Borderline low thyroid function and thyroid autoimmunity

Risk factors for coronary heart disease?

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SUMMARY Assessments were made of 945 consecutive hospital patients with regard to a relation between borderline low thyroid function (recognised by a slightly raised thyroid stimulating hormone), thyroid autoimmunity, serum cholesterol, and coronary heart disease. Men and women with a thyroid stimulating hormone of 4.0 mU/l or over had a higher prevalence of coronary heart disease than did age-matched controls, and this difference was significant in women. The excess of coronary heart disease was not explained by an excess of other risk factors such as a high cholesterol, hypertension, smoking, and diabetes. Women with thyroid antibodies had a slightly higher prevalence of coronary heart disease despite the unexpected finding of a lower serum cholesterol. The data point to an association between borderline thyroid function and autoimmunity and coronary heart disease which is not mediated through a raised serum cholesterol.

In hospital patients with coronary heart disease and in patients who died of myocardial infarction, Basténié *et al.*¹ have found a higher prevalence of thyroid antibodies and lymphocytic thyroid infiltrates than in matched controls. In a cohort of Finnish men aged 60 to 69 years thyroid antibodies were again correlated with the prevalence of coronary heart disease and with its incidence over a five year period.² Thyroid antibodies were also associated with known risk factors of coronary heart disease, such as diabetes, hypertension, smoking, and obesity. After correction for these associations thyroid antibodies remained a separate risk factor in women in Belgium and in men in Australia.^{3,4} Because of these complex interactions and conflicting findings, thyroid antibodies have not been undisputed as risk factors for coronary heart disease.⁵⁻⁷ None the less, the possibility that thyroid antibodies cause minor degrees of thyroid failure^{2,8,9} and hypercholesterolaemia and coronary heart disease as a consequence cannot be dismissed.¹⁰ We therefore measured thyrotropin (TSH) as the most sensitive test for mild thyroid failure in a non-selected hospital population and correlated the values with the serum cholesterol and the presence of thyroid antibodies and coronary heart disease. Preliminary data have already been published.¹¹

Methods and patients

Serum cholesterol (Boehringer cholesterol oxidase test kit) and basal TSH (radioimmunoassay test kit of Byk-Mallinckrodt, lowest detectable value 0.6 mU/l, interassay variation 6.7%) were measured in all patients entering the Department of Medicine of the Bürgerspital Solothurn from 15 February to 31 October 1977. Measurements were performed on the first available blood specimen which, often, but not always, was taken in the fasting state. In patients with a TSH of 4.0 mU/l or over and in a corresponding number of age- and sex-matched controls with a TSH below 4.0 mU/l thyroid antibodies in serum were determined. Titres against thyroglobulin (kit of Burroughs Wellcome) of 1:40 and against microsomal antigen (kit of Fujizoki, Japan) of 1:400 or over were considered positive.¹² Two of us (MT, GAL) independently examined the records of all patients for coronary heart disease without knowledge of the TSH values and antibody status according to the following criteria: (a) *Definite* coronary heart disease indicated by typical Q waves of previous infarction with or without corresponding history; ischaemic ST segment alterations in the absence of digitalis medication with typical anginal chest pain; acute myocardial infarction documented by serial electrocardiograms

and serum creatine kinase values. (b) *Probable* coronary heart disease indicated by bundle-branch block, disturbances in atrioventricular conduction or changes in ST segment, together with atypical chest pain, if not otherwise explained. (c) No coronary heart disease: no pathological Q waves and no ST segment changes in the electrocardiogram, no chest pain or unexplained cardiac failure. Known risk factors were tabulated for each patient from his clinical chart. Hypertension was considered present when the blood pressure exceeded 150 mmHg systolic and 95 mmHg diastolic or when the patient had previously documented and treated hypertension. Persons smoking 6 g or more of tobacco daily were considered smokers. Patients on over 20 units insulin daily or on oral hypoglycaemic drugs were classified as diabetics. The patient data were punched on cards and evaluation as well as age and sex matching was performed by computer, using the P-STAT Computing System (University of Basel Calculating Center).¹³ Mean ages and standard deviations were very similar in subjects at risk and controls, attesting to the quality of the matching (Tables 1, 2, and 4).

Results

During the study period there were 1298 admissions to our department; 179 of them entered the hospital twice during the study period and in 174 a blood sample could not be drawn, leaving 945 patients (469 women and 476 men) for analysis. The median age was 65 years.

Not unexpectedly, the prevalence of coronary heart disease in this elderly hospital population was quite high, depending mainly on sex and age (Fig. 1). This underlines the necessity for the strict age and sex matching used in the following analysis of risk factors. Fig. 2 shows that the distribution of the TSH values of the study population peaks around 2.5 mU/l. There is a small secondary peak of unknown significance between 4 and 6 mU/l. To document the sensitivity of the assay the TSH values of 29 hyperthyroid outpatients (not part of the study) measured in the same laboratory during the same period are also plotted in Fig. 2. Half of the hyperthyroid patients have a TSH of 1.0 mU/l or lower and all but two have a TSH below 2.5 mU/l. Thus, the division chosen for later analysis (4 mU/l) is in a range where the TSH assay used here is sufficiently sensitive. In agreement with others¹⁴ we also established that the mean TSH values in our population did not change with age, rendering unnecessary age adjustments of this variable.

The study patients were divided into three TSH groups: group 1 with a TSH <4.0 mU/l; group 2 with a TSH 4.0 to 5.9 mU/l; group 3 with a TSH ≥6 mU/l.

Fig. 1 Prevalence of coronary heart disease in different age groups of male (top) and female (bottom) patients.

Table 1 Serum cholesterol and coronary heart disease in women with thyroid antibodies and in age-matched controls

	No. of patients	Coronary heart disease		Cholesterol $\pm$ SD (mmol/l)	Age Mean $\pm$ SD (y)
		Definite	Sum of definite and probable cases		
Women with antibodies	30	11	14	4.58 $\pm$ 1.38	62.7 $\pm$ 11.8
Women without antibodies	30	8	12	5.22 $\pm$ 1.70	62.6 $\pm$ 11.7

Table 2 Coronary heart disease in subjects with a TSH of 4.0 mU/l or over compared with age-matched controls

		Definite coronary heart disease		Sum of definite and probable cases of coronary heart disease		Age Mean $\pm$ SD (y)
No. of patients		No.	%	No.	%	
Men:						
TSH $\geq$ 4.0 mU/l	69	33	47.8	44	63.8	60.5 $\pm$ 18.8
TSH < 4.0 mU/l	137*	52	37.9	73	53.3	60.9 $\pm$ 18.3
Women:						
TSH $\geq$ 4.0 mU/l	68	25**	36.8**	30	44.1	58.7 $\pm$ 14.4
TSH < 4.0 mU/l	136	27	19.8	48	35.3	58.8 $\pm$ 14.4

* For one subject only one matching partner was found; the other subjects at risk were matched with two controls each.

**p < 0.01 when compared by χ^2 test with controls with a TSH < 4.0 mU/l.

of antibodies was so low in comparison to the prevalence of coronary heart disease that thyroid antibodies were dropped from further analysis as a risk factor. In women the prevalence of thyroid antibodies was 16.7%, 17.1%, and 54.5% in TSH groups 1, 2, and 3. Thus, thyroid autoimmunity appears to be a frequent cause of borderline thyroid failure in women.

Table 1 shows that women with thyroid antibodies unexpectedly had a lower serum cholesterol, and despite this a slight preponderance of coronary heart disease, but neither one of the differences was statistically significant.

Men and women with a TSH of 4 mU/l or over have a higher prevalence of coronary heart disease when compared with age- and sex-matched controls with a lower TSH (Table 2). The difference, however, was significant only in women with definite coronary heart disease.

Table 3 analyses coronary risk factors of patients and matches of Table 2. Patients in the high TSH groups had a mean cholesterol similar to the controls. In addition, the percentage of patients with other risk factors for coronary heart disease was comparable in both groups, with the exception of a slight excess of

smokers and a slight deficit of diabetics in the high TSH group (both differences not significant).

For comparison, Table 4 tabulates the association of cholesterol with coronary heart disease in our patients. Men and women in the uppermost cholesterol quartile have a higher prevalence of definite coronary heart disease than age-matched controls from the lower two quartiles, but the association is significant in women only.

Discussion

Thyroid antibodies at titres which we consider significant¹² are so rare in the male population studied here that they can at best be a risk factor for only a small minority of our patients with coronary heart disease. This does not disprove the claim of others that thyroid antibodies in men are associated with coronary heart disease.¹⁻³ Rather it suggests that in our elderly population other risk factors assume an overwhelming importance. It is worth noting that male populations which showed an association between antibodies and coronary heart disease also had a much higher prevalence of thyroid antibodies than ours.^{2,3}

Table 3 Risk factors for coronary heart disease in subjects of Table 2

	No. of patients	Serum cholesterol Mean $\pm$ SD (mmol/l)	% of patients with hypertension	Diabetes	Smoking	Thyroid antibodies
Men:						
TSH $\geq$ 4.0 mU/l	69	4.91 $\pm$ 1.70	13.0	10.0	70.6	1.4
TSH < 4.0 mU/l	137	4.78 $\pm$ 1.47	21.9	12.4	59.0	6.4
Women:						
TSH $\geq$ 4.0 mU/l	68	5.27 $\pm$ 1.59	27.9	8.8	27.2	30.0
TSH < 4.0 mU/l	136	5.31 $\pm$ 1.70	27.2	17.6	22.7	11.8

Table 4 Prevalence of coronary heart disease in different cholesterol quartiles—patients from uppermost quartile were age- and sex-matched with patients from lower two quartiles

	Cholesterol	No. of patients	Definite coronary heart disease No.	Sum of definite and probable cases of coronary heart disease No.	Age Mean $\pm$ SD (y)
Men	Uppermost quartile	109	44	59	57.7 $\pm$ 15.0
	Lower two quartiles	109	38	54	57.9 $\pm$ 14.9
Women	Uppermost quartile	123	48*	68**	60.0 $\pm$ 16.3
	Lower two quartiles	123	31	47	60.0 $\pm$ 16.2

* $p < 0.025$.** $p < 0.01$ when compared by χ^2 test with women of lower two quartiles.

Antibodies were determined only in a fraction of our study population (see "Methods"). The relatively small number of patients available for matching might be the reason why the increased prevalence of coronary heart disease in women with antibodies was not statistically significant (Table 1). Even so, we consider our data at least compatible with earlier claims of an association between antibodies and coronary heart disease.¹⁻⁴ It is noteworthy in this context that even in Basténie's studies the association of thyroid antibodies and coronary heart disease was significant only in prospective analysis and not in his cross-sectional surveys comparable to ours.^{2,3} The relation between borderline low thyroid function or thyroid antibodies on one hand and serum cholesterol on the other is controversial. Some authors have found a higher cholesterol in patients with thyroid antibodies or borderline low thyroid function,^{1,10,15,16} while others found cholesterol unchanged or even lowered under these circumstances.^{3,9,17,18,19} Our data in Tables 1 and 3 agree with the latter view, since neither thyroid antibodies nor a TSH over 4 mU/l were associated with a change in cholesterol. The distribution of the TSH values (Fig. 2) closely resembles that reported by Tunbridge *et al.*¹⁴ About 15% of our patients have a TSH above 4 mU/l. While it is generally agreed that a TSH over 6 mU/l points to incipient thyroid failure, the thyroid status of persons with a TSH between 4 and 6 mU/l remains open to discussion. It is unknown whether they have metabolic abnormalities or any other sign of lower thyroid function when compared with persons with a TSH below 4 mU/l. We have used this cut-off value for three reasons: first there was a secondary incidence peak around this value, second we were confident that our assay was sufficiently sensitive at this value (Fig. 2), and, third it produced a sufficient number of subjects at risk. A higher cut-off at 6 mU/l gave basically the same results, that is an increased prevalence of coronary heart disease in persons with the higher TSH (data not shown), but the number of subjects at risk became too small (about 5% of the patients) compared with the high number of patients with coronary heart disease. The significantly

higher prevalence of definite coronary heart disease in women with a TSH of 4.0 mU/l or over (Table 2) cannot be attributed to a higher cholesterol or to a higher prevalence of other known risk factors (Table 3). Our observation is in agreement with Tunbridge *et al.*⁷ who found a higher prevalence of chest pain on effort, possible infarction, and minor electrocardiographic abnormalities in women with a TSH over 6 mU/l. In this work—contrary to our finding—the higher TSH was associated with a 7% higher serum cholesterol.

Table 4 illustrates the well-recognised limitations of cross-sectional prevalence studies such as ours. In agreement with others^{2,20} a high cholesterol loses its significance as a risk factor in men. This is not so surprising, since even in prospective studies a high cholesterol is a risk factor in men only in a younger age group.²¹ Despite these limitations Table 4 shows a significant association between a high cholesterol and coronary heart disease in women. When comparing Table 4 with Table 2 one is tempted to speculate that a high TSH is as important a risk factor for coronary heart disease as a high serum cholesterol in women.

We are unable to explain satisfactorily the association of a borderline increase in TSH with coronary heart disease on the basis of known thyroid and cardiovascular pathophysiology, but it is perhaps of interest that Santos *et al.*²² have recently shown that (overt) hypothyroidism almost always leads to hypertrophic cardiomyopathy. This condition is associated with angina and Q waves suggestive of infarction. Thus, the association might arise by changes in the myocardium rather than in the coronary arteries. The statistical association between a borderline high TSH and coronary heart disease does not of course establish a causal relation. None the less, and despite some conflicting results, a series of studies has now linked borderline low thyroid function with coronary heart disease. It seems appropriate therefore that this link be further explored, if possible by prospective incidence studies.

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