

Reduced Serum Lipids After Liothyronine Administration Combined with Diet High in Unsaturated Fat

LEO E. HOLLISTER, M.D.*

FORMULA diets high in unsaturated fats have been reported to reduce serum cholesterol and phospholipid values in several clinical states marked by high concentrations of serum lipids.¹⁻⁴ While patients have been maintained on such diets for long periods in some research institutions, the technic has obvious limitations. Our previous attempts to reduce serum lipids by supplementing the diet with modest amounts of vegetable oil were unsuccessful without other dietary changes.⁵ Other investigators⁶ have been moderately successful with concomitant dietary restriction of saturated fats. Drastic restriction of dietary fat to as low as 3 gm. daily has lowered some serum lipid fractions, although it has sometimes increased neutral fat; restriction to at least 40 gm. total fat was required to reduce serum cholesterol ester levels.⁷ Thus, neither dietary restriction of fat nor supplementation with oils alone has proved practical for controlling serum lipid levels. More recently, interest in thyroid hormones has been revived. The administration of l-triiodothyronine (liothyronine) and l-thyroxine have lowered serum lipid levels, although usually at the cost of increased metabolism, with its possible attendant hazards for some patients.^{8,9}

The aim of this study was to combine these technics, using a short-term formula diet followed by a modest restriction of dietary fat supplemented by vegetable oil and small doses of liothyronine. Such a program was conceived of as acceptable and applicable to pa-

tients treated in physicians' offices rather than limited to subjects on metabolic wards. Two separate experiments were made to determine whether or not combined use of liothyronine and unsaturated fats had any additive effect.

METHOD OF STUDY

Nineteen hospitalized psychiatric male patients, ranging in age from twenty-eight to seventy-two years (eleven of whom were over sixty years of age), were selected for treatment with liothyronine and soy bean oil emulsion supplements. Two patients were given two separate trials of treatment, making twenty-one trials in all. Treatment lasted from six to fifty-eight weeks, median length being thirty weeks. For several weeks before treatment from six to sixteen determinations of serum lipid fractions were obtained as control values. During treatment, determinations were made at intervals of two weeks, being continued after treatment whenever possible. Patients were weighed at intervals of two weeks. They were allowed to continue all normal activities.

The dietary regimen began with a formula diet administered for three weeks. Twelve feedings daily were given, six consisting of 30 ml. of 60 per cent soy bean oil emulsion and six of 200 ml. of skim milk solution (skim milk powder, granulated sugar, vanilla and water). Total calories from the formula were 1,722, derived from 120 gm. carbohydrate, 80 gm. protein and 108 gm. fat, the latter being 82 per cent unsaturated. Each daily diet was supplemented by one 6 ounce serving of orange juice, one soft-cooked egg, two servings of plain vegetables and three slices of plain bread or toast, increasing it to approximately 2,000 calories. While the formula diet was being administered, a multiple vitamin tablet was added daily.

After three weeks, patients were switched to a customary hospital "low-fat" diet of 1,800 calories derived from 225 gm. carbohydrate, 70 gm. protein

From the Veterans Administration Hospital, Palo Alto, California.

* Assistant Chief of Staff.

and 70 gm. fat. Daily fat intake was provided by two eggs, three pats of butter, three glasses of whole milk and a low-fat dessert. A daily supplement of 90 to 120 ml. of 60 per cent soy bean oil emulsion was added, increasing total calories to about 2,400 daily. About two-thirds of the total daily intake of fat was unsaturated. This dietary program was continued throughout the treatment period.

Liothyronine was administered concurrently in this dosage schedule: 5 μ g. daily for five days increased progressively until a dose of 50 μ g. daily was attained by the twenty-sixth day. This dose was maintained throughout treatment in one trial, raised to 75 μ g. in seventeen trials and to 100 μ g. daily in three trials.

Two separate groups of elderly patients were studied to compare the effects of liothyronine when given alone or combined with a supplement of unsaturated fatty acids while an *ad libitum* diet was taken. Thirteen patients were treated with 5 μ g. daily of liothyronine for one week, 20 μ g. daily for another week 25 μ g. daily for four weeks and 50 μ g. daily for seven weeks. Six patients received only the hormone while seven received an added supplement of 60 ml. daily of 60 per cent soy bean oil emulsion throughout the course. Prior to treatment a series of control determinations of serum lipids were made; during treatment serum cholesterol was measured weekly for five weeks, bi-weekly thereafter; total lipids were measured at two, seven and thirteen weeks; phospholipids at four and eleven weeks.

Another sixteen elderly patients were treated with liothyronine for ten weeks, reaching doses of 75 μ g. daily after a rapid build-up (total dose, 7,445.9 μ g.). During the last six weeks, 180 ml. daily of 60 per cent soy bean oil emulsion was added to the daily free-choice diet of eight patients, the others continued on liothyronine alone. At least six determinations of serum cholesterol were obtained in the four week period preceding treatment; weekly determinations were made during treatment; six determinations were made during a four week period following treatment.

RESULTS

Results of treatment with a diet high in unsaturated fatty acids and liothyronine in twenty-one trials (nineteen patients) are summarized in Table I. Satisfactory reduction of serum lipid fractions (20 per cent or more) was obtained in nineteen trials (seventeen patients). Mean serum cholesterol values

TABLE I
Changes in Serum Lipid Fractions in Twenty-One Trials in Nineteen Men Treated with Diet High in Unsaturated Fats and Liothyronine

Period	No.	Mean (mg. per 100 ml.)	Standard Error
<i>Cholesterol</i>			
Control	21	341	7.5
Treatment	21	248	9.2
Post-treatment	13	337	15.7
Control vs. treatment, $P = <0.001$; control vs. post-treatment, $P = \text{n.s.}$; treatment vs. post-treatment, $P = <0.001$			
<i>Phospholipids</i>			
Control	13	314	5.6
Treatment	14	231	9.6
Control vs. treatment, $P = <0.001$			
<i>Total Lipids</i>			
Control	13	1070	24.7
Treatment	14	784	32.6
Control vs. treatment, $P = 0.01$			

prior to treatment were reduced from 341 mg. per 100 ml. to 248; for total lipids, 1,070 to 784; for phospholipids, 314 to 231. The lower levels were sustained during treatment, although usually the level was not as low as it was during the period of formula diet. With a few exceptions, relapse occurred soon after the treatment program was discontinued. The limited range in the dose employed allowed no conclusion to be drawn in regard to the results which would have been obtained had larger doses of liothyronine been employed. Past experience with this agent suggested these limits to avoid excessive thyromimetic symptoms.

Weight loss was a conspicuous side effect of treatment, occurring in thirteen patients. The mean weight change for the group was an 8 pound loss, with a range from a 6 pound gain to a 23 pound loss. Neither the occurrence of weight loss nor its extent accounted for the fall

TABLE II

Serum Lipid Changes After Treatment with Liothyronine, Alone or Combined with Unsaturated Fatty Acid Supplement for Thirteen-Week Period (Low-Dose Regimen)

Period	No.	Mean (mg. per 100 ml.)	Standard Error	P
<i>Liothyronine Alone</i>				
<i>Cholesterol</i>				
Control.....	7	314	10.4	
Treatment.....	7	254	13.7	<0.01
<i>Phospholipids</i>				
Control.....	7	292	8.3	
Treatment.....	7	240	8.9	<0.001
<i>Total Lipids</i>				
Control.....	7	1,031	31.7	
Treatment.....	7	879	37.6	0.02
<i>Liothyronine + Unsaturated Fatty Acids</i>				
<i>Cholesterol</i>				
Control.....	6	306	23.7	
Treatment.....	6	240	16.4	<0.001
<i>Phospholipids</i>				
Control.....	5	281	25.5	
Treatment.....	5	240	13.6	n.s.
<i>Total Lipids</i>				
Control.....	6	1,048	52.8	
Treatment.....	6	858	37.7	<0.01

NOTE: No significant differences between treatments.

in serum lipids. Although the diet was calculated to provide adequate calories to provide for the patients' energy needs, intake may not have been complete in every case. In addition, the increased metabolism resulting from the administration of the thyroid hormone probably accounted for some of the more severe losses. Except for the patients' objection to three weeks of the formula diet and some mild

TABLE III

Serum Cholesterol Changes after Treatment with Liothyronine, Alone or Combined with Unsaturated Fatty Acid Supplement for Ten Week Period (High-Dose Regimen)

Period	No.	Mean (mg. per 100 ml.)	Standard Error
<i>Liothyronine Alone</i>			
Control.....	8	257	13.1
Treatment.....	8	200	12.0
Post-treatment.....	8	242	14.7
Control vs. treatment, P = 0.001; Control vs. post-treatment, P = n.s.; Treatment vs. post-treatment, P = <0.001			
<i>Liothyronine + UFA Supplement</i>			
Control.....	8	259	19.3
Treatment.....	8	209	16.3
Post-treatment.....	8	248	21.0
Control vs. treatment, P = <0.001; Control vs. post-treatment, P = n.s.; Treatment vs. post-treatment, P = 0.001			

NOTE: No significant differences between two treatments.

diarrhea associated with it, the program was well tolerated.

A specific reason for prolonged use of the formula diet was to see if it could replace the conventional Sippy diet in the treatment of duodenal ulcer. Two patients in the series and five others were treated with this diet for three weeks in addition to their usual anticholinergic medication. After three weeks of such treatment, six patients showed satisfactory x-ray evidence of healing, which was maintained whether they were subsequently switched to the low fat diet (two study patients) or to a bland diet. As might be expected, substantial falls in serum lipids were noted in patients treated with the formula diet alone, regardless of the initial starting levels. In patients resuming a bland diet, however, the serum lipids promptly returned to pretreatment levels.

Results of two additional studies of the comparative effect of liothyronine alone or com-

bined with supplemental unsaturated fatty acids failed to demonstrate any different effect from the combination. Summarized data on thirteen patients treated with low maximal doses of liothyronine (50 μ g. daily) and soy bean oil emulsion (60 ml. daily) are shown in Table II. Summarized data on sixteen patients treated with the higher doses of liothyronine (75 μ g. maximum) and soy bean oil emulsion (180 ml. daily) are shown in Table III. In each group of patients, both treatment programs reduced serum lipid fractions to a comparable degree. Discontinuation of treatment led to fairly rapid relapse.

COMMENTS

Combined treatment with a diet high in unsaturated fats and liothyronine was feasible and effective. Two major drawbacks were the formula diet and weight loss produced by the thyroid hormone. Unless there is some special reason for using the formula diet (e.g., treating duodenal ulcer in patients in whom serum lipid control is desirable), less drastic means may be used. A more liberal diet has been devised which includes fruit, juices, cereals, salads, fish, paste, cottage cheese and lean meat as well as a skim milk-soy bean oil emulsion. In this diet, which may be administered as three meals with three interval feedings, 1932 calories are provided by 165 gm. carbohydrate, 112 gm. protein and 92 gm. fat, about two-thirds of which is unsaturated. Newer analogues of thyroid hormones may retain the lipid-lowering effects while decreasing other metabolic effects, avoiding excessive weight loss.

One of the hypotheses of the study, that possible additive or synergistic effects could be obtained from combined treatment, was not confirmed by the two studies specifically testing this point. This being the case, one might question whether the dietary program was at all necessary. Results obtained after the discontinuation of liothyronine in four patients suggest that the diet had value. These patients all received prolonged treatment. Treatment values for serum cholesterol averaged 239, 254, 235 and 235 mg. per 100 ml., respectively. Liothyronine administration was

discontinued and measurements were obtained for sixteen weeks during which the four patients were maintained only on the low fat diet and supplemental soy bean oil emulsion. During this period, serum cholesterol values averaged 239, 252, 221 and 231 mg. per 100 ml., respectively. Thus the administration of thyroid hormone was discontinued without impairing therapeutic effect. These results are sharply different from abandoning the entire program. Furthermore, patients in this study showed no tendency to "escape" which sometimes happens when liothyronine is the only therapeutic agent used. Other clinical experience suggests that treatment with unsaturated fats may be slowly cumulative, eventually increasing their total proportion in the body. Thus, the combined treatment program may have advantages not readily apparent in short-term studies.

SUMMARY

Nineteen patients were given twenty-one trials of treatment (median duration thirty weeks) with a diet high in unsaturated fatty acids and a thyroid hormone, liothyronine. Satisfactory reduction of serum lipid fractions (20 per cent or more) was obtained in nineteen trials with seventeen patients. Mean serum cholesterol values prior to treatment were reduced from 341 mg. per 100 ml. to 248; for total lipids, 1,070 to 784; for phospholipids, 314 to 231. Weight loss was a conspicuous side effect, although not apparently related to the effect on serum lipid levels; possibly it represented evidence of increased metabolism induced by the administration of liothyronine. Use of an unsaturated fatty acid formula diet also proved an effective dietary management for treating patients with duodenal ulcer.

Two separate studies to determine if the combination of dietary management and liothyronine administration exceeded the effects of liothyronine alone failed to show any difference. Both treatment programs reduced serum lipid fractions to a comparable degree. The combined program may have advantages for long-term use, based on observations on four patients in whom only the administration of liothyronine was discontinued.



ACKNOWLEDGMENT

Supplies of liothyronine for these studies were furnished by William E. Kirsch, Smith, Kline & French Laboratories, Inc. I also wish to thank Drs. Frederick S. Glazener, Robert S. Mowry and John Withrow for their assistance.

REFERENCES

1. KINSELL, L. W., MICHAELS, G. D., PARTRIDGE, J. W., BOLING, L. A., BALCH, H. E. and COCHRANE, G. C. Effect upon serum cholesterol and phospholipids of diets containing large amounts of vegetable fat. *J. Clin. Nutrition*, 1: 224, 1953.
2. BRONTE-STEWART, B., ANTONIS, A., EALES, L. and BROCK, J. F. Effects of feeding different fats on serum-cholesterol level. *Lancet*, 1: 521, 1956.
3. MALMROS, H. and WIGAND, G. The effect on serum-cholesterol of diets containing different fats. *Lancet*, 2: 1, 1957.
4. AHRENS, E. H., JR., HIRSCH, J., INSULL, W., JR., TSALTAS, T. T., BLOMSTRAND, R. and PETERSON, M. L. The influence of dietary fats on serum lipid levels in man. *Lancet*, 1: 943, 1957.
5. HOLLISTER, L. E. and GLAZENER, F. S. Serum lipid levels in geriatric patients treated with a dietary supplement of unsaturated fatty acids. *J. Am. Geriatrics Soc.*, 7: 327, 1959.
6. TOBIAN, L. and TUNA, N. The efficacy of corn oil in lowering the serum cholesterol of patients with coronary atherosclerosis. *Am. J. M. Sc.*, 235: 133, 1958.
7. HATCH, F. T., ABELL, L. L. and KENDALL, F. E. Effects of restriction of dietary fat and cholesterol upon serum lipids and lipoproteins in patients with hypertension. *Am. J. Med.*, 19: 48, 1955.
8. STRISOWER, B., ELMLINGER, P., GOFMAN, J. W. and DE LALLA, O. The effect of 1-thyroxine on serum lipoprotein and cholesterol concentrations. *J. Clin. Endocrinol.*, 19: 117, 1959.
9. SACHS, B. A., DANIELSON, E., ISAACS, M. A. and WESTON, R. E. Effect of triiodothyronine on the serum lipids and lipoproteins of euthyroid and hyperthyroid subjects. *J. Clin. Endocrinol.*, 18: 506, 1958.

