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Hyperlipidaemia in children on regular haemodialysis

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SUMMARY Fasting plasma concentrations of triglycerides (TG), cholesterol, immunoreactive insulin (IRI), and blood glucose were raised in 16 children with chronic renal failure on regular haemodialysis compared with 18 healthy children. In the patients plasma IRI correlated positively with plasma TG, while blood glucose did not correlate with IRI or lipid concentrations. Dietary intake, expressed as percentage of recommended intake for height-age, did not correlate with plasma lipids, but there was a positive correlation between plasma TG and the proportion of calories derived from carbohydrate. The children were not malnourished as evidenced by normal plasma albumin and transferrin concentrations.

The mechanism of the hyperlipidaemia is unclear but it may be related to the glucose intolerance with hyperinsulinaemia which is found in uraemia. In view of the risk of premature atherosclerosis, plasma lipid concentrations should be monitored in children with chronic renal failure and attempts made to ameliorate hyperlipidaemia with appropriate dietary manipulations.

Hyperlipidaemia is a frequent finding in uraemic adults (Bagdade *et al.*, 1968; Gutman *et al.*, 1973; Ibels *et al.*, 1975). Many children with chronic renal failure are now being treated by regular haemodialysis and are often encouraged to take carbohydrate and fat supplements in their diet in an attempt to improve growth. An assessment of plasma lipids, particularly in relation to diet, therefore becomes important for rational management of these children.

We report plasma concentrations of triglycerides (TG) and cholesterol in children on regular haemodialysis with particular reference to diet, nutritional status, plasma concentrations of immunoreactive insulin (IRI), and blood glucose levels.

Patients

Sixteen children, 9 boys and 7 girls, with a mean age of 14 years (range 11–17 years) were studied. All patients were stable at the time of investigation and had been on dialysis for more than 6 months (range 7 months–6 years). None had the nephrotic syndrome, clinical or biochemical evidence of diabetes mellitus, or liver disease, or a known family history of hyperlipoproteinaemia. All the children were dialysed overnight at home for 30 hours per week in three sessions, 13 using Meltec Multipoint dialysers, 2 using Watson–Marlow Kiil type dialysers, and 1 using a Travenol Ultra-Flow dialyser. The dialysate had a dextrose concentration of 200 mg/100 ml. Apart from strict fluid and some sodium and potassium restriction, they ate a free diet with varying amounts of energy supplements based on a glucose polymer (Caloreen, Milner Scientific and Medical Research Co., Liverpool) and added double-cream (4 kcals/ml; 17 kJ/ml). Control values were obtained from 18 healthy British children in fasting state, 12 boys and 6 girls with a mean age of 12·3 years (range 10–17) requiring venepuncture for other reasons while inpatients for minor surgery. None had renal disease or systemic illness. They took a normal diet but intakes were not formally assessed. Consent was obtained in writing from the children's parents after full explanation of the procedures to both parents and children and the study was approved by the Medical School Ethical Committee.

Methods

Clinical. All patients were studied as outpatients at least 28 hours after dialysis and after an overnight fast of more than 12 hours. Blood samples were taken without stasis for the estimation of plasma concentrations of TG, cholesterol, IRI, albumin and transferrin, and blood glucose. The blood was immediately separated and plasma for IRI measurement was frozen at −20°C until assayed. Samples for plasma lipids were kept at 4°C and estimations and

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serum lipoprotein electrophoresis were carried out on the same day. Diet was assessed by prospective 3-day weighed records. All items of food and fluids taken by the child on three successive days, including one dialysis day, each month were recorded. Nutrient intakes were calculated from the diet records using standard tables (McCance and Widdowson, 1969). For this investigation the intake record closest to the time of study was used and was within 3 weeks of the blood specimens being obtained. The dietary intakes were expressed as a percentage of the recommended intake (% RI) for the height-age of the child (Department of Health and Social Security, 1969).

Analytical. Plasma TG was measured by the semi-automated fluorimetric method of Cramp and Robertson (1968) and plasma cholesterol by the automated method of Levine and Zak (1964). The double-antibody immunochemical technique was used to measure IRI (Morgan and Lazarow, 1963). Plasma transferrin was determined by a single radial immunodiffusion using Immuno-Plate III (Hyland). Plasma albumin was measured by autoanalyser (bromocresol dye-binding method, Technicon). Lipoprotein electrophoresis was performed on agarose gel. Blood glucose was measured by autoanalyser (ferricyanide method, Technicon).

Statistical. Student's *t* test was used to compare plasma lipids, IRI, albumin, transferrin, and glucose in patients and controls. The relationship between plasma lipids and nutrition, IRI and TG, were analysed by least squares linear regression.

Results

Clinical data of the patients are given in Table 1. Table 2 gives the plasma lipids, IRI, albumin, and transferrin concentrations and blood glucose levels in the patients and controls. There were significant increases in both the plasma TG and plasma cholesterol concentrations in the patients compared with controls. No relationship was found between plasma lipid levels and age or sex of the patients or their ideal body weight for height-age. No patient had detectable chylomicrons or a broad beta-band on lipoprotein electrophoresis. Type IV hyperlipoproteinaemia was the predominant finding, occurring in 10 of the children. Four had type IIb and 2 had normal patterns. There was a significant increase in basal IRI and fasting blood glucose in the patients compared with controls. The fasting plasma TG was positively correlated with basal IRI (Fig. 1), but not with fasting blood glucose. IRI and fasting blood glucose were not correlated. Plasma albumin

Table 1 *Clinical data of patients*

Case no.	*Sex*	*Renal disease*	*Age (yrs)*	*Height (cm)*	*Height centile*	*Weight (kg)*	*Duration on dialysis (yrs)*
1	F	Reflux nephropathy	17·8	151·1	<3rd	40	3·5
2	F	,, ,,	12·4	152·1	75th	45	1·0
3	M	,, ,,	12·0	132·1	<3rd	28·7	5·5
4	F	,, ,,	12·8	127·4	<3rd	23	3·0
5	F	,, ,,	11·3	128·1	3rd	24·5	0·58
6	M	Focal glomerulosclerosis	16·0	143·6	<3rd	56·9	2·0
7	M	,, ,,	12·3	141·4	25th	29	1·0
8	F	,, ,,	14·1	139·9	<3rd	41	3·0
9	M	Chronic glomerulonephritis	15·0	160·1	50th	45	1·5
10	M	,, ,,	14·6	139·1	<3rd	35·5	6·5
11	F	Juvenile nephronophthisis	12·8	142·1	10th	30·4	2·5
12	F	,, ,,	14·9	140·1	<3rd	49·2	0·75
13	M	Single dysplastic kidney	16·0	148·0	<3rd	40	1·5
14	M	Obstructive uropathy	14·8	136·6	<3rd	29·5	1·5
15	M	Cystinosis	14·5	127·4	<3rd	31	1·0
16	M	,,	11·7	129·3	<3rd	32	2·0

Table 2 *Biochemical results in patients and controls (mean ± 1SD)*

	n	*TG (mmol/l)*	*Cholesterol (mmol/l)*	*IRI (mU/l)*	*Blood glucose (mmol/l)*	*Plasma albumin (g/l)*	*Plasma transferrin (g/l)*
Patients	16	1·974±0·92	6·27±1·27	20·7±8·7	5·07±0·38	42±4·8	2·41±0·91
Controls	18	0·838±0·25	4·49±0·82	8·4±5·2	4·28±0·54	43±1·9	2·46±0·52
Significance of difference, P		<0·001	<0·001	<0·001	<0·001	NS	NS

TG = triglycerides; IRI = immunoreactive insulin.
Conversion: SI to traditional units—Triglyceride: 1 mmol/l ≈ 80·5 mg/100 ml. Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml. Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

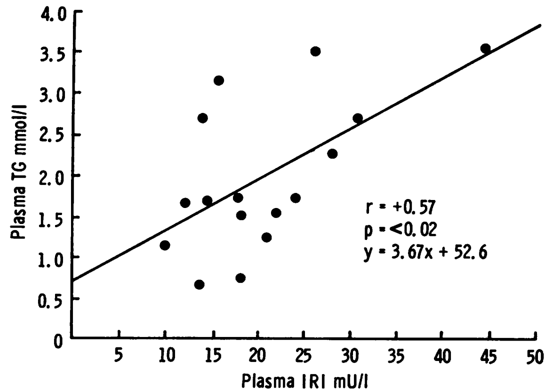

Fig. 1 *Plasma triglyceride (TG) concentrations related to plasma immunoreactive insulin (IRI) levels in 16 children on regular haemodialysis.*

and transferrin concentrations, as indices of nutritional state, were similar in patients and controls and did not correlate with plasma lipid levels.

Effect of diet. The dietary intakes of total energy, carbohydrates, total fat and proteins expressed as % RI for the height-age are presented in Table 3. The relationship between the dietary intakes and plasma TG and cholesterol concentrations in the patients is shown in Table 4. There was a tendency for those children with lower intakes of total energy, fats, and proteins to have higher TG levels but TG and carbohydrate intake were poorly correlated. However, when expressed as a percentage of the total energy intake, there was significant positive correlation between plasma TG concentration and percentage of calories derived from carbohydrate (Fig. 2). No correlation between plasma cholesterol concentration and food intakes could be shown.

Discussion

Raised plasma triglycerides have been commonly reported in adults on regular haemodialysis (Bagdade *et al.*, 1968; Gutman *et al.*, 1973) and recently Pennisi *et al.* (1976) and Broyer *et al.* (1976) reported raised TG levels in children on dialysis. Our group of children showed a similar phenomenon. Type IV hyperlipoproteinaemia is commonly found and the majority of our patients exhibited this pattern. Raised TG levels in uraemia are considered to be due to both increased hepatic TG production (Bagdade *et al.*, 1968; Cramp *et al.*, 1976) and decreased TG clearance from plasma (Cattran *et al.*, 1976; Murase *et al.*, 1975). Our finding of high basal plasma insulin levels in the face of raised fasting blood glucose is indicative of glucose intolerance. The positive

Table 3 *Diets of children on dialysis*

Case no.	*Energy*		*Protein*		*Carbohydrate*		*Fat*	
	kJ/day	*%RI*	*g/day*	*%RI*	*g/day*	*%RI*	*g/day*	*%RI*
1	9 520	99	60	103	303	101	97	114
2	12 127	126	132	228	244	82	156	184
3	14 102	134	84	133	378	109	171	184
4	10 964	125	56	106	321	118	128	162
5	15 911	181	118	183	396	132	198	251
6	11 698	112	79	125	327	101	135	145
7	10 983	105	77	122	246	102	150	161
8	12 493	130	64	110	389	130	215	253
9	12 001	102	66	88	265	80	173	166
10	4 886	47	46	73	136	42	51	55
11	—	—	—	—	—	—	—	—
12	10 306	107	68	117	297	109	116	136
13	18 684	159	128	70	389	107	268	258
14	6 415	61	46	73	183	56	71	76
15	9 175	104	55	104	237	87	116	147
16	8 010	91	18	34	302	111	76	96

%RI = percentage of recommended intake.
Conversion: SI to traditional units—Energy: 1 kJ≈0·239 kcal.

Table 4 *Relationship between diet (as % of RI for height-age) and plasma lipid concentrations*

	Total energy		*Fat*		*Carbohydrate*		*Protein*	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Triglycerides	−0·37	NS	−0·46	<0·1	−0·12	NS	−0·38	NS
Cholesterol	−0·13	NS	−0·06	NS	−0·18	NS	+0·13	NS

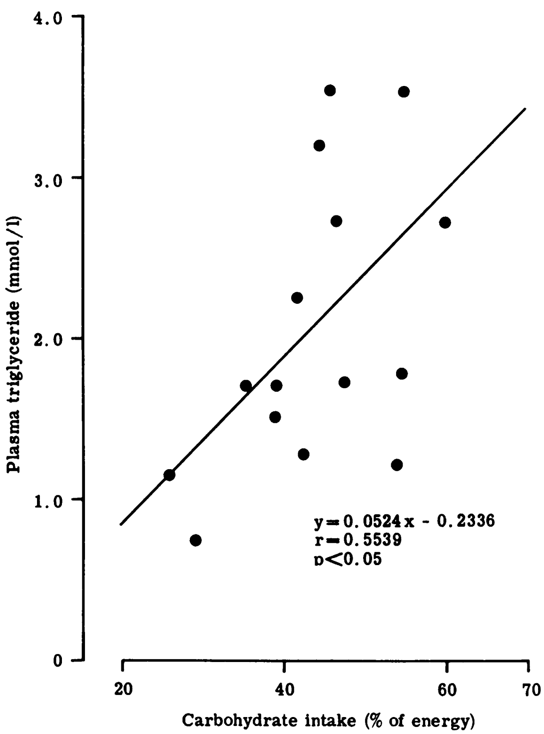

Fig. 2 *Plasma triglyceride concentrations related to carbohydrate intake (% of total energy intake) in 15 children on regular haemodialysis.*

correlation shown between plasma insulin and TG concentration is similar to that found in uraemic adults (Bagdade, 1970) and it is possible that hyperinsulinaemia might stimulate an increased hepatic TG production, as suggested for nonuraemic subjects (Reaven *et al.*, 1967; Olefsky *et al.*, 1974).

The role of diet in the pathogenesis of hypertriglyceridaemia in uraemia is not clear. No correlation existed between total energy intake and TG concentration, though higher total energy and protein intakes tended to be associated with lower levels. The TG levels reported here are about 65% lower than those reported by Broyer *et al.* (1976) in children on dialysis, and energy and protein intakes in our children were considerably greater than in their study. However, other differences exist in the management of these children, for instance our children dialyse for about 30 hours a week compared with 16 hours a week. The proportion of total energy intake derived from carbohydrate correlated significantly with TG concentrations. Both Pennisi *et al.* (1976) and Broyer *et al.* (1976) showed a similar relationship between dietary carbohydrate and plasma TG concentration. More recently, Sanfelippo *et al.* (1977) reported a reduction in plasma TG levels by feeding diet low in carbohydrate and high in polyunsaturated fat. Unfortunately it is not known from their study which of the two variables in the diet altered the TG levels.

Plasma cholesterol concentrations are usually found to be normal in uraemic adults whereas our patients showed considerable increases both compared with controls and with the children reported by Broyer *et al.* (1976), though 6 of 17 children in the latter study also showed significantly increased levels. We were unable to show any relationship between diet and plasma cholesterol, though Broyer *et al.* suggested a relationship with lipid intake. As our patients were taking energy supplements based on food high in saturated fats, it is possible that manipulation of the diet by increasing the polyunsaturated fat intake might lead to a fall in plasma cholesterol, and we are attempting this at present.

The finding of hyperlipidaemia in children on regular haemodialysis awaiting transplantation is disturbing in view of the relationship between hyperlipidaemia and arterial disease shown in prospective studies of normal populations (Kannel *et al.*, 1971; Carlson and Böttiger, 1972) and the increased incidence of premature atherosclerosis and cardiovascular disease reported in adult patients on long-term haemodialysis (Lowrie *et al.*, 1973; Lindner *et al.*, 1974; Bagdade, 1975). Pennisi *et al.* (1976) studied the morphology of coronary arteries in children who died while on regular haemodialysis for renal failure. In comparison with children dying of other diseases at a similar age, there were changes suggestive of fat deposition in the arterial walls.

While the exact mechanism of the hyperlipidaemia remains obscure, it obviously is important to measure TG and cholesterol concentration both in children on haemodialysis and in children with chronic renal insufficiency who have not yet required dialysis or transplantation. If raised levels are found, attempts can be made to lower them by dietary manipulation or increased dialysis. The need to ensure adequate nutrition in children in renal failure has been emphasized (Chantler and Holliday, 1973). Further studies of the effect of various dietary constituents on plasma lipids are required, but in the meantime it seems reasonable to try to ensure an adequate intake of total energy and protein. Regular diet surveillance is important and for those children with raised lipid levels the proportion of carbohydrate and saturated fat in the diet may need to be controlled.

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