Effect of a long-term fat-modified diet on serum lipoprotein levels of cholesterol and triglyceride in patients on home haemodialysis


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Summary

1. Changes in serum total and lipoprotein fraction triglyceride and cholesterol levels were studied in 24 adults on home haemodialysis. Half the patients were randomly allocated to a low cholesterol (mean 200 mg/day), fat-modified diet (mean polyunsaturated/saturated fat ratio of 1·0 with a mean of 43% of the total energy content derived from fat).

2. Before dietary manipulation, triglyceride levels in all lipoprotein fractions were significantly higher (P < 0·02) than in a control group of age and sex matched normal subjects. Total cholesterol, very-low-density-lipoprotein (VLDL) and low-density-lipoprotein (LDL) cholesterol were also significantly raised (P < 0·02), but high-density-lipoprotein (HDL) cholesterol was normal. In the patients on a fat-modified diet triglyceride levels did not alter in any of the lipoprotein fractions. Total cholesterol and LDL cholesterol levels fell significantly into the normal range (P < 0·002 and <0·001 respectively) but VLDL and HDL cholesterol levels did not change.

3. Hypertriglyceridaemia is the most common lipid abnormality in patients with renal failure and a long-term fat-modified diet is, therefore, of limited therapeutic importance in these patients unless there is a low HDL/LDL cholesterol ratio.

Key words: cholesterol, diet, haemodialysis, lipoprotein, triglyceride.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

Introduction

Patients on haemodialysis often have altered serum lipoprotein levels of both triglyceride and cholesterol (Bagdade, Casaretto & Albers, 1976; Norbeck, Orö & Carlson, 1976; Bagdade & Albers, 1977; Brunzell, Albers, Haas, Goldberg, Agadoa & Sherrard, 1977; Savdie, Gibson, Stewart & Simons, 1979). Very-low-density-lipoprotein (VLDL) triglyceride and cholesterol levels are usually raised (Bagdade et al., 1976; Norbeck et al., 1976). Low-density-lipoprotein (LDL) triglyceride is also increased, but the cholesterol content of this fraction may be normal (Bagdade et al., 1976) or low (Norbeck et al., 1976). High-density-lipoprotein (HDL) cholesterol is often markedly reduced (Norbeck et al., 1976; Bagdade & Albers, 1977; Brunzell et al., 1977; Rapoport, Aviram, Chaimovitz & Brook, 1978; Savdie et al., 1979). The role played by diet in the pathogenesis of these abnormalities is obscure. There is some evidence from short-term studies in adults with renal failure that reduction of dietary carbohydrate, together with a simultaneous increase in the polyunsaturated fat intake, decreases total serum triglyceride (Sorge, Castro, Nagel & Kessel, 1975; Sanfellipo, Swenson & Reaven, 1977). In our patients on haemodialysis, however, hypertriglyceridaemia persisted despite a relatively low and constant intake of carbohydrate (35–40% of the total daily energy content). We, therefore,
decided to start a group of adults on haemodialysis on a long-term, isocaloric, low cholesterol, fat-modified diet (polyunsaturated/saturated fat ratio of 1.0 or more), making no change in their carbohydrate intake and we report here the effect of this diet on their serum total and individual lipoprotein levels of triglyceride and cholesterol over a 6 month period.

Patients

Nineteen men and five women aged 18.0–54.4 years (mean 36.2 years) who had been on home haemodialysis for 0.4–7.7 years (mean 3.2 years) were studied. None had the nephrotic syndrome, diabetes mellitus or a known history of hyperlipoproteinaemia. All underwent dialysis three nights a week for 8–10 h sessions. One used an Organon Technica REDY system with Gambro Lundia dialysers (1 m²); the rest had a Dylade series B proportionating system and Meltec Multipoint dialysers (1 m²).

All were on free diets apart from restriction, as necessary, of fluids and of foods high in potassium and sodium content. Many patients had poor appetites and for several years they had been encouraged to maintain an adequate energy intake by eating more dairy products such as double cream and butter, which have a high energy content. As a result of this policy, they obtained on average 46% of their total daily energy from fat. The intake of carbohydrate was not restricted. Vitamin B, folic acid and iron supplements were given routinely and phosphate binding agents, vitamin D or phosphate supplements as indicated. No patient was taking steroids, diuretics, β-adrenoreceptor blocking agents or any other drug known to affect serum lipid levels.

Clinical methods

Dietary intake and serum lipoproteins were first assessed over a 3 month period when the patients continued to eat normally. Each was then randomly allocated by drawing a presealed envelope that assigned them either to a control group, these patients continued on their usual diet, or to a study group. Patients in the study group were started on a standard fat-modified diet low in cholesterol; they were instructed to reduce their intake of eggs to two per week, to avoid all other foods rich in cholesterol or saturated fats, to eat a cholesterol-free margarine high in polyunsaturated fat instead of butter and to replace all cooking oil or fat with sunflower seed oil. No change in carbohydrate intake was advised. Both groups took their allotted diets for 6 months. Dietary intake and serum lipoproteins were reassessed in both groups over the last 3 months of the study.

For each dietary and lipid assessment the method was identical. Once a month, the patient kept a prospective, weighted record of all fluids and foods consumed over a 3 day period (which included only one dialysis day) and mean nutrient intakes were calculated, by using a computerized program as described by Keen, Thomas, Jarrett & Fuller (1979) from the three assessments. After each dietary record, blood was taken (25–30 h after a dialysis and after an overnight fast of 12–14 h) for measurement of plasma creatinine, urea, albumin and glucose, and serum cholesterol and triglyceride. Additional blood was taken on the second of the three visits for lipoprotein fractionation and measurement of VLDL, LDL and HDL cholesterol and triglyceride.

Lipoprotein levels of triglyceride and cholesterol in the patients were compared with those measured in the same laboratory in a random sample, stratified by age and sex, of Greater London Council employees (by using an identical method which included storage at −40°C for a similar length of time). For each patient, two controls matched for sex and age decade were selected.

Biochemical methods

Plasma creatinine, urea and albumin were measured on the Vickers M300 Analyzer and plasma glucose was measured by using a Technicon glucose oxidase method. Serum lipoproteins were fractionated from fresh plasma by ultracentrifugation (Carlson, 1973) before being stored at −40°C with the total sera. For each patient all the samples were analysed together at the end of the study in the same assay. Cholesterol was measured by the Autoanalyzer method N-24A (Levine & Zak, 1964) and triglyceride by using a semi-automated method (Cramp & Robertson, 1968).

Statistical methods

Mean lipid values for the patients and Greater London Council employees were compared by the Wilcoxon rank-sum test. The distribution of all lipid values, except total cholesterol, was skewed to the right and was rendered approximately normal by log transformation. The biochemical, dietary and lipoprotein data for the patients were then analysed by using the computerized Statistical Package for the Social Sciences (1970).
Table 1. Body weight and plasma creatinine, urea, glucose and albumin
Assessment 1 was made before dietary change and assessment 2 3–6 months after dietary change. Values shown are means ± SD.

<table>
<thead>
<tr>
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<th>Control group</th>
<th>Diet group</th>
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<tbody>
<tr>
<td></td>
<td>Assessment 1</td>
<td>Assessment 2</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
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<tr>
<td>Body weight (kg)</td>
<td>64.3 ± 13.1</td>
<td>61.4 ± 12.3</td>
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<tr>
<td>Creatinine (μmol/l)</td>
<td>676 ± 126</td>
<td>689 ± 114</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>15.0 ± 3.3</td>
<td>14.3 ± 2.9</td>
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<tr>
<td>Glucose (mmol/l)</td>
<td>4.9 ± 0.3</td>
<td>4.8 ± 0.4</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>42.7 ± 3.2</td>
<td>43.8 ± 3.2</td>
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Table 2. Daily dietary intakes
Median and range values are shown. * Percentage of total daily energy intake.

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<td>Assessment 2</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
</tr>
<tr>
<td>Total calories (kJ)</td>
<td>80·8 (60.0–106·4)</td>
<td>79·5 (56·3–91·0)</td>
</tr>
<tr>
<td>Carbohydrate (%)*</td>
<td>41·3 (34·0–53·2)</td>
<td>38·4 (28·6–54·6)</td>
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<tr>
<td>Fat (%)*</td>
<td>45·7 (35·5–52·6)</td>
<td>46·9 (31·6–49·4)</td>
</tr>
<tr>
<td>Protein (%)*</td>
<td>12·9 (10·8–15·7)</td>
<td>13·5 (13·1–20·8)</td>
</tr>
<tr>
<td>Alcohol (%)*</td>
<td>0·9 (0·3–2)</td>
<td>0·9 (0·0–7·3)</td>
</tr>
<tr>
<td>Cholesterol (mg)</td>
<td>588 (163·7–755)</td>
<td>410 (148·5–525)</td>
</tr>
<tr>
<td>Polysaturated/saturated fat ratio</td>
<td>0·25 (0·15–0·30)</td>
<td>0·15 (0·12–0·35)</td>
</tr>
</tbody>
</table>

Results

Patients

All 24 patients completed the first assessment carried out before dietary manipulation. Seven then withdraw before completion of the second assessment on the diet, four from the control and three from the diet group; of these, four were transplanted, one was started on steroid therapy for thrombocytopenia and two felt they could no longer co-operate. The remaining 17 patients were stable on dialysis throughout the study. Table 1 gives the mean values of post-dialysis body weight, plasma creatinine, urea, glucose and albumin for the two assessment periods; none of which showed any statistically significant difference between either the two groups of patients or the two assessment periods.

Dietary assessment

The mean daily intake of nutrients for the two periods is detailed in Table 2. The study group significantly reduced their cholesterol intake to a mean of 173 mg/day with a mean polysaturated/saturated fat ratio of 0.9 compared with a mean cholesterol intake of 410 mg/day and a mean polysaturated/saturated fat ratio of 0.15 in the control group (P < 0.004 and <0.001 respectively). This was achieved without any statistically significant change in total calorie, carbohydrate, fat, protein or alcohol intake.

Lipoprotein assessment

Tables 3 and 4 give total HDL, LDL and VLDL cholesterol and triglyceride values for the normal controls and the two patient groups before (assessment 1) and after (assessment 2) dietary manipulation.

Assessment (1). Compared with the control values, there were statistically significant elevations in mean total cholesterol (P < 0.01), VLDL cholesterol (P < 0.01), LDL cholesterol (P < 0.05), total triglyceride (P < 0.01), VLDL triglyceride (P < 0.01), LDL triglyceride (P < 0.01) and HDL triglyceride (P < 0.05) in the patients; HDL cholesterol concentration did
TABLE 3. Serum lipoprotein cholesterol levels
Median and range of values (mmol/l) are shown. *P < 0·05, **P < 0·01 compared with normal controls (Wilcoxon test); †P < 0·001, ††P < 0·002 compared with assessment 1 (paired t-test on log values).

<table>
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<tr>
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<th>Diet group</th>
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<tbody>
<tr>
<td></td>
<td>Healthy subjects (n = 34)</td>
<td>Assessment 1 (n = 7)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5·1 (3·0–6·4)</td>
<td>7·2** (5·2–7·8)</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>0·3 (0·1–1·4)</td>
<td>3·8* (0·8–2·6)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3·7 (1·8–4·8)</td>
<td>2·1–4·7 (0·8–4·2)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1·3 (0·8–2·7)</td>
<td>1·1 (0·9–2·1)</td>
</tr>
<tr>
<td>HDL total cholesterol</td>
<td>0·26 (0·13–0·50)</td>
<td>0·21 (0·14–0·32)</td>
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TABLE 4. Serum lipoprotein triglyceride levels
Median and range of values (mmol/l) are shown. *P < 0·01 compared with normal controls (Wilcoxon test).

<table>
<thead>
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<tbody>
<tr>
<td></td>
<td>Healthy subjects (n = 34)</td>
<td>Assessment 1 (n = 7)</td>
</tr>
<tr>
<td>Total triglyceride</td>
<td>1·0 (0·3–2·8)</td>
<td>1·6* (0·7–4·6)</td>
</tr>
<tr>
<td>VLDL triglyceride</td>
<td>0·4 (0·1–2·2)</td>
<td>1·0* (0·7–3·1)</td>
</tr>
<tr>
<td>LDL triglyceride</td>
<td>0·3 (0·1–0·7)</td>
<td>0·2 (0·3–0·7)</td>
</tr>
<tr>
<td>HDL triglyceride</td>
<td>0·1 (0·0–0·3)</td>
<td>0·2 (0·06–0·3)</td>
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not differ significantly. Lipoprotein cholesterol levels did not correlate at a statistically significant level (P < 0·05) with any dietary or biochemical parameter, though the HDL cholesterol correlation with serum creatinine just escaped significance (r = −0·337; P = 0·054). Total serum triglyceride levels were correlated significantly only with body weight (r = 0·376; P = 0·035).

Assessment (2). In the patients on a fat-modified diet, total serum cholesterol and LDL cholesterol fell significantly (P < 0·002 and <0·001 respectively); mean total cholesterol levels still remained high compared with the normal control values, but LDL cholesterol levels were no longer significantly different. VLDL cholesterol, HDL cholesterol, total and lipoprotein fraction triglyceride levels did not alter significantly. In the control patients, lipoprotein levels of cholesterol and triglyceride were the same.

Discussion
At the start of the study, the mean total serum cholesterol level was significantly higher in our patients on haemodialysis than in healthy controls. Serum cholesterol levels in patients in renal failure have more often been reported as normal or low (Norbeck et al., 1976; Brunzell et al., 1977; Ibels, Simons, King, Williams, Neale & Stewart, 1975), but they may be high (Arora, Atkinson, Trafford, Sheldon & Nunn, 1973; Ibels et al., 1975). Our finding of raised cholesterol levels could relate to the high intake of saturated fat that the patients were encouraged to take, as fat contributed to 45–50% of the total daily energy intake compared with the average value of 42% for the general population (Ministry of Agriculture, Fisheries & Food, 1974). Furthermore serum cholesterol subsequently fell in all the patients taking the fat-modified diet, and at the end of the study was within the normal range in eight of the 11 patients.

Reduced levels of HDL cholesterol have been reported in patients with renal failure (Norbeck et al., 1976; Bagdade & Albers, 1977; Brunzell et al., 1977; Rapoport et al., 1978; Savdie et al., 1979). However, mean HDL cholesterol values in our patients did not differ significantly from the
normal control values and did not alter in the patients on the fat-modified diet. In addition, although in normal or hypertriglyceridaemic people HDL cholesterol levels are inversely correlated with plasma triglyceride levels (Schaefer, Levy, Anderson, Danner, Brewer & Blackwelder, 1978), in our uraemic patients, as in those of Norbeck et al. (1976), HDL cholesterol levels were not significantly correlated with total serum triglyceride values \( (r = 0.099) \). HDL cholesterol levels in our patients on haemodialysis did not therefore appear to be directly regulated by plasma triglyceride, or vice versa (Chan, Varghese, Persaud & Moorhead, 1979).

A weak inverse correlation between HDL cholesterol and plasma creatinine levels, which was almost significant at the \( P = 0.05 \) level, was found. The relatively normal HDL values may, therefore, relate to our practice of dialysing the patients for longer (24–30 h week) on an efficient 1 m² dialyser (Meltec) when compared with other renal units (Bagdade & Albers, 1977), as Bagdade et al. (1976) dialysed for only 20 h/week on a two-layer kill dialyser.

Most patients tolerated the fat-modified diet well, but a few resented the extra restrictions it imposed on their already rather regimented lives. These patients found it particularly difficult to limit their intake of eggs. However, total cholesterol fell and remained low in all the patients on the diet and this confirmed our clinical impression that they had complied, at least to some extent. In normal or hypertriglyceridaemic people similar diets also reduce serum triglyceride levels (Lewis, 1976a) but in our patients on haemodialysis triglyceride levels did not alter and remained high.

The importance of diet in the pathogenesis of uraemic hypertriglyceridaemia is not known. Bagdade (1970) suggested that in these patients increased hepatic production of VLDL triglyceride was caused by a high intake of carbohydrate (secondary to protein restriction) and raised insulin secretion. In our study, high triglyceride levels persisted although the intake of carbohydrate was normal. In children with renal failure plasma triglyceride levels are positively correlated with the percentage of total calories derived from carbohydrate (El Bishiti, Counahan, Jarrett, Stimmler, Wass & Chantler, 1978).

Sanfellipo, Swenson & Reaven (1978) showed a fall in insulin production when patients in renal failure took a low carbohydrate diet for 10 days and two small long-term studies also suggested that triglyceride levels could be reduced by dietary manipulation (Wahlquist & Hurley, 1977; Cianconi, Dairou, Delous, Naret, de Gennes & Jungers, 1978). Gokal, Mann, Oliver, Ledingham & Carter (1978) reported a fall in plasma triglyceride levels after 20 adults on haemodialysis had taken a fat-modified diet for 1 month, despite a rise in dietary carbohydrate from 40–50% of the total calories. However, after more than 1 year on this diet, triglyceride levels in the same patients were no longer significantly different from the pre-diet levels \( [J. I. Mann, Atherosclerosis Discussion Group, Cambridge (1979) unpublished work] \), although serum cholesterol had fallen significantly. Their findings are, therefore, consistent with ours.

Cardiovascular disease remains a major cause of death in patients on haemodialysis (Brunner, Brynger, Chantler, Donckerwolcke, Hathway, Jacobs, Selwood & Wing, 1980). Hypertriglyceridaemia is the most common lipid abnormality in these patients; the diet did not alter this. However, the significance of hypertriglyceridaemia \( per se \) as a risk factor for ischaemic heart disease remains controversial (Lewis, 1976b). On the other hand, the diet significantly decreased total cholesterol levels in our patients and a high total cholesterol level has been shown, more conclusively, to increase the risk of an individual developing cardiovascular disease (The Framingham Study, 1970). Similarly a high ratio of HDL/total cholesterol may protect against coronary heart disease (Gordon, Castelli, Hjortland, Kannel & Dawber, 1977) and in most of our patients on the diet this risk factor was reduced. However, a similar trend was also seen in the control group and no statistically significant change was seen in this risk factor. The fat-modified diet therefore has a theoretical place in the long-term management of these patients and, in view of their high mortality from ischaemic heart disease, it could prove to be a useful therapeutic measure in those patients who have high serum cholesterol or a low HDL/total cholesterol ratio.

**Acknowledgments**

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