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Dietary and Drug Treatment of Hyperlipidaemia

A Feasibility Study in Asymptomatic Middle-aged Men

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ABSTRACT

83 middle-aged men with different types of hyperlipoproteinaemia were recruited from a health examination survey. They were treated with diet for 3 months and with diet and drugs in combination over a 2-year period (63 men used drugs). The serum lipid reductions after the dietary period were 14% and 27% for serum cholesterol and triglycerides, respectively. After 2 years the corresponding reductions were 21% and 42%, indicating an additional effect of diet and drugs. There was an average body weight reduction of 4.3% during the first 3 months which was maintained over the 2-year period. Special considerations in treating asymptomatic individuals are discussed.

Prospective epidemiological studies have shown an association between elevated levels of cholesterol (8, 20) and triglycerides (TG) in serum (2) and development of coronary heart disease (CHD). Significant positive linear correlations between serum cholesterol and/or TG concentrations and risk of CHD have been demonstrated.

During the last 20 years several feasibility studies (5, 11, 13) as well as primary preventive trials have been performed aiming at lowering serum cholesterol by dietary regimen (4, 12, 17, 19) or drug therapy (15, 16). The results as to the lipid lowering effects have varied in different populations (14).

The aim of the present study was to investigate the effect of dietary and drug treatment on serum lipid levels in a group of asymptomatic middle-aged men with hyperlipidaemia.

MATERIAL

All men, born 1920–1924, who lived in the city of Uppsala were invited to a health examination survey with the main purpose of identifying and correcting risk factors for cardiovascular disease (6). The investigation was conducted at the Department of Medicine, University Hospital. The participation rate was 83.9%.

A total number of 174 asymptomatic men with "primary" hyperlipidaemia, defined as mean value of two samples of serum cholesterol and/or TG above the 80th percentile of the examined population, were invited to a special lipid clinic. One subject did not come to the lipid clinic. Five men came to the first visit but did not come for the complete serum lipoprotein (LP) analysis. The result of the classification of the LP pattern in the remaining 168 subjects is shown in Table I.

All 168 subjects were offered treatment after the LP analysis. Those with a normal LP pattern according to the limits used were given dietary prescriptions only and their serum lipids were reexamined after one year. This group comprised 30 men. All subjects with hyperlipoproteinaemia (HLP) were initially treated with a dietary regimen for 3 months, after which they were offered additional therapy with lipid-lowering drugs. The results presented here concern the effect of the therapy on serum lipid concentrations in the group of 83 men with HLP representing all men who at the follow-up had participated for at least 24 months after initiation of therapy.

METHODS

At the first visit to the lipid clinic the subjects were introduced to the programme and its long-term aspects were explained. The wives were invited together with the men to the second visit at the lipid clinic. Results of the LP determinations were then presented and a dietary information was given by a dietitian, often to a group of three or four couples together.

During the following three months of dietary treatment serum lipid analyses were performed at monthly intervals. The subjects were seen 2 weeks after each determination when they were informed of the result and had the possibility to see the dietitian if they desired.

Diet prescriptions. The subjects were advised to avoid food high in

(*a*) saturated fatty acids, e.g. fat meat and pork, dairy products such as butter, cream, cheese and whole milk and hard margarine.

(*b*) cholesterol, e.g. egg yolks and liver.

(*c*) simple sugars (mono- and disaccharides) e.g. refined sugar, sweets, sweet desserts, sweet beverages and sweet cakes (HLP type II B and IV).

The subjects were advised to use foods containing

(*a*) little or no saturated fatty acids, e.g. skimmed milk, lean meat, low-fat cheese.

Table I. *Lipoprotein patterns of 168 asymptomatic middle-aged men with serum lipids above the 80th percentile of the same population*

Lipoprotein pattern	No. of subjects	Subjects (%)
Normal	37	22.0
II A	38	22.6
II B	25	14.9
III	15	8.9
IV	51	30.4
V	2	1.2
Total	168	100.0

(*b*) polyunsaturated fatty acids, e.g. vegetable oils (with more than 50% linoleic acid), liquid margarine (containing more than 60% of linoleic acid), soft margarine (containing 25–45% linoleic acid).

The composition of the recommended diet should result in a P/S[1] ratio of 2, total fat 30–35% of the total calories and less than 300 mg cholesterol daily. The importance of using at least 50 ml of oil or liquid margarine daily was stressed. It was recommended to be used for frying, in dressings and in sauces. The subjects were advised that alcohol consumption should not exceed one bottle of beer a day. The daily caloric allowance was specified only when the subject had an actual over ideal weight >1.20.

Drug prescriptions. The subjects were offered drugs after the diet period, i.e. after 3 months. The drugs used were clofibrate (Atromidin®, ICI-Pharma, Göteborg, Sweden) and nicotinic acid (Nicangin®, Draco, Lund, Sweden). The men were informed about the most common side effects of the drugs. Clofibrate was given in a dose of 1 g twice daily, as a rule in the morning and in the evening and not necessarily after meals. Treatment with nicotinic acid was started with 0.25 g three times daily after meals. The dosages were increased by further 0.25 g three times daily every fourth day until a total dose of 3 g daily was reached. The intention was to use clofibrate as the first drug in HLP type IV and nicotinic acid in HLP type II A and II B.

Laboratory methods. At the screening examination the blood samples were drawn after an overnight fast. At the lipid clinic the blood samples were taken at the same time but the subjects were recommended to fast from 8 p.m. the evening before. Cholesterol and TG analyses were performed by semiautomatic techniques in a Technicon Auto-Analyzer type II (18). The separation and quantitative determination of LP density fractions by preparative ultracentrifugation as well as the analyses on agarose electrophoresis have been described in detail elsewhere (7).

The LP patterns were classified according to Fredrickson et al. using the recommendations by Beaumont et al. (1). The upper "normal" limits used, based on the 85th percentile of a local material of healthy men of different ages, were 200 mg/100 ml for low density lipoprotein (LDL) cholesterol and 1.40 mmol/l for very low density lipoprotein (VLDL) TG (3). These limits were used by the lipid clinic and were close to those obtained in a sample of healthy men from the present population study (7).

Statistical calculations. Conventional methods were used for calculation of mean value and standard deviation (S.D.). Significances of differences between mean values were estimated with Student's two-tailed *t*-test. When testing the means of serum TG concentrations the logarithm transformed values were used because the distribution of TG was skewed to the right (6). The differences between two values in the same subjects were estimated with the paired observation test using the Hewlett-Packard 9100 calculator programme. The accepted level of significance was $p<0.05$.

RESULTS

Subjects with normal LP pattern

The screening values (mean of two samples) of serum cholesterol and TG for 30 subjects with normal LP pattern at the lipid clinic were 299±33 mg/100 ml and 2.50±0.79 mmol/l, respectively. The average reduction between screening and the first analysis at the lipid clinic was 47 mg/100 ml (14.9%) for serum cholesterol and 0.57 mmol/l (18.8%) for serum TG although no lipid lowering regimen had been prescribed.

Table II. *Serum cholesterol concentrations (mean ±S.E.M.) in 83 asymptomatic middle-aged men with different types of hyperlipoproteinaemia (HLP) at initial examination and after 3 months of diet therapy and after 24 months of diet and drug therapy (drugs were used in 63 subjects)*

	Months		
	0	3	24
HLP type II A (n=20)			
Mean value, mg/100 ml	337±10	308±11	260±9
Mean change, mg/100 ml	–	29±2.3	75±2.5
Mean change, %	–	8.6±3.0	21.3±3.0
HLP type II B (n=17)			
Mean value, mg/100 ml	321±8	277±7	244±8
Mean change, mg/100 ml	–	44±2.1	77±2.4
Mean change, %	–	13.2±2.4	23.5±2.8
HLP type III (n=10)			
Mean value, mg/100 ml	303±19	242±17	229±9
Mean change, mg/100 ml	–	62±5.9	75±4.1
Mean change, %	–	19.1±5.6	23.4±2.8
HLP type IV (n=36)			
Mean value, mg/100 ml	278±6	235±7	221±6
Mean change, mg/100 ml	–	43±0.9	56±1.1
Mean change, %	–	15.4±1.8	19.4±2.2

[1] Ratio polyunsaturated fatty acids to saturated fatty acids.

Table III. *Serum triglyceride concentrations (mean ±S.E.M.) in 83 asymptomatic middle-aged men with different types of hyperlipoproteinaemia (HLP) at initial examination and after 3 months of diet therapy and after 24 months of diet and drug therapy (drugs were used in 63 subjects)*

	Months		
	0	3	24
HLP type II A (n=20)			
Mean value, mmol/l	2.37	2.12	1.47
Mean value, (log)	0.368±0.018	0.316±0.021	0.160±0.019
Mean change, mmol/l	–	0.26±0.03	0.90±0.02
Mean change, %	–	9.7±4.7	36.5±3.1
HLP type II B (n=17)			
Mean value, mmol/l	3.00	2.18	1.63
Mean value, (log)	0.471±0.019	0.326±0.025	0.195±0.030
Mean change, mmol/l	–	0.82±0.03	1.37±0.04
Mean change, %	–	26.9±3.4	44.4±4.6
HLP type III (n=10)			
Mean value, mmol/l	4.04	2.40	1.65
Mean value, (log)	0.593±0.036	0.347±0.058	0.211±0.025
Mean change, mmol/l	–	1.64±0.09	2.39±0.12
Mean change, %	–	40.1±6.0	56.4±4.5
HLP type IV (n=36)			
Mean value, mmol/l	3.36	2.19	1.85
Mean value, (log)	0.513±0.018	0.316±0.024	0.246±0.023
Mean change, mmol/l	–	1.18±0.02	1.51±0.03
Mean change, %	–	33.7±3.4	42.4±3.2

At the lipid clinic the subjects and their wives were given simple dietary recommendations by the physician only. When these men were reexamined one year later they still showed significantly lower serum cholesterol and TG concentrations than at the initial screening. The average reductions were 31 mg/100 ml (9.9%) for cholesterol ($p<0.001$) and 0.50 mmol/l (17.2%) for TG ($p<0.01$) compared to the screening levels. After one year 90% of the subjects had lower serum cholesterol and 77% had lower TG than initially. The mean body weight of the group was unchanged between the two visits at the lipid clinic one year apart.

Subjects with hyperlipoproteinaemia

Effect of dietary treatment. After 3 months of dietary treatment the serum cholesterol concentration was 262 mg/100 ml and the serum TG concentration was 2.19 mmol/l in the whole group of 83 men included in the 2-year study. These values corresponded to a reduction of 13.7% and 27.2% for serum cholesterol and TG, respectively. The degree of serum lipid changes was depending on the type of serum LP pattern the patient had before the treatment started (Tables II–III, Figs. 1–2). The greatest reductions, both in serum cholesterol and TG, were obtained in type III and the lowest in type II A.

The changes of individual serum lipid values are presented in Figs. 4–7. A few subjects with type II A had a higher serum cholesterol value after three months of dietary therapy compared with the initial values. Ten men with type II A had unchanged or higher serum TG values. Among patients with type II B pattern only one had an increased serum cholesterol value and none had higher serum TG after three months. Two men with type III had slightly higher serum cholesterol values while all serum TG values were considerably reduced during the dietary period. All but 2 individuals with type IV had lower serum cholesterol and TG values after the three months of dietary treatment.

The average body weight reduction was 4.3% in the whole group during the first 3 months. The weight was reduced in all types of HLP (Table IV, Fig. 3). The reduction was greatest in subjects with type II B, 4.6 kg, and lowest in those with type II A, 1.7 kg.

Effect of combined lipid lowering therapy. Sixty-

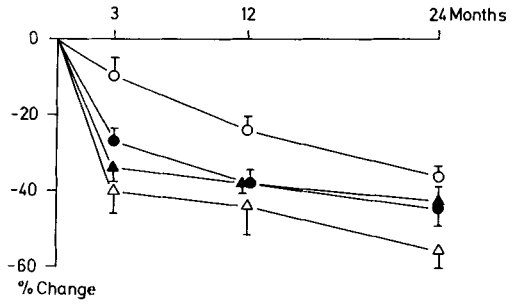

Fig. 1. Effect of lipid lowering therapy on serum cholesterol over a 2-year period in 83 asymptomatic middle-aged men with type II A hyperlipoproteinaemia (n=20, ○—○), type II B (n=17, ●—●), type III (n=10, △—△), and type IV (n=36, ▲—▲). (Mean ±S.E.M.)

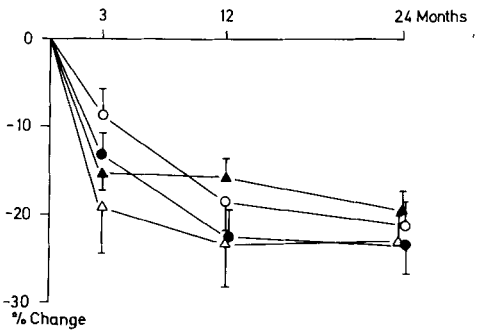

Fig. 2. Effect of lipid lowering therapy on serum triglycerides over a 2-year period in 83 asymptomatic middle-aged men with hyperlipoproteinaemia. Symbols as in Fig. 1.

three of the 83 men (75.9%) who were followed over the 2-year period were treated with lipid-lowering agents. In 44 men (69.8%) drug therapy was started immediately after the dietary period, i.e. after 3 months. In 8 subjects drugs were introduced at 6 months and in another 8 men between 6 and 12 months. Only 3 men were given medication later than one year after the hypolipidaemia treatment was started.

Table IV. *Body weight (mean ±S.E.M.) in 83 asymptomatic middle-aged men with different types of hyperlipoproteinaemia (HLP) at initial examination and after 3 months of diet therapy and after 24 months of diet and drug therapy (drugs were used in 63 subjects)*

	Months		
	0	3	24
HLP type II A (n=20)			
Mean value, kg	73.2±2.1	71.5±2.0	70.8±1.9
Mean change, kg	–	1.7±0.1	2.4±0.2
Mean change, %	–	2.2±0.5	3.1±0.9
HLP type II B (n=17)			
Mean value, kg	79.9±3.3	75.3±3.0	74.6±2.8
Mean change, kg	–	4.6±0.2	5.4±0.3
Mean change, %	–	5.6±0.7	6.4±1.3
HLP type III (n=10)			
Mean value, kg	82.6±3.5	78.7±3.3	78.5±2.8
Mean change, kg	–	3.9±0.2	4.1±0.4
Mean change, %	–	4.7±0.7	4.7±1.4
HLP type IV (n=36)			
Mean value, kg	81.3±1.5	77.7±1.4	76.2±1.4
Mean change, kg	–	3.8±0.1	5.1±0.1
Mean change, %	–	4.7±0.5	6.2±0.7

Nicotinic acid was given to 36 subjects. Their initial HLP types were type II 25 cases, type III 2 cases and type IV 9 cases. Clofibrate was given to 27 men, 7 with type II, 4 with type III and 16 with type IV. In type II A and II B 32 men (86.5%) used drugs. The percentage was lower, 69.4%, in type IV where 25 subjects were given drug therapy.

There were 9 men who declined drug therapy and 11 men were not offered drug therapy because the serum lipid concentrations on dietary treatment were already down to levels considered satisfactory. The mean serum lipid values after 3 months of dietary treatment in these 11 subjects were 197 mg/100 ml and 1.66 mmol/l for cholesterol and TG, respectively. The LP pattern in 3 of these men was classified as type III and as type IV in 5.

After 2 years the average serum cholesterol and TG concentrations were 236 mg/100 ml and 1.68 mmol/l respectively in the whole group of 83 men. These reductions corresponded to 21.2% and 43.1%. The serum lipid reductions in the 63 men

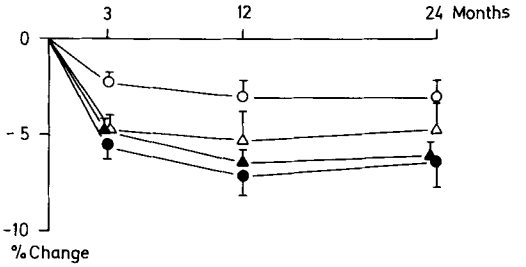

Fig. 3. Reduction of body weight in 83 asymptomatic middle-aged men with hyperlipoproteinaemia during 2 years of lipid lowering therapy. Symbols as in Fig. 1.

who were on diet and drug therapy in combination were 22.9% and 45.2% for serum cholesterol and TG, respectively.

The serum lipid changes in the four groups with different initial LP patterns are shown in Tables II–III and Figs. 1–2. The serum cholesterol reduction was similar, around 75 mg/100 ml, in all HLP types except for type IV. In all types the reduction was around 20% after 2 years. The greatest reduction of serum TG was obtained in type III, 2.39 mmol/l, which corresponded to 56.4%.

The individual changes of serum lipid concentrations after 2 years are shown in Figs. 4–7. In type II A (Fig. 4) 5 patients, all treated with drugs, had serum cholesterol values above the limit used as cut-off point (291 mg/100 ml) at the screening. The serum TG values were below the cut-off point (2.64 mmol/l) in all patients.

In type II B two individuals, both on drug therapy, had serum cholesterol values above the cut-off limit while the serum TG values were below the screening limit in all patients (Fig. 5). In a few subjects the serum lipids were higher than after the dietary period.

All the subjects with type III had serum lipid values below the cut-off limits (Fig. 6).

The serum cholesterol values of all men with type IV were below the cut-off values (Fig. 7). However, there were 14 men with higher values after 2 years than they had after the dietary period. Most of them had initially low serum cholesterol concentrations. Nine of them were without drug therapy. In 11 subjects the serum TG had increased after the first 3 months. Three individuals had values above the screening limit.

The serum lipid values of the 11 men without drug therapy were 210±31 mg/100 ml and 1.60±0.44 mmol/l for serum cholesterol and serum TG, respectively, corresponding to a reduction of 20.8% and 46.8%.

The 9 men who declined advice of drug therapy had significantly higher serum TG values after 2 years than the remaining subjects. The values were 2.20 mmol/l and 1.62 mmol/l, respectively ($p<0.001$). The serum cholesterol values were not significantly different.

The average body weight reduction in the total group after 2 years was 4.4 kg corresponding to 5.3%. The reductions in the different types of HLP are shown in Table IV and Fig. 3. The initial reductions after 3 months were maintained throughout the

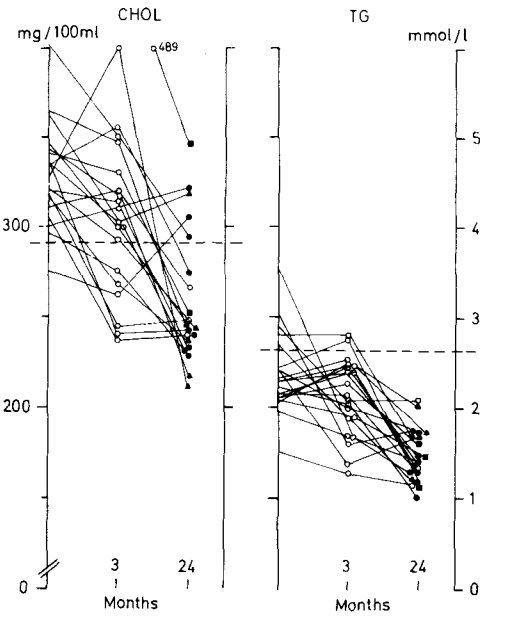

Fig. 4. Serum cholesterol and triglyceride concentrations in 20 men with type II A hyperlipoproteinaemia after 3 months of dietary therapy and after 2 years of diet and drugs in combination. ○=diet, ●=diet+clofibrate, ▲=diet+nicotinic acid, ■=diet+clofibrate+nicotinic acid.

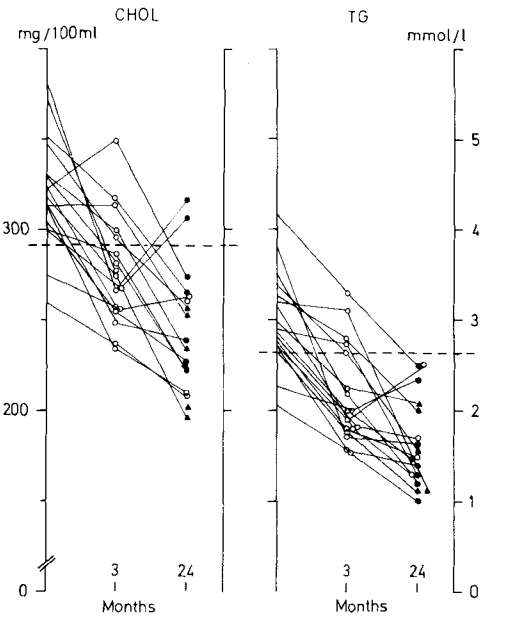

Fig. 5. Serum cholesterol and triglyceride concentrations in 17 men with type IIB hyperlipoproteinaemia after 3 months of dietary therapy and after 2 years of diet and drugs in combination. Symbols as in Fig. 4.

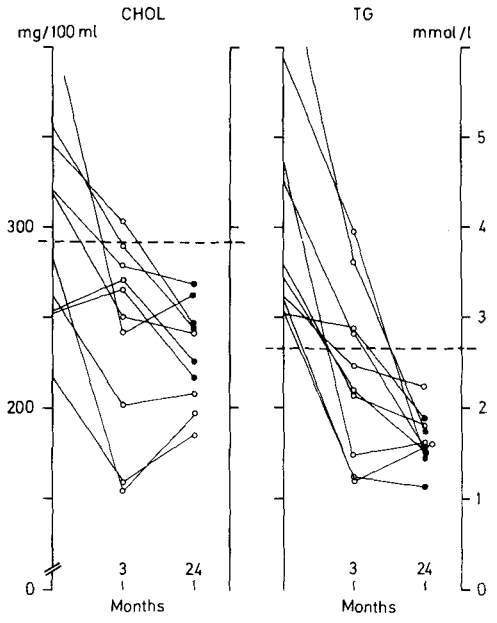

Fig. 6. Serum cholesterol and triglyceride concentrations in 10 men with type III hyperlipoproteinaemia after 3 months of dietary therapy and after 2 years of diet and drugs in combination. Symbols as in Fig. 4.

2 years. The greatest reduction, 5.4 kg, was obtained in subjects with type II B and the lowest, 2.4 kg, in those with type II A.

Out of the 168 men in whom the LP pattern was classified (Table I), 9 men (5.4%) dropped out during the following 18 months. If the six men who did not come for the LP analysis, are included the total drop-out rate over a 18-month period was 8.6% of those invited to the lipid clinic.

Side effects of drug therapy. Nicotinic acid was discontinued in 19 men (52.8%) because of side effects. The reasons were: flushing in 13 cases (combined with pruritus in 3 cases) and gastrointestinal irritation in 5 cases. One withdrawal was caused by psychosomatic complaints, this patient complained of blurred vision.

In 9 men nicotinic acid treatment was discontinued within 2 months, in 6 of them because of flushing. In the remaining 10 subjects the drug was withdrawn on average after 11 months (range 6–22). Liver function tests were checked regularly. In 3 cases there was a slight elevation of alkaline phosphatase. No case of hyperuricaemia was seen.

Clofibrate was well tolerated by all patients. When nicotinic acid had to be withdrawn, clofibrate was given instead.

DISCUSSION

The hyperlipidaemia found in this population was moderate. The LP pattern was classified as normal in 22% of the subjects with lipid values over the 80th percentile at the initial examination. In 30 of them a lipid reduction of 15% in serum cholesterol and 19% in serum TG had occurred between the screening and the first visit to the lipid clinic, i.e. usually within 3 months. This reduction was obviously caused by dietary changes induced by the information of elevated serum lipids. A moderate but significant serum lipid reduction was maintained over a one-year period. This indicates that among subjects with hyperlipidaemia there is a number of individuals, perhaps 20%, with moderate hyperlipidaemia in whom a substantial lipid reduction can be achieved by simple dietary recommendations.

The actual serum cholesterol reduction of 10% in these 30 men can be compared to that of the National Diet Heart Study where the cholesterol level was reduced by 11% over a one-year period (13). However, more impressive reductions have been reported in patients with CHD. In male survivors of myocardial infarction a serum cholesterol reduction of 17.6% over a 5-year period was obtained with diet therapy alone (9).

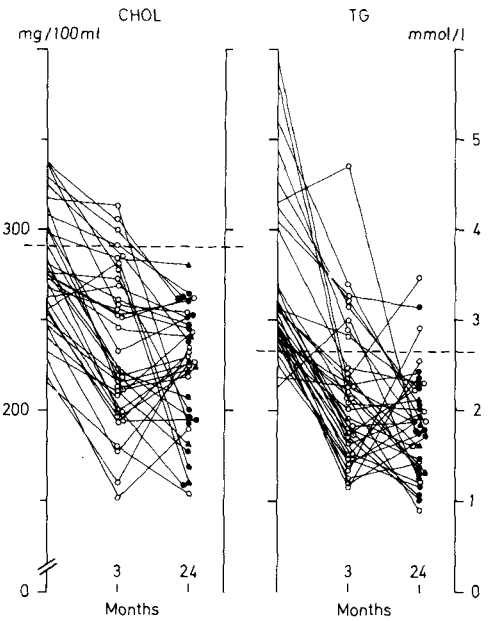

Fig. 7. Serum cholesterol and triglyceride concentrations in 36 men with type IV hyperlipoproteinaemia after 3 months of dietary therapy and after 2 years of diet and drugs in combination. Symbols as in Fig. 4.

There are several advantages, reviewed by Levy et al. (10), in defining the type of HLP that is causing the hyperlipidaemia. Thus, it is well known that the different types of HLP differ in responsiveness to the therapy. This was illustrated during the diet therapy by a serum cholesterol reduction of 19% in subjects with HLP type III compared to 9% in men with HLP type II A. The serum TG reductions ranged from 10% in type II A to 40% in type III.

The average serum lipid reductions obtained by diet therapy were maintained or increased over the 2-year period when drugs were added. Sixty-three men were given drug therapy. The effect of drugs may to some extent have been counteracted by decreased adherence to diet. On the other hand, the unchanged mean weight in all types of HLP may indicate that the instituted dietary regimen was followed satisfactorily. The reductions obtained in the present study by diet and drugs in combination (23% for serum cholesterol and 45% for TG) could be compared to those of 18% for serum cholesterol and 28% for serum TG reported from a primary preventive trial using clofibrate without advising any change in the usual diet (15).

Concerning drug therapy, most subjects accepted this therapy after the diet period. However, there were individuals who wanted to continue with diet alone for a longer period. No attempts were made to dissuade them. Later it was generally easier to motivate them to accept drug therapy. There were also 9 men who for different reasons were not willing to use drugs.

Nicotinic acid was discontinued due to side effects in over half of the subjects who had received this medication. Flushing was the most common side effect. Some subjects could not overcome the initial flushing. Others discontinued the drug because of flushing accentuated by irregularities in work and meals. This is an important aspect when a drug causes discomfort when not taken regularly, especially when introducing medications in asymptomatic individuals. Clofibrate, on the other hand, was well tolerated. This drug has also the advantage of being administered twice daily why the subjects do not have to take their medication during work.

A high participation rate at the screening examination and few drop-outs during the therapeutical trial indicates that middle-aged men are concerned about their health. A low frequency of side effects to the therapy is of particular importance when dealing with asymptomatic individuals, who may already have a tendency to blame the regimen, diet or drug, to cause every possible complaint.

This study indicates that an acceptable degree of dietary adherence and patient cooperation can be accomplished in the treatment of asymptomatic middle-aged men with hyperlipidaemia. The serum lipid reductions can be maintained at least over a 2-year period.

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