history of ischemic episode or antianginal medication was assumed as a positive history for coronary heart disease (CHD).

2.1 Laboratory tests

Fasting blood was drawn in all participants between 8 and 10 a.m. Serum TSH was determined by a microparticulate immunoenzyme analysis (MEIA) at an automated analyser AxSYM, (ABBOTT, USA). TSH reference range was 0.39-4.20 mUI/L and it was accepted as a criterion for euthyroid state. Serum FT4 was determined in subjects with TSH outside the reference range, by a microparticulate immunoenzyme analysis (MEIA) at an automated analyser AxSYM, (ABBOTT, USA). FT4 reference range was 9.0-19.0 pmol/l.

Subjects with TSH values below 0.39 mU/l were grouped as hyperthyroid and those with values above 4.20 – as hypothyroid. Subclinical hypothyroidism was defined as TSH >4.20 mU/l with normal FT4 levels (9.0-19.0 pmol/l) and overt hypothyroidism – as TSH>4.20 mU/l with FT4 <9.0 pmol/l. Subclinical hyperthyroidism was defined as TSH <0.39 mU/l with normal FT4 levels (9.0-19.0 pmol/l) and overt hyperthyroidism – as TSH <0.39 mU/l with FT4 >19.0 pmol/l.

Serum total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were determined by standard enzyme methods and the HDL and LDL by direct enzyme assay. Test kits produced by HUMAN (Germany) were applied at an automated analyzer Cobas Mira Plus (ROCHE, Switzerland).

2.2 Statistical methods

All data are presented as means and standard deviation or median, minimum and maximum depending of normality of distribution. The latter was assessed by the Kolmogorov-Smirnov test. Frequency analysis was utilized when appropriate. One-sample independent variable t-test was applied for comparison of independent variables. Nonparametric tests and binary logistic regression analysis were used for categorical data. Two-sided p-values below 0.05 were considered as statistically significant. In all tests 95% confidence intervals were applied. The data processing was done by SPSS for Windows v. 13. (SPSS Inc., Chicago, Il, USA).

3. Results

Two thousand four hundred and two adults at median age 47.7 y (20-94) were enrolled into the study. Of them 1347 (56%) were female, median age 48.0 y (20-94) and 1055 (44%) were male, median age 45.5 y (20-91), p<0.001. The anthropometric data are presented in Table 1.

Table 1. Anthropometric and laboratory data of the studied subjects.

Studied parameter	Total group	Female	Male	P
	Mean±SD	Mean±SD	Mean±SD	M/F
BMI (kg/m²)	26.9±5.1	26.3±5.5	27.7±4.3	<0.001
Waist circumference (cm)	90.2±13.9	84.4±13.0	97.5±11.4	
Systolic pressure (mmHg)	131.7±18.7	129.8±19.9	134.2±16.6	<0.001
Diastolic pressure (mmHg)	84.0±12.0	82.0±12.0	86.5±11.5	<0.001
TSH (mU/l)	1.99±4.60	2.10±3.75	1.84±5.49	NS
tChol (mmol/l)	5.51±1.19	5.52±1.19	5.49±1.20	<0.001
HDLc (mmol/l)	1.38±0.35	1.48±0.34	1.24±0.31	NS
LDLc (mmol/l)	3.23±0.98	3.17±1.00	3.31±0.96	<0.001
Tgl (mmol/l)	1.38±1.20	1.14±0.70	1.68±1.57	<0.001

3.1 Thyroid function

The overall prevalence of hypothyroidism was 6.3% (151 subjects) and that of hyperthyroidism - 3.7% (88 subjects). In 53 (2.2%) of the subjects there was a history of hypothyroidism and in 20 (0.8%) – of hyperthyroidism. Elevated TSH was found in 98 of the subjects without history of thyroid dysfunction (4.1%) and suppressed TSH – in 68 (2.9%) (Table 2). Eighty-four per cent of the hypothyroidism and 87% of the hyperthyroidism in the males and 60% and 65% in the females were newly-diagnosed.

The hypothyroidism was subclinical in 76 (3.2%) of the newly diagnosed cases and overt in 22 (0.9%). The hyperthyroidism was subclinical in 59 (2.5%) of the newly diagnosed subjects and overt – in 9 (0.4%).

3.2 Serum lipids, BMI and waist circumference

The lipid levels are presented in Table 1. Elevated total cholesterol levels above 5.20 mmol/l were found in 59.6% of the subjects with suppressed TSH, in 56% of the euthyroid subjects and in 65% of the ones with elevated TSH (Pearson chi-square p=0.042 for the pair euthyroid/hypothyroid). The prevalence of elevated cholesterol and triglycerides in both genders is presented in Table 3. No significant differences were observed between the genders and within genders except for the hypertriglyceridemia prevalence between the genders.

Table 2. Types of Thyroid Dysfunction in the studied subjects by gender.

	Total	Female	Male
	N (%)	N (%)	N (%)
Overt Hypothyroidism	22 (0.9%)	13 (1.0%)	9 (0.9%)
Subclinical Hypothyroidism	76 (3.2%)	59 (4.4%)	17 (1.6%)
Known Hypothyroidism	53 (2.2%)	48 (3.6%)	5 (0.5%)
Euthyroid	2163 (90.0%)	1180 (87.6%)	983 (93.2%)
Subclinical Hyperthyroidism	59 (2.5%)	27 (2.0%)	32 (3.0%)
Overt Hyperthyroidism	9 (0.4%)	4 (0.3%)	5 (0.5%)
Known Hyperthyroidism	20 (0.8%)	16 (1.2%)	4 (0.4%)
Total	2402	1347	1055

BMI was significantly higher in the subjects with overt hypothyroidism (30.1 kg/m²) as compared to those with subclinical (27.1 kg/m², p=0.011), the euthyroid subjects (26.9 kg/m², p=0.04) and the subclinically hyperthyroid (26.3 kg/m², p=0.001). Increased waist circumference was observed in 811 (60.2%) of the females and 667 (63.2%) of the males (NS). The differences between the genders were not significant in the different thyroid function groups. No significant differences were found among the three thyroid function groups either. The prevalence of abdominal obesity in the groups with overt and subclinical hypothyroidism was 82% and 66% (NS).

3.3 Arterial blood pressure and CHD history

Arterial hypertension was found in 1034 subjects (43%). It was more prevalent in the males (496 subjects, 46.9%) than in the females (538 subjects, 39.9%) (p<0.001). Newly diagnosed AH was also more common in the males (222 subjects, 44.8% of the hypertensive men) than in the females (132 subjects, 24.5% of the hypertensive women), p<0.01. Among the hypothyroid females, 50.8% were hypertensive vs. 38.9% of the euthyroid (p=0.011). Sixty six percent of the hypothyroid males were hypertensive vs. 46% for the euthyroid (p=0.028). The logistic regression analysis showed

Table 3. Prevalence of hypercholesterolemia and hypertrigyceridemia in the studied population by gender and thyroid function.

Gender		Elevated Cholesterol		Elevated Triglycerides		Total
		<= 5.2	>5.2	<=1.7	>1.7	
Female	Euthyroid	502 (42.7%)	674 (57.3%)	988 (84.1%)	**187 (15.9%)	1175
	Hypothyroid	42(35%)	78(65%)	95(79.2%)	25(20.8%)	120
	Total	544(42.0%)	752(58.0%)	1083(83.6%)	*212(16.4%)	1295
Male	Euthyroid	446 (45.6%)	531 (54.4%)	644 (66.0%)	**332 (34.0%)	976
	Hypothyroid	12 (37.5%)	20 (62.5%)	22 (68.75%)	10 (31.25%)	32
	Total	458 (45.4%)	551 (54.6%)	666 (66.1%)	*342 (33.9%)	1008

** and ** p<0.001*

dependence of the arterial hypertension on abdominal obesity, dyslipidemia, age and male gender, but not on smoking status and thyroid function (Table 4). The differences of the hypertension prevalence between the groups with overt and subclinical hypothyroidism were not significant (59% and 54%, NS).

No difference in the prevalence of CHD history was found between the genders. The logistic regression analysis showed dependence of the positive CHD history on suppressed TSH and age, but neither of the other factors.

4. Discussion

By tradition thyroid disease – both autoimmune and non-autoimmune with few exceptions has been widely discussed as a "female domain" [8]. O'Leary et al. for instance investigated the male to female ratio in different age groups and found hypothyroidism in 12.8% of the elderly females and 3.6% in the elderly males. The percentage was much smaller in younger subjects but the gender difference persisted (2.5% of the younger women and 1.6% of the younger men were hypothyroid). Several large studies have revealed relatively high prevalence of thyroid dysfunction among males as well [3,4,9]. We found thyroid dysfunction in a comparatively high proportion of the studied males, close to the numbers reported by Canaris et al. [4].

We observed a very high proportion of previously undiagnosed thyroid dysfunction (61.2% of the hypothyroid subjects and 73.5% of the hyperthyroid subjects). Though thyroid dysfunction was more prevalent in the females (12.4%), than in the males (7.4%), the percentages of newly diagnosed hyperthyroidism and hypothyroidism were higher in the latter. Eighty-four per cent of the hypothyroidism and 91% of the hyperthyroidism in the males were unknown and therefore untreated. In the females hypothyroidism was newly diagnosed in 60% and hyperthyroidism – in 68.6%. As a comparison, Empson et al. [10] reported the opposite ratio. They found previously diagnosed hypothyroidism in 10% of the studied elderly population and only 3.6% new cases. It is well known, that the lack of specific symptoms may prevent the early diagnosis of thyroid dysfunction, especially bearing in mind that in the majority of the cases the thyroid dysfunction is subclinical, as we observed with our series. Approximately 20% of the respective dysfunction was overt and 80% - subclinical. Subclinical thyroid disease is such by definition, but a large proportion of the subjects experience subtle or more pronounced signs and symptoms [11]. Thus careful history and clinical examination can direct the attention of the physician towards a possible thyroid dysfunction. That is especially crucial for the elderly.

It is well known that men do not engage as unwillingly in regular prevention medical checks and tests, despite all the available data demonstrating the benefit of the latter [12]. The latter observation explains why we found, among the subjects with thyroid dysfunction, a larger proportion of men with previously unknown disease than women.

One factor that needs elaboration when discussing thyroid dysfunction is the iodine state of the population. Approximately half of the Bulgarian population lives in an iodine deficient environment. With the successful implementation of a national program of iodine supplementation virtually all of the population currently has a sufficient iodine intake [13]. Unfortunately no consistent data on thyroid disorders prevalence for the previous decades is available, and a comparison based on the changed iodine state is not possible. The data

Table 4. Binary logistic regression analysis. Arterial hypertension and CHD history are the dependent variable and thyroid function, Triglycerides >1.7 mmol/l, cholesterol >5.2 mmol/l, smoking, male gender and increased waist circumference are the independent. The reference category for thyroid function is euthyroidism, The reference category for age group is 20-44 y. R-square for the arterial hypertension model is 0.379 and for the IHD it is 0.354.

Factor	Arterial Hypertension				History of CHD			
	p	Odds Ratio	95.0% C.I.for Odds Ratio		p	Odds Ratio	95.0% C.I.for Odds Ratio	
			Lower	Upper			Lower	Upper
Thyroid function (elevated TSH)	.684	.86	.43	1.75	0.224	1.50	0.78	2.86
Thyroid function (suppressed TSH)	.341	.79	.49	1.28	0.038	2.27	1.05	4.93
Increased triglycerides	<0.001	1.96	1.50	2.55	0.689	1.09	0.70	1.71
Male gender	<0.001	1.60	1.27	2.01	0.244	1.29	0.84	1.96
Increased total cholesterol	<0.001	1.55	1.23	1.95	0.370	0.82	0.53	1.27
Increased WC	<0.001	3.04	2.39	3.86	0.106	1.53	0.91	2.56
Smoker status	.096	.82	.65	1.04	0.321	0.76	0.45	1.30
Age group (middle age)	<0.001	4.38	3.41	5.61	<0.001	36.00	4.85	267.16
Age group (elderly)	<0.001	10.69	7.73	14.78	<0.001	292.55	40.08	2135.21
Constant	<0.001	.09			<0.001	0.001		

from other countries demonstrate marked differences between iodine deficient and iodine sufficient regions and a transition in the thyroid morbidity that could be expected in areas of previous iodine deficiency [14-17].

An association between thyroid dysfunction and cardiovascular disease has been well established, though data are frequently contradictory [5,18-20]. A possible explanation of the diverse results is the confounding by various additional factors, age being by far the most important, especially in subclinical hypothyroidism. In a reanalysis of the Wickham study, Ravzi S et al. [21] demonstrate clearly an association between ischemic heart disease and subclinical hypothyroidism. Their observations confirm the conclusions of two earlier meta-analyses. Singh S et al. [22] and Ochs N et al. [23] found in them an increased CV morbidity and mortality in association with subclinical hypothyroidism. The authors' conclusions however diverge concerning subclinical hyperthyroidism. As both thyroid dysfunction and cardiovascular morbidity increase with age, it could be speculated that there may be two parallel and independent phenomena. To address this issue we explored several logistic regression models with arterial hypertension or history of CHD as dependent variable and thyroid dysfunction as an independent. We found no significant association between thyroid function and hypertension. CHD history was more prevalent in the subjects with both hypothyroidism (OR 1.5) and hyperthyroidism (OR 2.27). Several recent publications suggest that CV morbidity and mortality is increased with subclinical hypothyroidism in middle-subjects [25]. While subclinical hyperthyroidism is an independent risk factor for CV morbidity and all-cause mortality in all age groups, there is compelling evidence, that links subclinical hypothyroidism to better survival in subjects, over the age of 70 or 80 [19,24,26]. As a result, the adoption of a higher upper reference limit for TSH in the elderly has been recently advised [27]. The number of hypothyroid and hyperthyroid subjects in our study was relatively small and therefore a type II error cannot be excluded, especially when comparing the subjects overt to those with subclinical hypothyroidism or the euthyroid subjects.

We observed a higher OR of arterial hypertension in the males (1.60, 1.27 to 2.01, Table 4) and a higher prevalence of hypertension in the hypothyroid subjects in both genders. Hypothyroidism may induce diastolic hypertension by increasing the peripheral vascular resistance, but also through the influence on the renin-angiotensin-aldosterone system, the atrial natriuretic peptide and vascular properties. That complexity indicates, that increased systolic blood pressure probably reflects more profound large artery hemodynamic alterations in the hypothyroid subjects [28]. Several authors report both higher systolic and higher diastolic arterial pressure in hypothyroid subjects, as well as a positive correlation between arterial blood pressure and TSH [29,30]. In our series TSH did not correlate with either systolic, or diastolic arterial pressure that may be explained by the small subject number.

We demonstrated a trend to a higher prevalence of abdominal obesity in the hypothyroid group and the observation was more apparent in the male subjects. In contrast to WC, the correlation of BMI to thyroid function was more apparent. Some links between hypothyroidism and obesity have been reported, but a clear causal relationship between high-grade obesity and thyroid dysfunction has not been established [31]. In our cohort for instance a weak positive correlation with TSH levels was observed in the euthyroid women. A similar trend was reported by Fox et al. [32]. Clearly, the changes in thyroid hormone levels cannot out-weight the impact of other factors related to body weight control and obesity. A possible pathogenetic association between hypothyroidism and body fat is suggested by the reported increased insulin resistance in hypothyroid patients [33]. As abdominal visceral fat is related to impaired insulin sensitivity, we can assume a possible similar association in our group, though we have not measured insulin sensitivity.

Moreover, the link between thyroid dysfunction and obesity possibly follows a two way model. Obesity leads to multiple metabolic alterations, which increase the risk of developing diabetes and cardiovascular diseases. Altered thyroid function tests and structure have been often described in obese children and adults. It is not clear however whether the altered thyroid function is the cause or the consequence of fat excess [34]. An interesting hypothesis has been proposed by Duntas L and Biondi B [35], who describe a CNS and leptin-dependent effect of obesity on thyroid autoimmunity. Nevertheless, both functional and structural alterations seem to improve after weight loss and therefore usually no treatment is needed.

We did not find a correlation between total cholesterol levels and TSH. LDL and HDL cholesterol levels suggested a more atherogenic lipid profile in the males, despite the lack of differences in the total cholesterol levels between the genders.

The study has several limitations that preclude more generalized conclusions. 1. A possible selection bias can be discussed due to the recruitment procedure. A shift in the estimation of the disease prevalence may be caused by the partially voluntary recruitment procedure, more probably in the direction of overestimating disease prevalence (possibly, more subjects with morbidities volunteering). 2. Despite the relatively large studied popula-

tion, the absolute numbers of the subjects with thyroid dysfunction and CVD risk factors are small, especially if stratified by age. This makes statistical processing of the small subgroups unreliable. The real hypothyroidism and hyperthyroidism prevalence may deviate from the estimated since transient mild thyroid dysfunction on the one hand and transient suppressed TSH on the other cannot be ruled out without a longitudinal follow up. 3. Finally, the self-reported subject history should always be accepted with reserves, therefore both under- and overestimation of CVD prevalence is possible. The adopted criteria were aimed at reducing the possible overestimation error, but we cannot rule out certain underestimation of undiagnosed atherosclerotic artery disease.

5. Conclusions

This is the first population-based study of thyroid morbidity and certain CV risk factors in Bulgaria. We found a high proportion of undiagnosed thyroid dysfunction, especially in the males. The CV risk factors were more prevalent in the males and they were clearly associated with hypothyroidism and less so with hyperthyroidism. Despite the fact that thyroid dysfunction is more common in the women, it seems that it is time to reassess our views. Both hypothyroidism and hyperthyroidism may add to the CV risk in the males, especially when other risk factors are present. Thyroid function testing recommendations in high risk men and careful clinical assessment thus seem worth discussing.

Conflict of interests

The work was supported solely by the Bulgarian Society of Endocrinology and it did not receive any other specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

We would like to thank the following participants in the study: Kristina Pantcheva, Gergana Antalavitcheva, Tatiana Kornilova, Donka Bogilova, Elena Stavreva. The study was conducted, analyzed and interpreted by the investigators independent of the industry.

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