Prevalence and Correction of Hypothyroidism in a Large Cohort of Patients Referred for Dyslipidemia

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**Background:** Treatment of hypercholesterolemia can reduce the risk of developing premature atherosclerosis. The hypercholesterolemia caused by hypothyroidism is potentially reversible by thyroid hormone replacement therapy. We determined the prevalence of hypothyroidism in patients referred to a university lipid research clinic and studied the changes in lipid and lipoprotein levels on restoration of the euthyroid state.

**Methods:** A retrospective follow-up study was performed. In all 1509 consecutive referrals for severe dyslipidemia, thyrotropin levels were measured. Patients with hypothyroidism were identified by means of a computed database, from January 1, 1989, to July 1, 1993, first by serum thyrotopin sodium medication and second by serum thyrotopin values greater than 5 mU/L. Twenty-one patients were available to evaluate the effect of restoration of the euthyroid state on plasma lipid and lipoprotein levels.

**Results:** The observed prevalence of hypothyroidism proved to be 4.2% (64/1509). The disorder was previously known in 25 patients and newly diagnosed in 39 patients (11 with overt hypothyroidism and 28 with subclinical hypothyroidism). Significant reductions in total cholesterol and low-density lipoprotein cholesterol levels occurred only in patients with pretreatment thyrotropin values of 10 mU/L or more.

**Conclusions:** The prevalence of newly diagnosed cases of overt hypothyroidism in patients referred to a lipid clinic is approximately two times that in the general population. The absence of significant reductions in total cholesterol and low-density lipoprotein cholesterol levels on levothyroxine treatment in patients with minor subclinical hypothyroidism (thyrotopin level, <10 mU/L) does not support the view that this condition is a risk factor for atherosclerosis mediated by an elevated low-density lipoprotein cholesterol level. All patients referred for diagnosis and treatment of dyslipidemia should be screened for hypothyroidism by measurement of thyrotopin values.

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**Elevated Levels of Low-Density Lipoprotein (LDL) Cholesterol have been identified as a major risk factor for the development of premature atherosclerosis. Diagnosis and treatment of severe disorders of lipoprotein metabolism are complicated and consequently specialized. Lipid clinics have emerged to improve diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in these patients.**

**Hypothyroidism is a well-known cause of dyslipidemia characterized by elevated levels of total and LDL cholesterol as a consequence of decreased uptake of LDL cholesterol by its receptor on liver cell surfaces.**

**The prevalence of thyroid disorders among patients with elevated total cholesterol levels is likely to be greater than that in the general population because the former have a greater pretest likelihood of hypothyroidism.**

**Hypercholesterolemia elicited by hypothyroidism is potentially reversible by restoration of the euthyroid state. The absolute level of cholesterol in plasma is probably in part determined by the duration and severity of hypothyroidism.** After correction of the hypothyroid state by supplementation with levothyroxine sodium, a reduction in total cholesterol level has been reported, notably in patients with thyrotopin levels greater than 40 mU/L. The desired level of cholesterol that should be achieved with levothyroxine supplementation is some-

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See Patients and Methods on next page
PATIENTS AND METHODS

PATIENTS

The study population consisted of all consecutive patients referred to the Lipid Research Clinic—Amsterdam during a 4½-year period (January 1, 1989, to January 7, 1993). Criteria for referral were abnormal lipoprotein levels with total cholesterol level greater than 6.5 mmol/L (>251 mg/dL) and/or high-density lipoprotein (HDL) cholesterol level less than 0.9 mmol/L (<35 mg/dL) and/or triglyceride level greater than 2.3 mmol/L (>204 mg/dL). Dyslipidemic patients were not deliberately screened for hypothyroidism by their referring physicians. Relevant data were retrieved from a computed database. Patients with hypothyroidism were identified first by the use of levothyroxine medication for already known thyroid hormone deficiency and second by plasma thyrotropin concentrations above the upper normal limit of 5.0 mU/L in the absence of levothyroxine medication, indicating previously unknown hypothyroidism. From these data, the prevalence of hypothyroidism in referred patients could be deduced.

The medical records of patients with untreated hypothyroidism on referral were examined for sex and age of the subjects, the cause of the hypothyroid state, and any medication known to interfere with lipid metabolism. A retrospective follow-up study was done in the patients with untreated hypothyroidism, excluding those who received lipid-lowering drugs besides levothyroxine on restoration of the euthyroid state. Plasma thyrotropin, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels were measured before treatment and 6 months after correction of the hypothyroid state. Patients were divided in three groups according to pretreatment thyrotropin values: group 1 (5.0 to 9.9 mU/L), group 2 (10.0 to 39.9 mU/L), and group 3 (≥40 mU/L).

LABORATORY ANALYSIS

Serum thyrotropin was measured with a microparticle immunoassay using monoclonal goat antithyrotropin conjugated with alkaline phosphatase (IMX Abbott, North Chicago, Ill.). Microsomal and thyroglobulin antibodies were determined by hemagglutination (Wellcome Laboratories, Kent, England). Plasma cholesterol was measured with an enzymatic assay with cholesterol esterase and cholesterol oxidase; HDL cholesterol was measured with an enzymatic assay with cholesterol esterase and cholesterol oxidase after precipitation of very-low-density-lipoprotein cholesterol and LDL cholesterol with phosphotungstate and magnesium chloride.\(^7\) When triglyceride concentrations exceeded 4.5 mmol/L (>398 mg/dL), plasma lipoproteins were measured by a dual precipitation method.\(^8\) Triglyceride was measured with an enzymatic assay with lipase, glycerokinase, and glycerol phosphate-oxidase.\(^9\)

STATISTICAL ANALYSIS

Statistical analysis within groups was performed by means of Students' \(t\) test for paired data and between groups by Students' \(t\) test for unpaired data. The level of significance was taken as \(\alpha=.05\). All \(P\) values given were generated by the result of two-tailed tests.

RESULTS

PATIENTS

A total of 1509 patients (800 men and 709 women) were referred to the Lipid Research Clinic in the period under study. Twenty-five patients (three men and 22 women) were already known to have primary hypothyroidism and were receiving levothyroxine at the first visit. In 39 other patients (five men and 34 women), previously unknown hypothyroidism was found by the detection of thyrotropin levels greater than 5.0 mU/L. The overall prevalence of hypothyroidism was therefore 4.2% (64/1509), and that of newly discovered cases of hypothyroidism was 2.6% (39/1509). The causes of previously unknown hypothyroidism were autoimmune thyroiditis (n=35), thyroidectomy (n=3), and treatment with radioactive iodine (n=1). Although hypothyroidism was not suspected by the referring physicians, the clinical picture of hypothyroidism was evident in retrospect in all patients with thyrotropin levels greater than 40 mU/L. Five patients with newly discovered hypothyroidism received lipid-lowering therapy on referral to the Lipid Research Clinic.

LIPIDS AND LIPOPROTEINS

Twenty-one patients with primary hypothyroidism were available for follow-up to evaluate the effect of restoration of the euthyroid state on the lipid profile; no other lipid-lowering drugs were prescribed in this follow-up period. When the patients were divided in three groups according to pretreatment thyrotropin levels, the age, sex distribution, HDL cholesterol levels, and triglyceride levels were similar in all subgroups, but total cholesterol and LDL cholesterol levels were highest in patients with the highest thyrotropin levels (Table 1). After levothyroxine treatment, thyrotropin levels returned to normal and were similar in all groups. Total cholesterol and LDL cholesterol levels decreased only in patients with pretreatment thyrotropin values greater than 10.0 mU/L, not in those with lower levels. Moreover, the decrease in total...
cholesterol and LDL cholesterol levels in patients with pretreatment thyrotropin values greater than 40 mU/L was greater than in those with levels with between 10 and 40 mU/L (Table 1 and Figure 1). Total cholesterol and LDL cholesterol levels after treatment with thyroxine were similar in all groups. No significant changes in any group were observed in plasma HDL cholesterol or triglyceride levels (Table 1) apart from a small decrease in HDL.
choleroterol level in patients with pretreatment thyrotro-

pin values between 10 and 40 mU/L. The decrease in to-
tal and LDL cholesterol levels was positively correlated
with the decrease of plasma thyrotropin levels in all 21
patients (Figure 2). Conversion factor from millimole
per liter to milligram per deciliter: for choleroterol mul-
tiplay millimole per liter by 38.7, for triglyceride multi-
play millimole per liter by 88.5.

The prevalences of hypothyroidism calculated for pa-

tients with dyslipidemia are summarized in Table 2. Com-
pared with the frequency of newly discovered cases of

ovet hypothyroidism in the general population

(0.3%), we identified approximately twice as many
cases in our selected population with hypercholesterol-
emia (0.7%). The number of patients with newly di-

agnosed subclinical hypothyroidism (1.9%), however, was

only one fifth that reported by Tunbridge et al11 (10.6%).
The reason for this last finding is not clear. Geo-

graphic differences in iodine intake or genetic dif-

ferences between populations in the United Kingdom

and the Netherlands might be a possible explanation.
Oetgen et al10 reported a prevalence of hypothyroidism

(thyrotropin level, >10 mU/L) among inpatients with

hypercholesterolemia that was two times that of normo-

cholesterolemia patients (8% vs 4%).

Sex-specific prevalence figures show that our dys-

lipidemic women had a prevalence of newly discovered

cases of hypothyroidism of 4.8% (34/709). This figure

is only slightly higher than the prevalence of 4.0% for

newly discovered cases of hypothyroidism (thyrotropin

level, >4.2 mU/L) found among apparently healthy

middle-aged women in a Dutch epidemiologic survey con-
ducted by Geul et al.17 The small number of patients with

hypothyroidism in our study might be explained by the

difference in age, the latter group having a mean age of

55 years, which was 10 years older than our group.

Although there was a fairly even sex distribution in

our referred population (53% men and 47% women), there

was a markedly uneven sex distribution for hypothy-

roidism; significantly more women than men were di-

gnosed as having hypothyroidism. The male-female sex

ratio of 1:7 in conjunction with a mean age of 58 years

is in accordance with the known prevalence of hypo-

thyroidism in older women.

Hypothyroidism varies in severity. The need for treat-

ment in subclinical hypothyroidism is controversial. Sub-

clinical hypothyroidism has been suggested as a risk fac-

tor for coronary heart disease.18-23 The underlying

mechanism for this enhanced risk is unclear but likely

mediated by changes in lipoprotein levels. Using a re-
fined classification system with three grades of subclini-

cal hypothyroidism, Staub et al19 studied the metabolic

impact of lack of thyroid hormone in 69 women. Only

at thyrotropin levels above 12 mU/L were there in-

creased levels of LDL cholesterol, although total choles-

terol level was normal. Aren and Patsch25 noticed a sig-

nificant decrease in total and LDL cholesterol levels after

hormone replacement therapy in 13 patients with a mean

thyrotropin value of 16 mU/L. Both Lithell et al26 and Kuty-

et et al6 showed that only patients with more severe hypo-

thyroidism (thyrotropin level, >40 mU/L) exhibited a

significant decrease in total and LDL cholesterol levels

after correction of the hypothyroid state. We demon-

strated a significant decrease in total and LDL choles-
terol levels in patients with both severe (thyrotropin level,

≥40 mU/L) and less severe (thyrotropin level, 10.0 to

39.9 mU/L) hypothyroidism. In subclinical hypothyroid-

ism (thyrotropin level, <10 mU/L), no significant de-

crease in any lipid or lipoprotein level could be demon-

strated. There was a high risk of type II statistical error

Figure 2. Correlation between the decrease in serum thyrotropin level and the decrease in plasma total cholesterol level (top) and low-density lipoprotein (LDL) cholesterol level (bottom) in 21 patients with hypothyroidism treated with levothyroxine sodium. Regression equations are as follows: top, y=−2.0504(logx)+1.0452 (r=−.810, P<.01); bottom, y=−1.9373(logx)+0.9970 (r=−.594, P<.01).

COMMENT

The prevalences of hypothyroidism have been investi-
gated in a number of studies with different popula-
tions. The reported frequencies vary considerably, since pa-
tient selection and sex and age distribution were dissimi-
lar and different classifications (overt vs subclinical) for

hypothyroidism were applied. Tunbridge et al11 were the

first to provide a reliable estimate of the prevalence of

hypothyroidism (thyrotropin >6 mU/L) in the general

adult population, demonstrated by means of a commu-
nity screening program (Table 2).11-14 Since an age- and

sex-related increase in prevalence of hypothyroidism ex-
sists, most other studies focused on older subjects and

especially on women.15 In these subsequent studies, the

prevalence of overt hypothyroidism was increased, but,

interestingly, for subclinical hypothyroidism it was simi-
lar to that reported for the general population.
in this conclusion because of the small number of patients. Studies by Cooper et al., Althaus et al., and Caron et al. that included 98 women with subclinical hypothyroidism (mean thyrotropin level, 8 to 12 mU/L) failed to show a reduction in total cholesterol levels (or LDL cholesterol levels in the study by Althaus et al.) after treatment with levothyroxine. Franklyn et al. suggested that levothyroxine replacement in subclinical hypothyroidism (mean thyrotropin level, 13.8 mU/L) only lowered serum lipid levels if subsequently mild hyperthyroidism was induced by excessive doses of levothyroxine. The trend found in our study is in agreement with these reports and does not support the view that a minor degree of hypothyroidism (thyrotropin level, <10 mU/L) is a risk factor for premature atherosclerosis or that levothyroxine treatment is indicated in this situation.

Other studies favor treatment of subclinical hypothyroidism to reduce the cardiovascular risk modulated by altered lipid and lipoprotein levels. Although Caron et al. did not find a significant decrease in total or LDL cholesterol levels, they did find an increase in HDL cholesterol levels and decrease in the total cholesterol-HDL cholesterol ratio on restoration of the euthyroid state, thereby possibly reducing the risk of cardiovascular disease. Tailoring levothyroxine treatment in patients with subclinical hypothyroidism is advocated by Bogner et al. Their group of 40 patients with subclinical hypothyroidism had low mean basal thyrotropin levels (the subgroup with highest median thyrotropin levels reached 5.5 mU/L [range, 4.8 to 7.5 mU/L]) and did not show differences in mean levels of total, LDL, or HDL cholesterol as compared with controls. Individual analysis disclosed nine patients with hyperlipoproteinemia who did benefit from levothyroxine treatment, with marked lowering of total and LDL cholesterol levels.

We observed variable hypercholesterolemic responses between individuals (Figure 2). This could be accounted for by other coexistent causes of hyperlipoproteinemia but also by variability in the gene encoding for the LDL receptor. After correction of the hypothyroid state, increased levels of total and LDL cholesterol were still present in all groups with the exception of one patient from group 1. Other factors predisposing to hypercholesterolemia were identified in five patients from group 1 (one patient with familial hypercholesterolemia, two with familial combined hyperlipidemia, and two with polygenic hypercholesterolemia) and in six patients from group 2 (one patient with familial hypercholesterolemia, two with familial combined hyperlipidemia, one with nephrosis, one with diabetes mellitus, and one with marked obesity [body mass index, >34]). In group 3, no other predisposing factors were identified. Subsequent lipid-lowering therapy was based on individual risk profiles.

The yield of new cases of hypothyroidism by routinely measuring thyrotropin as an initial screening test in our Lipid Research Clinic amounted to 26 per 1000 persons. To identify these 26 patients, the risks and benefits of substitution therapy with levothyroxine must be weighed against the costs of performing 974 thyrotropin assays. This yield could probably be improved by measuring thyrotropin levels only in the group at high risk for hypothyroidism, i.e., women older than 40 years. Applying this criterion in our population would have meant missing three cases, in two men and one woman, all with thyrotropin levels of 10 mU/L or more, who would have benefited from levothyroxine therapy. On the other hand, treatment of 26 patients with hydroxymethylglutaryl coenzyme A reductase inhibitors would have been 20 times more expensive than treatment with levothyroxine and would not have balanced the cost of performing extra thyrotropin assays. The thyrotropin assay has been widely accepted as the screening method for hypothyroidism, as its sensitivity and specificity in this respect are greater than those of the free thyroxine assay. The rare patients with central hypothyroidism (prevalence, 0.0002% to 0.005%) are usually recognized by other symptoms despite normal thyrotropin values. We therefore advise routine measurement of thyrotropin levels in all new referrals to a lipid clinic.

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REFERENCES


