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Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years

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Summary

OBJECTIVE Mild thyroid failure is associated with an increased risk for development of atherosclerosis, but whether subclinical hypothyroidism is related to risk for cardiovascular disease is controversial. The purpose of the present study was to examine a possible association between subclinical hypothyroidism and cardiovascular disease.

DESIGN Cross-sectional study of a general population.

PATIENTS Twelve hundred and twelve subjects, men and women, between 20 and 69 years old without thyroid disease not treated with drugs interfering with thyroid function or analysis of TSH were included.

MEASUREMENTS Clinical signs of cardiovascular disease based on a questionnaire and medical records and laboratory analysis of lipids, atherothrombotic risk markers, C-reactive protein and TSH.

RESULTS The main findings were a high incidence of subclinical hypothyroidism (19·7%) in a general population. Subclinical hypothyroidism was associated with higher concentrations of triglycerides and C-reactive protein. Below 50 years of age cardiovascular disease was more frequent in males with subclinical hypothyroidism compared to euthyroid males. Subclinical hypothyroidism was a predictor of cardiovascular disease in males below 50 years with an odds ratio of 3·4 (95% confidence interval 1·6–6·8) for developing cardiovascular disease compared to euthyroid age-matched males.

CONCLUSION Our study demonstrates that patients with subclinical hypothyroidism have increased levels of triglycerides and signs of low-grade inflammation (raised C-reactive protein levels) and that subclinical hypothyroidism might be a risk factor for development of cardiovascular disease in younger males.

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Subclinical hypothyroidism (subHypo), defined as an asymptomatic state characterized by normal serum concentrations of free thyroxine and elevated serum concentrations of TSH (Surks & Ocampo, 1996), is highly prevalent in elderly women (Rivolta *et al*., 1999). Whether subHypo is related to risk for cardiovascular disease (CVD) is controversial, although it has been concluded recently that mild thyroid failure is associated with an increased risk for development of atherosclerosis (McDermott & Ridgway, 2001), and that subHypo is a strong indicator for risk of atherosclerosis and myocardial infarction in elderly women (Hak *et al*., 2000). In contrast, the Wickenham study did not find an association between subHypo and a history of ischaemic heart disease (Vanderpump *et al*., 1996).

The aim of the present study was to examine if subHypo is connected with CVD in a general population and to examine a possible association between thyroid function and alterations in lipids, haemostatic factors and inflammatory markers, all reportedly associated with risk for evolution of CVD.

Methods

Study design

The study was conducted as a cross-sectional, population-based study including screening of a general practice population for clinical signs of CVD and laboratory analysis of lipids, atherothrombotic risk markers and TSH. The local ethical committee approved the protocol, and all participants gave their informed written consent.

Study participants

Between 1998 and 2000 a survey was carried out in a Danish primary health care centre in order to evaluate the presence of CVD risk markers, clinical signs of CVD and thyroid disease. A

total of 3108 persons were listed with the practice, and 2082 were between 20 and 69 years old. A cohort of 1374 persons (66% of the eligible population; 532 refused to participate, 48 did not respond, 85 moved before invitation, two died, 18 had diabetes mellitus and 23 had severe mental or physical illness and were not able to participate) gave written informed consent. The same investigator (PEH) carried out the physical examination of all 1374 participants. Blood pressure (BP) was measured in the seated position by auscultation over the brachial artery to the nearest 2 mmHg (Hawksley Random Zero Mk II Mercury Sphygmomanometer) using Korotkoff sound 1 and 5. The manometer was placed at the heart level. BP was measured on the dominant arm, and in case of ambidextricity the right arm was chosen. Thyrotropin (TSH) was measured in all patients, and if TSH was above 5 mU/l or below 0·60 mU/l the tests were supplemented with free thyroxine (T4) and free triiodothyronine (T3). Patients with hyperthyroidism or hypothyroidism based on these measurements or with known thyroid disease or treated with drugs known to interfere with the hypothalamic–pituitary–thyroid axis or analysis of thyroid hormones and TSH were excluded. Questionnaires (London School of Hygiene Cardiovascular Questionnaire; Rose, 1982) concerning signs of CVD: myocardial infarction, angina pectoris, stroke or intermittent claudication, present or previous to the examination, were completed by the patients and compared with the clinical medical record (Heldgaard *et al*., 2003). The diagnosis of CVD was established by the results from the clinical examination, the medical record (including information on the present use or the use within 1 year of drugs prescribed for treatment of CVD) and the information in the questionnaire. The questions were presented so that each item [myocardial infarction (based on hospital record), angina pectoris (detailed self reported in the questionnaire), intermittent claudication (detailed self-reported in the questionnaire), and stroke (based on hospital record)] was unambiguous answered (previous and/or present, present, never present). When a discrepancy between the questionnaire and the medical record was detected, the information in the medical record was used.

Biochemical methods

Blood samples were drawn from an antecubital vein after an overnight fasting period of 10 h, and after further 15 min rest. A sphygmomanometer cuff was inflated for stasis, and the pressure was maintained at 40 mmHg throughout the sampling period in order to minimize mechanical damage to the vessel wall and thus prevent a rise in haemostasis variables.

Serum was prepared for analysis of TSH, T4, T3 (AutoDELFIA™ automatic immunoassay system, Wallac, Oy Turku, Finland), total cholesterol (CV 5·0%; Colorimetric test, VITROS Ektachem 950 IRC, Eastman Kodak, Rochester, NY, USA), high-density lipoprotein (HDL) cholesterol (Liquid-N-geneous HDL-C, Genzyme, Islands Brygle, KBH, Denmark, RA 1000; CV 4·0%), glucose (Enzymatic amperometric test, EBIO Eppendorf-Netheler-Hinz GmbH, Hamburg, Germany; CV 3·3%) and triglycerides (TG; Colorimetric test, VITROS Ektachem 950 IRC; CV 4·0%). Serum was frozen to –20 °C within 90 min and analysed at Department of Clinical Biochemistry (Viborg Sygehus, Denmark).

Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula: LDL cholesterol = total cholesterol – 0·45 × triglyceride.

Citrate-stabilized plasma was prepared for analysis of plasminogen-activator-inhibitor (PAI)-1 antigen (Imulyse PAI kit, Biopool, Umeå, Sweden; CV 2·4%), tissue-plasminogen-activator (t-PA) antigen (Imulyse t-PA kit, Biopool; CV 3·5%), C-reactive protein (CRP; monoclonal antibodies, BN II analyser, DadeBehring, Marburg, Germany; CV 6·3%), fibrinogen (modified Clauss procedure, ACL 7000, Instrumentation Laboratory, Milano, Italy; CV 2·2%), and von Willebrand factor (vWF; ELISA-method, Dako, Copenhagen, Denmark; CV 9·5%). These blood samples were placed in icewater and centrifuged at 4 °C and 1800 ***g***. Plasma samples were frozen at –20 °C within 30 min and stored at –80 °C until analysis at Department for Trombosis Research, University of Southern Denmark, Esbjerg.

Blood sampling throughout the time of investigation and all preparations of blood for shipment to other laboratories were performed by the same thoroughly instructed medical laboratory technician.

Based on the laboratory standards, the thyroid status was defined as: euthyroid (TSH between 0·60 and 2·80 mU/l) and subHypo (TSH between 2·81 and 10 mU/l and S-T4 and S-T3 within the reference interval).

Statistics

Continuous variables were compared using a *t*-test for unpaired observations.

Values for TSH, triglycerides, cholesterols, CRP, PAI-1, t-PA, waist/hip ratio and body mass index (BMI) were not Gaussian distributed and therefore evaluated with the nonparametric Mann–Whitney test. The discontinuous variables were compared with a χ^2-test. The Spearman correlation coefficient was used to evaluate the correlation of the variables.

Forward multiple logistic regression analysis with CVD as the dependent variable and subHypo and possible confounder variables (after log transformation of skewed variables: lipids, haemostatic factors, inflammatory markers, smoking, blood pressure, BMI, waist/hip ratio) as independent variables was used to evaluate the association between subHypo and CVD.

Results

Of the initial 1374 patients, 1212 patients not taking medications known to interfere with thyroid hormone analysis or being neither

Table 1 Baseline characteristics in subjects with subclinical hypothyroidism and euthyroidism

	subHypo ($n = 249$)	Euthyroid persons ($n = 963$)	P
Sex ratio (male/female)	42%/58%	55%/45%	0·026†
Age (years)	42 ± 13	43 ± 12	0·06*
Smokers	32%	32%	0·966†
Systolic blood pressure (mmHg)	124 ± 20	124 ± 22	0·55*
Diastolic blood pressure (mmHg)	79 ± 12	79 ± 14	0·60*
TSH mU/l (0·60–2·89)	3·70 (2·91–8·61)	1·66 (0·60–2·80)	0·001‡
BMI (kg/m^2)	25 (16–56)	25 (15–57)	0·77‡
Waist/hip ratio	0·88 (0·71–1·11)	0·89 (0·71–1·65)	0·23‡

*t-test mean ± SD, †chi square test, ‡Mann–Whitney test, median and range.

Table 2 Lipids, haemostatic factors, and inflammatory markers measured in subjects with subclinical hypothyroidism and euthyroidism

	subHypo ($n = 249$)	Euthyroid persons ($n = 963$)	P
Cholesterol (3·2–7·7 mmol/l)	5·2 (2·9–8·1)	5·3 (2·7–10·2)	0·83†
HDL cholesterol (0·70–2·15 mmol/1)	1·46 (0·70–4·42)	1·50 (0·77–3·10)	0·23†
LDL cholesterol (< 4·5 mmol/1)	2·84 (0·10–6·29)	2·95 (0·26–8·18)	0·36†
Triglyceride (0·50–2·00 mmol/1)	1·40 (0·30–14·29)	1·25 (0·45–10·28)	< 0·001†
Fasting glucose (3·6–6·1 mmol/1)	4·8 ± 0·6	4·7 ± 0·8	0·13*
PAI-1 ag (4·0–43·0 ng/ml)	6·6 (0·9–70·7)	5·8 (0·9–74·3)	0·11†
Fibrinogen (2·32–5·04 g/1)	3·07 (1·87–6·28)	3·02 (1·51–6·28)	0·08†
CRP ag (0·29–6·63 mg/1)	1·13 (0·17–49·10)	0·95 (0·17–50·40)	0·01†
vWF ag (50–192%)	102 (37–210)	99 (29–294)	0·09†
t-PA ag (3·0–10·0 ng/ml)	7·5 (1·5–20·2)	7·4 (1·5–30·4)	0·94†

*t-test, mean ± SD, †Mann–Whitney test, median and range.

hypothyroid (TSH > 10 mU/l) nor hyperthyroid (TSH < 0·30 mU/l) were included.

SubHypo was observed with a frequency of 19. 7% (15·7% in males and 22·9% in females). The baseline characteristics are shown in Table 1. Table 2 demonstrates that patients with subHypo had higher levels of trigycerides and CRP compared to the levels in euthyroid persons and that there was a trend towards higher concentration of fibrinogen and vWF in the subHypo group.

TSH in this population was correlated with triglyceride concentrations (Spearman $R = 0{\cdot}1060$, $P < 0{\cdot}001$), CRP concentrations (Spearman $R = 0{\cdot}0770$, $P = 0{\cdot}005$) and waist/hip ratio (Spearman $R = 0{\cdot}0670$, $P < 0{\cdot}001$).

Forward multiple logistic regression analysis with CVD as dependent and cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, PAI-1 ag, vWF ag, fibrinogen, CRP, t-PA ag, smoking, blood pressure, BMI, waist/hip ratio and subHypo as independent variables showed that subHypo in males below 50 years was the strongest and only significant contributor of CVD ($\beta = 0{\cdot}1084$, $P = 0{\cdot}02$). In contrast, there was no prediction of CVD by subHypo in males and women over 50 years (CVD in this group was predicted by fasting blood glucose, systolic blood pressure and t-PA ag) or in women below 50 years (CVD in this group was predicted by PAI-1 ag and CRP).

The odds ratio for developing CVD in the group of males below 50 years with subHypo was 3·3 (95% confidence interval = 1·6–6·8) compared to euthyroid males below 50 years. The distribution of the manifestations of CVD in Table 3 which demonstrates a significantly higher incidence of CVD in young males < 50 years with subHypo compared to euthyroid young males.

When examining the subgroup of young males (< 50 years) with subHypo ($n = 72$) compared to young males with normal TSH ($n = 438$), triglycerides concentrations were significantly higher and CRP concentrations and diastolic blood pressure tended to be higher, whereas HDL cholesterol was significantly lower (Table 4).

Discussion

In this study, we observed a frequency of subHypo of 19·7% in a general population. This condition is associated with higher concentrations of triglycerides and CRP (Table 2) and may be a predictor of CVD in males below 50 years.

Table 3 Distribution of manifestations of CVD in the total study population and in the group of males below 50 years

		Manifestation of CVD		
	Total CVD	Intermittent claudication	Angina pectoris	Stroke, myocardial infarction, cardiac incompensation
Euthyroid persons	$n = 195$	$n = 6$	$n = 19$	$n = 170$
$n = 963$	20·3%	0·6%	2·0%	17·6%
SubHypo	$n = 52$	$n = 2$	$n = 6$	$n = 44$
$n = 249$	20·7%	0·8%	2·3%	17·7%
Euthyroid males	$n = 40$	0%	$n = 6$	$n = 34$
< 50 year, $n = 438$	9·1%		1·3%	7·7%
SubHypo males	$n = 13$	0%	0%	$n = 13$
< 50 year, $n = 72$	17·6%§			17·6%

§Chi square test, $P = 0·029$ compared to euthyroid males < 50 years.

Table 4 Basal characteristics, lipids, haemostatic factors, and inflammatory markers measured in young males (< 50 years) with subclinical hypothyroidism and euthyroidism

	subHypo ($n = 72$)	Euthyroid persons ($n = 438$)	P
Systolic blood pressure (mmHg)	122 ± 18	119 ± 20	0·15*
Diastolic blood pressure (mmHg)	81 ± 13	79 ± 15	0·06*
Age (years)	35 ± 8	36 ± 8	0·13
Smokers	46%	43%	0·86†
BMI (kg/m^2)	25 (17–44)	25 (16–40)	0·80‡
Waist/hip ratio	0·93 (0·79–1·07)	0·92 (0·79–0·01)	0·71‡
Cholesterol (mmol/l)	5·2 (3·3–7·2)	5·0 (2·7–9·5)	0·43‡
HDL cholesterol (mmol/l)	1·34 (0·77–2·90)	1·40 (0·77–2·90)	0·04‡
LDL cholesterol (mmol/l)	3·02 (0·77–7·25)	2·98 (0·38–7·25)	0·81‡
Triglyceride (mmol/l)	1·58 (0·30–14·29)	1·25 (0·45–10·28)	< 0·01‡
Fasting glucose (mmol/l)	4·7 ± 0·4	4·8 ± 0·7	0·17*
PAI-1 ag (ng/ml)	7·1 (0·9–70·7)	7·1 (0·9–74·3)	0·72‡
Fibrinogen (g/l)	2·82 (1·93–5·27)	2·77 (1·51–5·92)	0·31‡
CRP ag (mg/l)	0·83 (0·17–23·8)	0·71 (0·17–39·2)	0·09‡
vWF ag (%)	90 (38–189)	93 (36–238)	0·81‡
t-PA ag (ng/ml)	8·5 (1·5–19·0)	7·7 (1·5–14·4)	0·30‡

*t-test, mean ± SD, †chi square test, ‡Mann–Whitney test, median and range.

We observed a higher frequency of subHypo in the total population as well as in sex-stratified groups than in the Milan study (Rivolta *et al*., 1999), the Colorado study (Canaris *et al*., 2000) and a previous Danish study (Knudsen *et al*., 1999). This observation is somewhat surprising as the criteria for definition of subHypo in these studies (TSH > 3 mU/l and normal T4 and T3) are comparable to the criteria used in the present study. An explanation could be that the region of Jutland in which the study was conducted, is characterized by iodine deficiency or depletion (Mathiasen, 1962; Munkner, 1969), a condition known to be connected with thyroid hypofunction (Laurberg *et al*., 1998). Also, the incidence of subHypo and CVD may be overestimated because patients with symptoms due to subHypo (including signs of CVD) were more likely to participate in the study, i.e. the nonresponders were the healthy part of the population. If we anticipate that all nonresponders were euthyroid and without CVD, the incidence of subHypo would be 16·7%, which is still higher than the incidence reported in other studies, and the incidence of CVD would be 13%. This anticipation would, however, not affect the conclusion of our study concerning the association of subHypo and CVD and the observed increased levels of triglycerides and CRP in patients with subHypo compared to euthyroid subjects.

Recently, the literature concerning hypothyroidism and atherosclerosis has been reviewed (Cappola & Ladenson, 2003). The review emphasizes the thyroid hormone effect on lipids, blood pressure, vascular smooth muscle cells, CRP, coagulation, endothelial function, vascular reactivity and cardiac and peripheral vascular functions. It is controversial whether atherothrombotic risk markers are expressed in overt hypothyroidism and subHypo.

Although it is the impression that subjects with overt hypothyroidism have more atherosclerotic disease, is it still controversial whether there is a causal association between subclinical hypothyroidism and atherosclerotic disease.

We observed that concentrations of triglycerides were higher in patients with subHypo compared to euthyroid subjects, an observation which may not be surprising as hypothyroidism is known to exert widespread effect on hepatic triglycerides assembly and secretion (Davidson *et al*., 1988). A previous study (Müller *et al*., 2001) reported a trend towards higher triglycerides in patients with subHypo although they did not find a significant difference. We also observed a lower level of HDL cholesterol in the group of younger men with subHypo, but no significant alterations in LDL cholesterol and total cholesterol. This observation contrasts a previous study (Bakker *et al*., 2001) in which it was observed that the increased cardiovascular risk associated with subHypo was associated with LDL cholesterol. An explanation might be that the population differed as a number of patients in those studies had previously been treated for hyperthyroidism by thyroidectomy or by ^{131}I.

Our observations on increased lipid concentrations and diastolic blood pressure in younger patients with subHypo may correspond a recent study (Luboschitzky *et al*., 2002) in middle-aged women. SubHypo was associated with hypertension, hypertriglyceridaemia and elevated triglyceride/HDL cholesterol ratio, factors that may increase the risk of accelerated atherosclerosis.

In a recent meta-analysis of data from studies concerning patients with subHypo (Danese *et al*., 2000), it was concluded that T4 therapy in individuals with mild thyroid failure lowers mean serum total and LDL cholesterol concentrations. However, it is still unknown if patients with subHypo and normal lipoproteins should be treated.

Our observation of a correlation between TSH and CRP and higher CRP concentrations in patients with subHypo, suggests an association between thyroid function and factors significant for low-grade inflammation and CVD. This observation corresponds recent observations of significantly increased values of CRP in patients with subHypo (Christ-Chrain *et al*., 2003), although it was concluded in their study that the association between subHypo and CRP was weak.

It could be speculated whether inflammatory mechanisms *per se* may be involved in detoriation of thyroid function and at the same time increase the risk of CVD. It might therefore be suggested that an increase in CRP was caused by thyroiditis causing subHypo, but this possibility was examined in a recent study in which it was concluded that inflammation associated with thyroiditis was not significant (Christ-Chrain *et al*., 2003).

Multiple logistic regression analysis demonstrated subHypo as a predictor of CVD in younger men with an odds ratio of 3·4 for developing CVD compared to euthyroid young men. Also, there was a significant difference in the incidence of CVD between the two groups (Table 3). It is well known that CRP is a strong predictor of vascular events and future coronary heart disease in men (Gram *et al*., 2000; Ridker, 2003), probably because of atherothrombosis. Here it is of interest to note that flow-mediated vasodilatation, a marker of endothelial function, is impaired in patients with subHypo (Lekakis *et al*., 1997), and it has recently been suggested that subHypo *per se* causes an impairment of endothelium-dependent vasodilatation (Taddei *et al*., 2003).

An increasing number of studies have revealed that the regulation of cellular energy metabolism include not only T3, but also other iodothyronines present in the biological fluids, such as 3,5-diiodothyronine (3,5-T2) (Kvetny, 1991; Soboll, 1993). T2 seems to act principally via mitochondria, while one of the most important effects attributed to T3 is the transcriptional or post-transcriptional regulation of those target genes encoding components of the mitochondrial energy-transducing apparatus. It might be suggested that cellular hypothyroidism induces an energy lack leading to a chronic intracellular inflammatory process, affecting the endothelial cells causing development of atherosclerosis.

The results of the present study demonstrate that subHypo in males below 50 years is associated with lipids, inflammation and risk of CVD. Other atherogenic dispositions as smoking, obesity or fasting blood glucose did not differ between the groups with and without subHypo. The absent effect of subHypo on CVD in the other groups, persons above 50 years of age and women, could be explained by the fact that other predominant factors in older men and women might disclose this effect. In our study, CVD was predicted by glucose, systolic blood pressure and t-PA ag in men and women over 50 years, and by PAI-I and CPR in women below 50 years. Alternatively, the young men died from CVD before entering the population of older men. While we have observed associations between subHypo and lipids/inflammation, we were not able to demonstrate an association between subHypo and alteration of coagulation factors as reported in other studies (Chadarevian *et al*., 2001; Müller *et al*., 2001). In a recent study it is reported that patients with subHypo have elevated levels of fibrinogen and vWF corresponding the borderline significant observations in the present study, but also elevated levels of PAI-1 ag and decreased levels of t- PA ag (Canturk *et al*., 2003), observations that could not be reproduced in the present study. The reason for the deviating results remains unknown, but differences in study population (size and gender) may be of importance. Our study was based on an unselected sample from a primary health care centre including both males and females, whereas most previous studies only included females.

In conclusion, our study demonstrates that subjects with subHypo have increased levels of triglycerides and signs of low-grade inflammation (raised CRP levels). This low-grade inflammation,

which might account for the increased risk of developing CVD in younger men, may be elicited by the raised level of triglyceride or be an independent effect of an intracellular hypometabolic state or of a combination of these.

Future studies are needed to evaluate whether screening of the general population to trace subjects and treat subHypo would be a new approach to reduce the risk of CVD. One central issue would be to find out, whether substitution therapy targeting normal thyroid function may reduce the risk of future cardiovascular events.

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