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# Evaluation of cardiac ischaemia in cardiac asymptomatic newly diagnosed untreated patients with primary hypothyroidism

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## ABSTRACT

**Background: Hypothyroidism is regarded as a risk factor for coronary artery disease. Possible factors involved in this association are hyperlipidaemia and hypertension, both occurring with increased frequency in hypothyroid patients. The aim of our study was to evaluate signs/symptoms of cardiac ischaemia in untreated hypothyroid patients without angina pectoris, since this has never been performed before.**

**Methods: 51 consecutive cardiac asymptomatic patients (mean age 47, range 22 to 86 years) were studied by dobutamine stress echocardiography and bicycle ergometry.**

**Results: Mean values of body mass index, resting heart rate and blood pressure were 28.5 kg/m², 68 beats/min and 129/81 mmHg, respectively. Median TSH was 51.9 mU/l, mean FT4 7.3 ± 2.9 pmol/l (mean ± SD), TT3 1.6 ± 0.6 nmol/l and total cholesterol was 5.8 ± 1.6 mmol/l. None of the patients had symptoms of angina pectoris during dobutamine stress echocardiography or bicycle ergometry and no evidence of myocardial ischaemia was demonstrated. Exercise tolerance, assessed by dividing the maximum achieved workload by the target performance (depending on body height, sex and age), was diminished in 38% of patients, and significantly related to the degree of hypothyroidism.**

**Conclusion: No angina pectoris or cardiac ischaemia at exercise or stress was found in cardiac asymptomatic hypothyroid patients. The precise role of hypothyroidism as a risk factor for coronary artery disease should be further elucidated.**

## INTRODUCTION

Hypothyroidism and cardiac diseases have been associated for almost a century now. In 1918, Zondek introduced the term 'myxoedema heart', referring to pericardial effusion, ventricular dilatation and hypertrophy, and interstitial oedema with swelling of myocardial fibres.[1] In 1924, a first case of angina pectoris associated with myxoedema was reported.[2] Subsequently, several authors warned of the danger of initiating or aggravating angina pectoris, or even precipitating acute myocardial infarction, during thyroid replacement therapy in patients with both hypothyroidism and coronary artery disease.[3-6] Moreover, autopsies performed in hypothyroid patients before or during thyroid hormone therapy demonstrated coronary atherosclerosis and even fresh coronary occlusion.[3,6-8] Independently of age, sex and associated disorders, hypothyroidism was found to favour the development of coronary artery atherosclerosis.[7,8]

Several mechanisms might be involved in this historical association of hypothyroidism with ischaemic heart disease. Since both abnormalities of lipid metabolism (increased serum total cholesterol and low density lipoprotein cholesterol) and arterial hypertension occur with increased frequency in hypothyroidism, those two factors are regarded as possible causal factors.[9-15] Furthermore, it has been suggested that pathological immune reactivity in autoimmune thyroiditis, a common cause of thyroid failure, may be important in the above-referenced association.[16] As a consequence, most physicians are still hesitant about initiating the treatment of hypothyroid patients with a full dosage of thyroxine, even though Singer *et al.* suggest starting with a full replacement dosage of levothyroxine in those under the age of 50 without known

cardiac disease.[17] A systematic prospective study examining the prevalence of cardiac ischaemia before and during treatment, however, has never been performed. Most of the published studies on the association of hypothyroidism with coronary artery disease were retrospective, based only on the patient's history without the application of diagnostic tests, the numbers of the patients studied were often small and, particularly in earlier studies, patients were treated with desiccated thyroid containing differing amounts of triiodothyroxine.

The prevalence of coronary artery disease in untreated hypothyroid patients needs to be known to be able to determine the risk of angina pectoris developing during thyroid replacement therapy. By excluding patients with a known history of cardiac disease we were able to study only those patients in whom the development of angina pectoris due to coronary artery disease would be unexpected.

We therefore conducted a prospective study in which we determined the prevalence of cardiac ischaemia in untreated hypothyroid patients without symptoms of angina pectoris.

## METHODS

### Study population

All hypothyroid patients who presented to our hospital between September 1999 and August 2002 were screened for inclusion. Of these patients, only those with longstanding primary autoimmune hypothyroidism (TSH>4.2 mU/l and FT4<10 pmol/l) were included; the exact duration of hypothyroidism was, therefore, unknown. Subjects with a history of cardiac disease or taking cardiac medication were excluded from our study in order to evaluate the prevalence of ischaemia in asymptomatic patients and to avoid interference of the cardiac test results by the use of β-blockers and other cardiac medication. In total, we studied 51 consecutive patients with untreated hypothyroidism.

At diagnosis, before thyroid hormone replacement therapy was started, dobutamine stress echocardiography and bicycle ergometry were performed to identify signs and/or symptoms of myocardial ischaemia. In addition, an electrocardiogram was acquired, body height and weight were measured for calculation of body mass index (BMI, $kg/m^2$), blood pressure was measured in a supine position and free thyroxine ($FT_4$), total triiodothyroxine ($TT_3$), thyroid stimulatory hormone (TSH), total cholesterol and cholesterol subfractions and creatine phosphokinase (CK) were assayed at that time.

Clinical and biochemical characteristics of the study population were compared with those of 35 euthyroid, healthy control subjects chosen from hospital personnel and their relatives of comparable age who were not taking medication.

The study protocol was approved by the local medical ethics committee, and informed consent was obtained from each subject.

### Assays

TSH plasma levels (reference range 0.4-4.2 mU/l), serum $TT_3$ levels (range 1.3-2.5 nmol/l) and $FT_4$ levels (range 10-23 pmol/l) were determined in a highly sensitive chemiluminescent enzyme immunoassay (ACS 180, Bayer Diagnostics, USA). Total cholesterol (range 2.5-6.5 mmol/l), cholesterol subfractions (high-density lipoprotein (HDL) cholesterol range 1.0-1.8 mmol/l, low-density lipoprotein (LDL) cholesterol 1.5-4.5 mmol/l, triglycerides (TG) 0.0-2.0 mmol/l) and creatine phosphokinase (CK 11-200 U/l) were measured with a Hitachi 911 (Japan).

### Electrocardiography

All 12-lead electrocardiograms (ECGs) were analysed by one cardiologist and scored according to previously published criteria.[18]

### Dobutamine stress echocardiography

This test was performed as previously described.[19]

In summary, a rest ECG and a two-dimensional echocardiogram were carried out and intravenous access was secured. Dobutamine was then administered intravenously by an infusion pump, starting at 10 μg/kg/min for three minutes, increasing by 10 μg/kg/min every three minutes up to a maximum of 40 μg/kg/min. In patients not achieving 85% of their estimated maximal heart rate (220 beats/min minus age for men, 200 beats/min minus age for women), atropine was administered on top of the maximal dosage of dobutamine, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg. Throughout dobutamine infusion, the ECG was continuously monitored and recorded at three-minute intervals. Blood pressure was measured and recorded by an automatic device every three minutes. Images were digitised in quad screen to allow later visual analysis of wall motion. Two experienced independent and blinded cardiologists analysed the echocardiogram. Myocardial ischaemia was defined as development of new or worsening of pre-existing wall motion abnormalities in at least two segments of the left ventricle.

### Bicycle ergometry

A Lode bicycle ergometer was used. Workload was started at 30 watts with 20-watt increments every minute. A constant pedalling rate of 60 revs per minute was required and exercise was terminated if the patient was unable to maintain the requested cycling frequency. The ECG was continuously monitored and blood pressure was measured and recorded by an automatic device every two minutes. Ischaemia was defined as development of ST depression

of ≥0.1 mV during exercise, according to the criteria described by Roelandt *et al.*[20]
Bicycle ergometry can also be used to assess exercise tolerance, which could be a parameter of hypothyroid myopathy. Therefore, at the start a target performance was assessed for each patient, depending on body height, age and sex. Exercise tolerance was determined by dividing the maximum achieved workload per patient by his or her target performance. An exercise performance of less than 80% of the target performance is considered insufficient.

**Statistical analysis**
Data are expressed as mean ± standard deviation (SD). Statistical comparisons were performed by means of a two group unpaired Students t-test. A p value <0.05 was considered significant.

## RESULTS

Seventy-four consecutive patients with primary hypothyroidism were screened for inclusion, of whom 23 patients were excluded. Clinical and biochemical characteristics of the remaining 51 patients and 35 control subjects are given in *table 1*. The resting blood pressure of the experimental patients was 129/81 ± 17/12 mmHg. The mean body mass index (BMI) was significantly higher in hypothyroid patients compared with euthyroid controls (28.5 ± 4.7 *vs* 24.1 ( 4.9 kg/m$^2$, p=0.0004), resting heart rate was lower (68 ± 13 *vs* 80 ± 9 beats/min, p=0.0001), HDL cholesterol was lower (1.4 ± 0.4 *vs* 1.5 ± 0.4 mmol/l, p<0.05), TG were higher (1.6 ± 1.0 *vs* 1.2 ± 0.6 mmol/l, p<0.05) and CK was significantly higher (296 ± 746 *vs* 72 ± 39 U/l, p=0.02).

Twenty-three patients were excluded: 14 for cardiovascular reasons, such as a history of cardiac disease (myocardial infarction: n=4; angina pectoris: n=5) and cardiac medication for longstanding hypertension (n=5). Other reasons were unwillingness to participate in the study (n=5), hypothyroidism due to postpartum thyroiditis (n=2), pregnancy (n=1) and myxoedema (pre)coma (n=1). Except for age (included *vs* excluded patients: 47 ± 17 *vs* 63 ± 18 years, p<0.001) and mean TSH level (100.8 ± 136.5 *vs* 51.9 ± 30.4 mU/l, p<0.01), clinical and biochemical characteristics did not differ significantly between the two groups.
Electrocardiographic abnormalities were observed in 24 patients: inversion of the T waves (n=4), ST-segment depression (n=1), sinus bradycardia (heart rate <60 beats/min, n=16), prolongation of the Q-T interval corrected for heart rate (QTc >0.43 msec, n=4) and low P wave, QRS and T wave amplitudes (n=5). Six of the electrocardiograms showed two different abnormalities.

**Dobutamine stress echocardiography**
The echocardiogram at rest showed normal wall motion and normal left ventricular function in all patients. During dobutamine and later atropine administration, none of the patients complained of angina pectoris and none demonstrated wall motion abnormalities signifying myocardial ischaemia. This test is not designed for the evaluation of diastolic function.

**Bicycle ergometry**
As with dobutamine stress echocardiography, none of the patients had symptoms of angina pectoris during bicycle ergometry and no ischaemia was demonstrated. No serious arrhythmias occurred.

**Table 1**
*Clinical and biochemical characteristics of the included patients and controls*

| | INCLUDED | CONTROLS | P VALUE |
|---|---|---|---|
| Number | 51 | 35 | |
| Male/female | 12/39 | 4/31 | |
| Age (years) | 47 ± 17 | 50 ± 12 | NS |
| BMI (kg/m$^2$) | 28.5 ± 4.7 | 24.1 ± 4.9 | 0.0004 |
| Heart rate (beats/min) | 68 ± 13 | 80 ± 9 | 0.0001 |
| TSH (mU/l) | 100.8 ± 136.5 | 2.3 ± 1.1 | <0.0001 |
| $FT_4$ (pmol/l) | 7.3 ± 2.9 | 13.2 ± 2.1 | <0.0001 |
| $TT_3$ (nmol/l) | 1.6 ± 0.6 | 2.0 ± 0.6 | 0.002 |
| Total cholesterol (mmol/l) | 5.8 ± 1.6 | 5.7 ± 1.0 | NS |
| HDL cholesterol (mmol/l) | 1.4 ± 0.4 | 1.5 ± 0.4 | <0.05 |
| LDL cholesterol (mmol/l) | 3.7 ± 1.5 | 3.8 ± 1.1 | NS |
| Triglycerides (mmol/l) | 1.6 ± 1.0 | 1.2 ± 0.6 | <0.05 |
| CK (U/l) | 296 ± 746 | 72.3 ± 38.7 | 0.02 |

*Data as mean ± SD.*

Exercise tolerance was insufficient in 38% of patients (performance of 77 ± 8% of target) and normal in 62% of patients (performance 110 ± 13% of target). The mean TSH levels of the patients performing insufficiently were higher than in those with an exercise performance that was normal according to body height, sex and age: 154.3 mU/l *vs* 70.2 mU/l ($p<0.05$, *table 2*). $FT_4$ was lower in the group with reduced exercise tolerance: 6.4 pmol/l *vs* 7.9 pmol/l ($p<0.05$). Median CK did not differ significantly between both groups.

## DISCUSSION

Our study clearly showed that no cardiac ischaemia was demonstrated in 51 consecutive patients with untreated primary hypothyroidism without previous cardiac symptoms. Secondly, bicycle ergometry showed that 38% of patients performed insufficiently, indicating a significant inter-relationship between exercise performance and degree of hypothyroidism. This might in part be explained by impaired cardiac performance with low cardiac output, caused by bradycardia, a decrease in ventricular filling and a decrease in cardiac contractility.[21,22] Although cardiac output was not measured in our patients the absence of impaired left ventricular function makes this a very improbable explanation. Moreover, heart rate did not differ significantly between patients with normal or impaired exercise performance. Another explanation might be the existence of hypothyroid striated muscle myopathy,[23,24] supported by the finding of elevated serum CK in our patients. However, median CK levels did not differ significantly between patients with normal or impaired exercise performance. Finally, we observed electrocardiographic abnormalities in almost half of the included patients. It should be stressed, however, that the resting ECG is not a diagnostic tool for demonstrating cardiac ischaemia. Electrocardiographic abnormalities that are frequently observed in patients with hypothyroidism are sinus bradycardia (heart rate <60 beats/min, 31% of patients in this study), prolongation of Q-T interval (8% in this study) and abnormalities associated with pericardial effusion: flattening or inversion of the T waves (8% in this study) and low P wave, QRS and T wave amplitudes (10% in this study).[14,15] Obviously, these changes also occur when pericardial effusion is absent, since none of our patients had pericardial effusion.

Some possible limitations to our study should be mentioned. First, the average age of included patients is relatively low. An explanation for this is that we excluded patients with cardiac history or symptoms who were relatively older. However, the included patients did represent all ages (range 22 to 86 years, median 46 years). Second, bicycle ergometry may have limited sensibility and specificity for the presence of coronary artery disease: 55 to 70% and 85 to 95%, respectively,[25] with the lowest sensitivity in young women. However, an advantage of this test is that we were also able to assess exercise tolerance, something that has never been done before in untreated hypothyroid patients. Dobutamine stress echocardiography is the most specific noninvasive test for assessing coronary artery disease, with sensitivity and specificity of 80 and 84%, respectively.[19] Third, in patients who performed insufficiently during bicycle ergometry, evaluation of ischaemia may be suboptimal. However, dobutamine stress echocardiography with achievement of target heart rate was performed in these patients and did not show ischaemia. Finally, the included patients did not have hypertension and dyslipidaemia. This might be caused by the fact that nowadays hypothyroidism is often diagnosed at an early stage due to more frequent testing of serum TSH.

While in our study no ischaemia was demonstrated, earlier studies have repeatedly demonstrated the association of hypothyroidism with coronary artery disease, even in previously cardiac asymptomatic patients, and of hormone replacement therapy with angina pectoris.[1-9,15,26-27] However, a retrospectively reviewed Mayo Clinic series of

**Table 2**
*TSH and FT4 in patients with insufficient and normal exercise performance*

| | INSUFFICIENT | NORMAL | P VALUE |
|---|---|---|---|
| Number | 19 | 31 | |
| Male/female | 8/11 | 4/27 | |
| Ever smokers | 8 | 8 | |
| TSH (mU/l) | 154.3 ± 202.6 | 70.2 ± 58.8 | 0.047 |
| $FT_4$ (pmol/l) | 6.4 ± 3.2 | 7.9 ± 2.6 | 0.045 |
| $TT_3$ (nmol/l) | 1.3 ± 0.7 | 1.6 ± 0.5 | NS |
| Systolic BP (mmHg) | 124 ± 15 | 132 ± 17 | 0.046 |
| Diastolic BP (mmHg) | 80 ± 11 | 80 ± 12 | NS |
| Heart rate (beats/min) | 69 ± 11 | 67 ± 14 | NS |

*Data as mean ± SD.*

over 1500 patients with myxoedema shows that angina pectoris and myocardial infarction are rather infrequent among hypothyroid patients: just 4% had angina pectoris before thyroid replacement therapy was started and 2% of cardiac asymptomatic patients developed angina pectoris after treatment had begun. Thirty-eight percent of patients with angina pectoris before initiating thyroid hormone replacement were even reported to improve.[6] This may be explained by the fact that thyroid hormone replacement improves myocardial oxygen consumption.[28] Most of the above-mentioned studies on hypothyroidism and coronary artery disease, however, can be criticised for being either retrospective or uncontrolled, for small sample sizes or for using desiccated thyroid containing differing amounts of levothyroxine and triiodothyroxine. Patients are now treated by L-$T_4$ only: as this first has to be converted by the liver into $T_3$ by type I deiodinase, the heart is probably protected against high elevations of plasma $T_3$ levels. A systematic consecutive study on this association has never been reported.

Interestingly, few studies have been published in which dobutamine stress echocardiography is performed in asymptomatic patients with other known risk factors for coronary artery disease and no studies in hypothyroid patients have been performed before. We found one study in which dobutamine stress echocardiography was performed in asymptomatic diabetic patients having at least three added risk factors but without rest ECG abnormalities. The authors concluded that asymptomatic coronary artery disease is common in diabetes associated with other risk factors. Moreover, dobutamine stress echocardiography appeared useful in its detection with a predictive positive value of 69%.[29] We did not find any studies of cardiac asymptomatic subjects with hyperlipidaemia and no studies of dobutamine stress echocardiography in cardiac asymptomatic subjects without risk factors for coronary artery disease.

Further research should include a prospective study in which development of angina pectoris during thyroid replacement therapy is monitored, as this could have important implications for future therapy. It is imaginable that patients who are treated initially with a higher dose of thyroxine will be euthyroid, and might feel better, much sooner than patients treated according to the present principle of starting low and increasing slow. Moreover, elevated arterial blood pressure and high serum cholesterol, both predisposing factors for coronary artery disease, might decrease sooner.

## CONCLUSION

In conclusion, our data show that none of the cardiac asymptomatic patients with untreated hypothyroidism showed angina pectoris during stress testing and that no signs of ischaemia were found in these patients. The precise role of hypothyroidism as a risk factor for coronary artery disease should further be elucidated.

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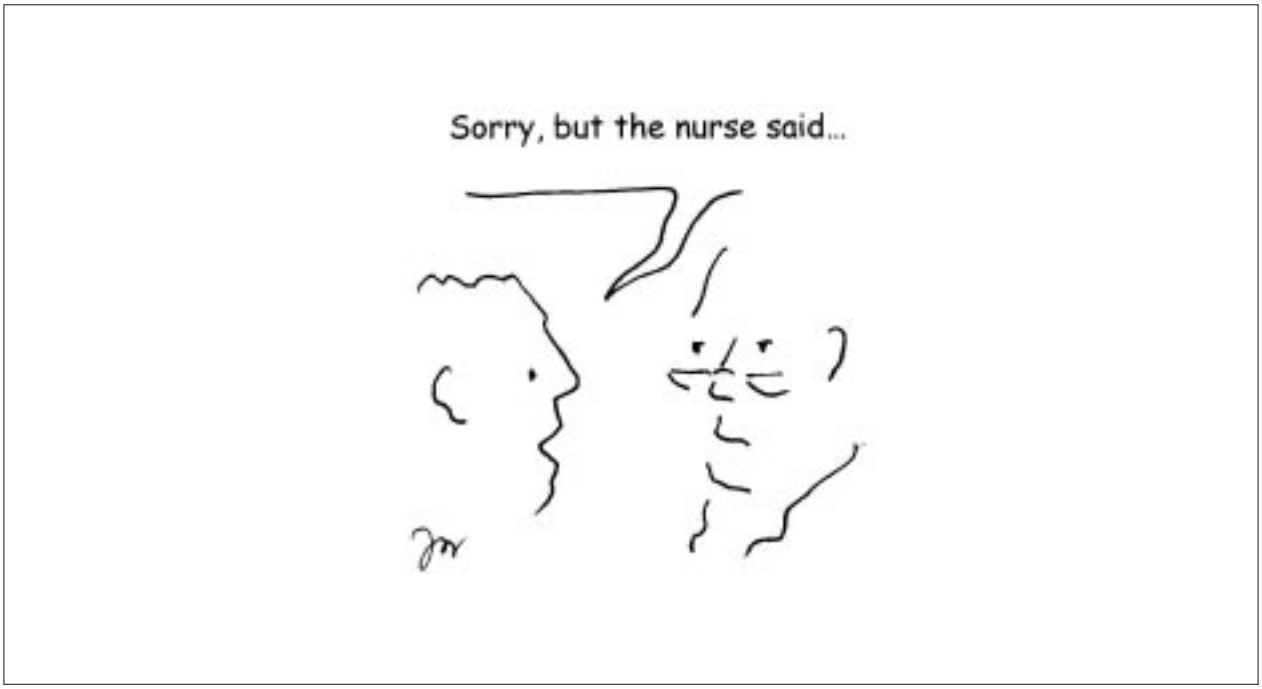


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