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Cholesterol-Lowering Effect of Dextro-Thyroxine in Patients with Hypercholesterolemia and Coronary Disease[1]

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Abstract

Sixty-three patients with hypercholesterolemia and coronary disease were treated with d-thyroxine for an average period of 16 months. D-thyroxine decreased serum cholesterol without increasing the metabolic rate significantly when amt ranging from 4–8 mg/day were used.

In 56 patients with essential hypercholesterolemia d-thyroxine lowered the serum cholesterol in a little over half of the patients. In five patients with hypothyroidism and hypercholesterolemia treated with thyroid extract, the addition of d-thyroxine resulted in marked and sustained lowering of serum cholesterol without causing hypermetabolism.

In two patients with diabetes mellitus and hypercholesterolemia d-thyroxine lowered the serum cholesterol without significantly affecting the diabetic state and the insulin requirement. Increase in angina was seen in 13% of the patients.

In man, d-thyroxine lowers the serum cholesterol by increasing the degradation and excretion of cholesterol.

Introduction

IN ADDITION TO FACTORS such as heredity, obesity and high blood pressure, elevated blood cholesterol is considered one of the most important factors in the development of atherosclerosis. As a result, extensive research has been carried out in order to find or develop agents that would lower elevated blood cholesterol. It has been known for many years that the hormones of the thyroid gland influence cholesterol metabolism and lower the blood cholesterol. However, they also increase the metabolic rate which is undesirable especially in patients with coronary heart disease and angina pectoris. In recent years considerable effort has been made to synthesize thyroid analogs with minimal metabolic effects, yet retaining their cholesterol-lowering ability. A great number of analogs have been studied. Except for the d-isomers of thyroxine, other thyroid analogs showed no specific promise in this regard.

Sodium dextro-thyroxine (d-thyroxine) has been reported to lower the blood lipids with no significant rise in the basal metabolic rate when the dose is not greater than 16 mg/day. Although there are numerous reports regarding the cholesterol-lowering effect and other effects of sodium dextro-thyroxine, long-term clinical studies are relatively few.

The purpose of this paper is to report on the results of long-term use of sodium dextro-thyroxine in patients with hypercholesterolemia, arteriosclerotic heart disease and angina pectoris, and also to review briefly the effect of d-thyroxine and other thyroid analogs on cholesterol metabolism.

Materials and Methods

Sixty-three ambulatory patients with hypercholesterolemia, arteriosclerotic heart disease and angina pectoris followed in the Heart Clinic of the University of Minnesota Hospitals for over six months were selected for study. Fifty-six patients were clinically euthyroid and had essential hypercholesterolemia (cause unknown) and normal serum protein-bound iodine levels. Family history of hypercholesterolemia was obtained in seven patients only.

Five patients had hypothyroidism and were on a maintenance dose of thyroid extract. Two patients had diabetes mellitus and were under good control with diet and insulin. Table I shows the age and sex distribution of patients.

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In the control period, weekly serum cholesterol determinations were obtained in every patient at least four times after overnight fasting.

The serum protein-bound iodine was determined in each patient in the control period and at least once during the treatment period. Serum phospholipids and total lipids were determined only occasionally.

All patients had coronary heart disease, manifested by angina pectoris and/or arteriosclerotic heart disease with cardiomegaly, and with or without heart failure.

The diets remained unchanged during the control and treatment periods. After at least a one-month control period, patients were given orally 4 mg sodium dextor-thyroxine (choloxin) [Sodium dextro-thyroxine (choloxin) was kindly supplied by the Baxter Laboratories, Inc.] daily, for a period of 6–28 months (average of 16 months).

Patients were examined periodically and the serum cholesterol was determined every two weeks for the first two months, and monthly thereafter. The average of serum cholesterol values obtained during the control period constituted the "control" or the "pre-treatment" level and the average of serum cholesterol values obtained during the period of sodium dextro-thyroxine administration constituted the "after treatment" level. Patients kept records of the number of anginal attacks and the number of nitroglycerine pills taken every day.

If no cholesterol lowering was noted in one month, the sodium dextro-thyroxine dose was increased to 6 mg/day. If there was no response to this increased dose in one month, it was further increased to 8 mg/day and finally to 12 mg/day, if there was no response to 8 mg/day.

Sodium dextro-thyroxine was decreased or discontinued in patients who developed angina or noted an increase of pre-existing angina pectoris. A 50% or over increase in the number of anginal attacks was accepted, arbitrarily, as significant.

Serum cholesterol levels after treatment were compared with those before treatment and the degree of difference between these two periods was determined using the Student t-test. When P was less than 0.05 the differences were regarded as significant.

Results

Table II summarizes the cholesterol-lowering effect of d-thyroxine in various groups of patients with hypercholesterolemia and coronary disease.

In the entire group of 63 patients the control and the post-treatment serum cholesterol values were 316 ± 7.1 mg% and 274 ± 8.6 mg%, respectively. The decrease of 42 mg% (13%) is statistically significant ($p < 0.002$).

In the entire group of 56 euthyroid patients with essential hypercholesterolemia, the control and post-treatment serum cholesterol values were 306 ± 7.8 mg% and 279 ± 8.1 mg%, respectively. The decrease of 27 mg% is statistically significant ($p < 0.02$).

However, not all patients responded to treatment. Out of these 56 patients with essential hypercholesterolemia, sodium dextro-thyroxine decreased the serum cholesterol in 31 patients (56%) from a control value of 326 ± 7.3 mg% to 261 ± 7.9 mg%. The decrease in serum cholesterol of 65 mg% (20%) is statistically significant ($p < 0.001$).

There was no significant lowering of serum cholesterol in the remaining 25 patients. The control and post-treatment serum cholesterol values of this group were 298 ± 9.2 mg% and 282 ± 10.1 mg%, respectively. The decrease in serum cholesterol of 16 mg% (5%) is not statistically significant ($p > 0.2$).

The serum cholesterol returned to control levels in four patients after an initial significant decrease lasting from six weeks to three months. Gradual increase of sodium dextro-thyroxine did not alter the response. In the remaining patients, the serum cholesterol-lowering effect was noted about two weeks after the onset of sodium dextro-thyroxine treatment and continued as long as the patient remained on the drug. A prompt rise in serum cholesterol, approaching the control values, was observed in several patients who had temporarily discontinued treatment. The serum cholesterol decreased in all these patients who started taking sodium dextro-thyroxine again. Figure 1 shows the serum cholesterol changes in one patient with essential hypercholesterolemia when the drug was discontinued and then resumed. This type of response is typical for patients in whom sodium dextro-thyroxine is effective.

Eight patients (13%) discontinued the drug because of an increase in angina pectoris.

Serum protein-bound iodine increased from 6.6 mcg% to 9.8–12 mcg% in all patients taking the medication.

The body wt, the blood pressure and the pulse rate of these patients did not change significantly. Except for the increase of angina in some patients, as indicated above, the clinical findings were not altered significantly.

One patient died from what clinically appears to be acute myocardial infarction two weeks after he had discontinued the sodium dextro-thyroxine. Necropsy could not be performed.

TABLE I

Patients with Hypercholesterolemia and Coronary Disease Treated with D-Thyroxine

Types of patients	Number of patients	Sex		Age (years) mean and range	
		males	females	males	females
Euthyroid (essential hypercholesterolemia)	56	40	16	54 (35–70)	61 (26–74)
Hypothyroid	5	2	3	55	71
Diabetes Mellitus	2		2		64

TABLE II

Long-Term Cholesterol-Lowering Effect of D-Thyroxine in Patients with Hypercholesterolemia and Coronary Disease

Types of patients	Number of patients	Serum cholesterol (mg %) Mean and S.E.[a]		Decrease (mg %)	P value
		Control	After d-thyroxine		
Euthyroid (essential hypercholesterolemia)	56				
Euthyroid responders	31	326 ± 7.3	261 ± 7.9	65	<0.001
Euthyroid nonresponders	25	298 ± 9.2	282 ± 10.1	16	>0.2
Hypothyroid	5	Av 383 (368–514) range	Av 247 (220–260) range	136	
Diabetes mellitus	2	Av 265 (248–282)	Av 234 (218–250)	31	

[a] S.E. = Standard Error of the Mean.

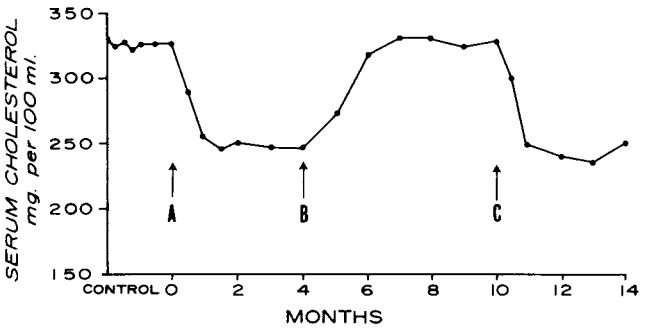

FIG. 1. The effects of discontinuing and then resuming d-thyroxine administration on the serum cholesterol of a 70 year old man with essential hypercholesterolemia.

A. D-thyroxine, 4 mg/day, started.
B. D-thyroxine discontinued.
C. D-thyroxine, 4 mg/day, resumed.

Marked decrease of serum cholesterol was noted in five patients with hypothyroidism whose symptoms were well controlled with thyroid extract (USP), but had elevated serum cholesterol values.

The average control and post-treatment serum cholesterol values in this group were 383 mg% (range: 368–415) and 247 mg% (range: 220–260), respectively. This represents a decrease of 136 mg% (36%).

Significant decrease in serum cholesterol was observed in two patients with hypercholesterolemia and diabetes mellitus controlled by insulin and diet. In one patient the serum cholesterol decreased only after sodium dextro-thyroxine was increased from 4 to 8 mg.

Discussion

The results of this study are in general agreement with those reported by others (1–43).

Increase in the severity of angina was not as marked as was reported by Robinson et al., who observed it in seven out of 16 patients receiving 4 mg of dextro-thyroxine (44). The incidence of angina pectoris in patients receiving d-thyroxine is not known. Although most authors claim that it will increase anginal attacks in patients with coronary disease, there are some who report decrease of angina in such patients after long-term therapy with d-thyroxine (15,16,95,96).

Boyd and Oliver have indicated that d-thyroxine produces angina less often than other thyroid analogs (9). Since many factors can precipitate or increase angina pectoris, it is not always possible to relate the increase in symptoms to the drug under study. In this regard it is of interest that no increase in angina was observed in three patients in this study who were started again on 4 mg of dextro-thyroxine after the drug had been discontinued for four weeks because of aggravation of angina. There was no significant change in the cardiovascular functions of patients on drug. From the available information it is not possible to know whether or not d-thyroxine increases the death rate in patients with coronary disease. One death that occurred in a patient who received the drug was most likely not related to treatment. The patient was off drug for at least two weeks at the time of death.

Difficulty in diabetic control was observed in some patients with diabetes mellitus receiving d-thyroxine (41). However, there was no aggravation of diabetic state in the majority of cases reported. In this study in two patients with diabetes mellitus, sodium dextro-thyroxine did not alter the clinical picture significantly.

The drug has been reported to be effective in lowering the serum lipids of diabetic patients although some have reported unpredictable and variable results (15,40,41,92).

D-thyroxine has been used in myxedematous or hypothyroid patients with clinical benefit and marked reduction of serum lipids (9,93,97,98,99).

In our patients with hypothyroidism and hypercholesterolemia receiving thyroid extract, sodium dextro-thyroxine lowered the serum cholesterol without causing hypermetabolism. In these patients thyroid extract could not be increased without producing symptoms.

The largest number of patients treated with d-thyroxine have been those with essential hypercholesterolemia with or without angina pectoris. Although most authors have reported significant lowering of serum cholesterol in this group of patients, there are some who consider d-thyroxine either ineffective or having minimal hypocholesterolemic effect (20,100).

In euthyroid patients with hypercholesterolemia reported here, sodium dextro-thyroxine lowered the serum cholesterol in only 56% of the cases. In the remaining patients the drug was either ineffective or it had to be discontinued because of increase in angina.

The proportion of patients escaping from the effect of drug is relatively small.

Although the number of patients is not large, the findings indicate that patients with hypothyroidism who are treated with thyroid extract, but still maintain an elevated serum cholesterol, appear to be most responsive to sodium dextro-thyroxine treatment.

The number of patients reported in the literature as receiving or having received d-thyroxine for periods ranging from several months to several years is ca. 2000. It has been used in a variety of clinical conditions associated with hypercholesterolemia with or without heart disease.

The dosage used varies between 0.5–16 mg/day. The most frequently used dosage is 4–6 mg/day. Side effects have been reported in about 10% of the cases and consisted of angina, arrhythmias, nervousness, wt loss and insomnia. Increase of prothrombin time was observed in patients on coumadin (94). Like other cholesterol-lowering substances, the higher the initial level of serum cholesterol the greater the effect of d-thyroxine will be (15,24). Increasing the daily intake of d-thyroxine will increase the effect; however, increases over 8 mg/day usually will not be accompanied by greater effect (24).

Sodium dextro-thyroxine has general properties which are quite similar to those of other thyroid analogs used to lower serum cholesterol. The effect of iodothyronines and various iodinated compounds on plasma cholesterol of man, rabbit, rat, pigeon and chick has been studied extensively (9,45–69). Their ability to arrest the atheromatous process or cause regression of atheromatous lesions in rabbit, rat and chick has also been studied (50,70–76).

The pharmacology as well as the biochemistry of sodium dextro-thyroxine have been studied extensively.

In mice and rats, sodium dextro-thyroxine has ca. 2–10% the calorigenic activity of l-thyroxine. It can replace the thyroid hormone in thyroidectomized rats (77).

D-thyroxine, like l-thyroxine, will raise serum protein bound iodine. It will prevent the development of goiter in propylthyouracil treated rats. Its effect in

this regard is only ca. one-fourth of l-thyroxine. In rats, the cardiac effects of d-thyroxine, as judged by 50% acceleration of heart rate, is only 1–2% of the effect of l-thyroxine (48).

Studies done with isolated rabbit atrial myocardial strips show that d-thyroxine has practically no effect on excitability (78). In rats the amt of d-thyroxine that reduces serum cholesterol to 50% of initial value is 35 times less than the amt that increases the pulse rate by 50% or more (48). D-thyroxine stimulates the liver and increases the oxidative catabolism and excretion of cholesterol and its degradation products into gut and feces (79–85).

When given parenterally, d-thyroxine is concd in the liver and kidney and to a lesser extent in the heart, brain, muscle and skin (80). It is deiodinated and excreted in urine and feces more rapidly than l-thyroxine (86). In man, d-thyroxine increases the synthesis of cholesterol; however, there is greater increase in the degradation and excretion of cholesterol resulting in lower serum cholesterol values (87–89). It was found that in addition to serum cholesterol d-thyroxine also decreased the serum phospholipids, betalipoproteins and total lipids (5,19,90,91). Its effect on triglycerides and alphalipoproteins is variable (5,8,92–93).

Our findings demonstrate that d-thyroxine is effective in lowering the serum cholesterol of some patients with hypercholesterolemia and coronary disease. Its greatest promise appears to be in cases with hypercholesterolemia associated with hypothyroidism, where the dosage of l-thyroxine cannot be increased without producing hypermetabolism and angina pectoris. It is less effective in essential hypercholesterolemia. The incidence of side effects and escape from the effect of drug in the group studied is relatively small.

The discussion of the virtues of lowering the serum cholesterol as a means of treating arteriosclerotic heart disease is beyond the scope of this paper.

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