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Hyperlipidemia in Children with Chronic Renal Insufficiency

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Summary

Total serum cholesterol, phospholipids, and triglyceride levels, lipoprotein fractionation, and plasma parathormone levels were measured in a group of 31 nonnephrotic children with various levels of renal function and on hemodialysis. Group A served as controls and consisted of eight healthy children with glomerular filtration rate (GFR) greater than 110 ml/min/1.73 m². Group B consisted of six children with GFR of 60 to 95 ml/min/1.73 m². Group C consisted of nine children with GFR of 10 to 40 ml/min/ 1.73 m², and group D consisted of eight children on maintenance hemodialysis with GFR of 0 to 5 ml/min/1.73 m². Among the groups, there were no significant differences in total serum cho- lesterol and phospholipid levels. A significant ($P < 0.05$) increase in triglyceride levels was observed in patient groups C and D.

Lipoprotein fractionation revealed a significant increase ($P < 0.05$) in the pre-beta lipoprotein levels (very low density lipopro- teins) in patients in group D with 63% of these patients demon- strating a type IV lipoprotein pattern. There were no significant differences observed in the beta lipoproteins (low-density lipopro- teins). However, the alpha lipoproteins (high-density lipoproteins) decreased significantly ($P < 0.05$) in patients whose GFR was below 40 ml/min/1.73 m² (group C) as well as patients in group D.

Absolute plasma parathormone levels did not significantly cor- relate with serum triglyceride levels and remained normal until after the onset of hemodialysis when they increased significantly in all patients.

Speculation

Evidence has been accumulating over the past few years that chronic hemodialysis and renal transplant adult patients have shortened survival because of accelerated atherosclerotic cardio- vascular disease for which hyperlipidemia could be one of several etiologic factors. Similar epidemiologic studies have not been performed in children. We have demonstrated for the first time in children that alterations in serum triglycerides and alpha lipopro- teins (high-density lipoproteins) occur early in chronic renal insuf- ficiency and before the onset of uremia when the glomerular filtration rate falls below 40 ml/min/1.73 m². These lipid abnor- malities become further aggravated with the onset of hemodialysis. If pediatric renal transplant patients show similar lipid abnormal- ities, then the potential for cardiovascular complications will be of importance in the early medical management of these children.

Alterations in lipid metabolism in adult uremic patients were initially described when lactescent serum was observed in patients with chronic renal disease (2). More recent studies have demon- strated that hyperlipidemia associated with elevated triglyceride levels is a frequent finding in adults with end-stage renal disease as well as in those patients undergoing chronic hemodialysis (3, 6, 7, 19, 29, 39).

Various types of lipoprotein abnormalities (example, high-den- sity lipoproteins) are well recognized as predictors of athero- sclerotic disease (23), and recent evidence highlights a high rate of mortality from arteriosclerotic complications in adults on long- term hemodialysis with persistent hyperlipidemia (4, 6, 11, 27, 28, 30). Furthermore, transplantation does not significantly reduce the incidence of cardiovascular complications because hyperlip- idemia has been shown to exist after renal transplantation (8, 12, 18, 22, 30).

Children have been considered as acceptable candidates for dialysis and transplantation for the past few years, but there have been no systematic studies as to the occurrence of hyperlipidemia in this young age group. The objective of the present study was to investigate the lipid profile in a group of nonnephrotic children with various degrees of renal insufficiency and while undergoing chronic hemodialysis. In addition, absolute parathyroid hormone (PTH) levels were measured in patient groups B, C, and D because it has been postulated that in uremia the increased levels of PTH may be associated with an increased rate of hepatic gluconeogen- esis (17) and thus possibly contribute to the pathogenesis of hyperlipidemia.

MATERIALS AND METHODS

Total serum cholesterol, phospholipids, and triglyceride levels, and lipoprotein fractionation were measured in 31 nonnephrotic children. Patients were assigned to groups according to various levels of renal function. Group A served as controls and consisted of eight healthy children with glomerular filtration rate (GFR) greater than 110 ml/min/1.73 m². Group B consisted of six children with GFR of 60–95 ml/min/1.73 m². Group C consisted of nine children with GFR of 10 to 40 ml/min/1.73 m², and group D consisted of eight children on maintenance hemodialysis with GFR of 0 to 5 ml/min/1.73 m². None of the patients in groups A, B, and C were known to have pre-existing diabetes mellitus, hyperlipidemia, or heart disease. The age, sex, GFR and under- lying renal disease in the four groups of patients are depicted in Table 1. The controls ranged in age from 4 to 18 years. Three were females, and five were males. In group D, patients 24, 25, and 26 had the nephrotic syndrome but had been anephric for 12 to 17 months before the study. Their serum protein electrophoresis was within normal range. Duration of hemodialysis treatment was between 1 to 36 months (13 months on the average). Dialysis was performed for 5 hr three times per wk using either Gambro Optima or Cordis Dow dialyzers. The dialysate contained 200 mg of dextrose per dl. All dialysis patients were in a stable state receiving approximately the same renal diet calculated on a weight basis to supply the recommended daily caloric allowance with the protein intake ranging between 1.5 and 2.5 g/kg depending on the age of the child. Children in groups A, B, and C received a regular diet. Amphogel was administered to patients in groups C and D whose serum phosphorus level exceeded 5.5 mg/dl.

Table 1. *The age, sex, GFR,[1] and underlying renal disease in the four groups of patients*

Patient groups and case nos.	Age (years)	Race/sex	GFR[1] (ml/min/ 1.73 m^2)	Underlying renal disease
Group A (GFR 110–134 ml/min/1.73 m^2)				
1	12	W/M	126	None
2	11	W/M	118	None
3	7	W/M	124	None
4	6	B/F	116	None
5	7	B/M	114	None
6	8	B/M	120	None
7	4	W/F	110	None
8	18	W/F	134	None
Mean	9.1			
Group B (GFR 60–95 ml/min/1.73 m^2)				
9	12	W/M	95	Dysplastic kidneys
10	11	W/F	92	Recurrent UTI
11	17	W/F	74	Bilateral hydronephrosis
12	18	B/M	71	Hypertension
13	6	W/M	69	Polycystic kidneys
14	9	W/M	66	Bilateral hydronephrosis
Mean	12.2			
Group C (GFR 10–40 ml/min/1.73 m^2)				
15	3	B/M	38	Interstitial nephritis
16	18	B/M	33	Chronic glomerulonephritis
17	11	W/F	33	Chronic pyelonephritis
18	17	B/M	29	Bilateral hydronephrosis
19	14	W/F	27	Chronic pyelonephritis
20	14	B/F	25	Dysplastic kidneys
21	4	W/M	18	Bilateral hydronephrosis
22	8	W/M	17	Dysplastic kidneys
23	12	W/M	10	Bilateral hydronephrosis
Mean	11.2			
Group D (Hemodialysis)				
24	15	B/F	Anephric	Membranoproliferative GN
25	14	B/M	Anephric	Membranoproliferative GN
26	16	B/F	Anephric	Focal segmental glomerulosclerosis
27	17	B/F	Anephric	Dysplastic kidneys
28	15	W/M	5	Hereditary nephritis
29	12	W/M	5	Bilateral hydronephrosis
30	8	W/M	3	Dysplastic kidneys
31	10	W/M	2	Cystinosis
Mean	13.4			

[1] GFR: Actual glomerular filtration rate as estimated by the endogenous clearance of creatinine.

Venous blood samples were obtained in the recumbent position following a 12- to 14-hr fast. For patients in group D, blood samples were collected before the beginning of hemodialysis and approximately 48 hr after the last dialysis treatment. Lipoprotein fractionation of the serum was accomplished by means of the Beckman microzone electrophoresis technique using Agarose gel (34). Serum triglycerides and phospholipids were measured by the method of Kessler (25), and total serum cholesterol was measured by the method of Wybenga *et al.* (40). Changes in the serum lipids were statistically compared among the four groups of patients and were further compared with published reports of 95th percentiles for plasma lipids and lipoproteins in children (16, 26, 33, 38). PTH levels were measured by radioimmunoassay using an antiserum specific for the carboxy-terminal region (21). PTH levels were plotted as a function of the serum calcium level (21). Glomerular filtration rate was estimated by the endogenous clearance of creatinine. Creatinine was determined by the method of Hare (20).

All statistical calculations and correlations were determined by employing the Student t test.

RESULTS

The results (mean ± standard error) of the total serum cholesterol, phospholipids, and triglycerides for the four groups of patients are summarized in Table 2 together with the P values as compared to controls. Among the groups, there were no significant differences in total serum cholesterol and phospholipid levels. There was, however, a significant increase in the triglyceride levels observed in patients with GFR less than 40 ml/min/1.73 m^2 (group C) as well as in patients in group D. The values obtained in these groups were significantly higher ($P < 0.05$) than in controls and group B patients who had only a mild reduction of the GFR. Mean triglyceride concentration was 107 ± 14 mg/dl (range, 77 to 209 mg/dl) in patients in group C and 171 ± 27 mg/ dl (range, 105 to 292 mg/dl) in patients in group D as compared to control values of 68 ± 8 mg/dl (range, 41 to 101 mg/dl). Furthermore, patients on hemodialysis (group D) had even significantly higher triglyceride levels than did patients in group C ($P < 0.05$). A threshold effect of GFR on hypertriglyceridemia

could not be ascertained because there were no patients whose GFR ranged between 40 and 60 ml/min/1.73 m². A regression analysis using the least square method showed a correlation coefficient between GFR (independent variable) and serum triglyceride levels (dependent variable) to be 0.60 with a P value < 0.002. Clearly, the serum triglyceride levels became significantly elevated once the GFR decreased below 40 ml/min/1.73 m².

The lipoprotein pattern in the patient groups is shown in Table 3 together with the P values as compared to controls. The pre-beta lipoprotein levels [very low density lipoproteins (VLDL)] were significantly elevated (P < 0.05) only in group D. Five of eight children in this group (63%) had the type IV lipoprotein

Table 2. *Total serum cholesterol, phospholipids, and triglycerides in the four groups of patients in order of decreasing GFR*

Patient groups and case nos.	Total serum cholesterol (mg/dl)	Phospholip-ids (mg/dl)	Triglycerides (mg/dl)
Group A (Controls, GFR 110–134 ml/min/1.73 m³)			
1	214	233	78
2	189	200	101
3			
4	137	159	62
5	132	151	68
6	147	180	41
7			
8	180	171	57
Mean ± S.E.	167 ± 13	182 ± 12	68 ± 8
Group B (GFR 60–95 ml/min/1.73 m²)			
9	171	192	68
10	162	168	60
11	260	258	45
12	168	208	78
13	149	171	20
14	191	261	62
Mean ± S.E.	184 ± 16	210 ± 17	56 ± 8
Group C (GFR 10–40 ml/min/1.73 m²)			
15	206	272	77
16	156		105
17	204	229	94
18	179		86
19	125	145	209
20	246	330	83
21	209		120
22	182		113
23	266		79
Mean ± S.E.	197 ± 14	244 ± 39	107 ± 14[1]
Group D (Hemodialysis)			
24	167	178	154
25	174	188	105
26	172	196	105
27	251	332	120
28	151	254	209
29	193	275	115
30	215	238	292
31	255	303	264
Mean ± S.E.	197 ± 14	246 ± 20	171 ± 27[1,2]

[1] P < 0.05 as compared to controls.
[2] P < 0.05 as compared to group C.

Table 3. *The lipoprotein pattern in the four patient groups according to decreasing GFR*[1]

Patient groups and case nos.	Pre-beta lipo-proteins (%) (VLDL)	Beta lipo-proteins (%) (LDL)	Alpha lipo-proteins (%) (HDL)
Group A (Controls, GFR 110–134 ml/min/1.73 m²)			
1	5.5	44.8	48.8
2	19.2	50.7	28.6
3	11.0	46 9	35.2
4	13.6	46.4	39.7
5	11.7	50.9	34.4
6	13.2	43.0	43.8
7	7.9	51.2	39.8
8	5.4	43.7	50.9
Mean ± S.E.	10.9 ± 1.6	47.2 ± 1.2	40.1 ± 2.7
Group B (GFR 60–95 ml/min/1.73 m²)			
9	15.2	47.7	36.1
10	17.3	47.0	35.7
11	17.4	41.5	41.0
12	9.7	54.0	35.5
13	3.6	48.0	48.4
14	5.6	60.0	34.4
Mean ± S.E.	11.5 ± 2.5	49.7 ± 2.6	38.5 ± 2.1
Group C (GFR 10–40 ml/min/1.73 m²)			
15	17.9	64.5	10.9
16	20.8	45.5	31.4
17	14.8	53.7	25.5
18	19.3	46.9	31.9
19	28.2	37.2	34.7
20	4.1	54.1	33.3
21	6.5	70.0	23.0
22	23.1	54.6	16.0
23	4.5	62.0	32.5
Mean ± S.E.	15.5 ± 2.9	54.3 ± 3.4	26.6 ± 2.8[2]
Group D (Hemodialysis)			
24	33.3	46.0	20.8
25	31.8	41.7	31.5
26	20.7	49.2	28.4
27	19.3	25.7	
28	29.0	38.9	32.2
29	12.1	53.2	34.7
30	20.5	52.5	27.0
31	18.4	68.7	12.8
Mean ± S.E.	23.1 ± 2.6[2]	46.9 ± 4.4	26.8 ± 2.9[2]

[1] The pre-beta, beta and alpha lipoproteins are depicted as the percentage of the total lipoproteins.
[2] P < 0.05 as compared to controls.

phenotype, and one had the type II b pattern. In patients in group C, with GFR below 40 ml/min/1.73 m², although the mean level of the pre-beta lipoproteins was not significantly elevated from control values; nevertheless in three of these children (33%) the actual levels were more than two standard deviations greater than were controls demonstrating the type IV lipoprotein phenotype. There were no significant differences observed in the beta lipoproteins [low-density lipoproteins (LDL)]. However, the alpha lipoproteins [high-density lipoproteins (HDL)] decreased significantly (P < 0.05) in patients with GFR below 40 ml/min/1.73 m² (group C) as well as in patients in group D. The correlation

coefficient with alpha lipoproteins as the dependent variable and the GFR as the independent variable was 0.5 with a P value $<$ 0.02. As in the case of serum triglycerides, this linear regression analysis was limited by the absence of GFR values between 40 and 60 ml/min/1.73 m^2. It is clear, however, that once the GFR is below 40 ml/min/1.73 m^2 the alpha lipoprotein levels are significantly lower than are the levels noted when the GFR is greater than 60 ml/min/1.73 m^2.

Absolute PTH levels did not significantly correlate with serum triglyceride levels (correlation coefficient, 0.161). Serum PTH levels remained normal until after the onset of hemodialysis when they increased significantly in all patients.

DISCUSSION

The data demonstrate for the first time in children that alterations in serum triglycerides and alpha lipoproteins (HDL) occur early in chronic renal insufficiency and before the onset of uremia when the GFR falls below 40 ml/min/1.73 m^2. In these patients, the serum triglyceride levels become significantly elevated, and the alpha lipoproteins (HDL) markedly decreased as renal function deteriorates. These lipid abnormalities become further aggravated with the onset of hemodialysis. On the other hand, the serum total cholesterol, phospholipids, and beta lipoproteins (LDL) remain essentially unchanged.

Various published reports on plasma lipids and lipoprotein levels in normal children indicate that serum triglyceride levels tend to increase with age in all race-sex groups whereas serum cholesterol levels remain relatively constant until adolescence at which time they become slightly reduced (16, 26, 33, 38). The elevation of the serum triglyceride levels in our patient groups C and D were significantly higher than the median and the 95th percentile values reported for normal children of various age groups (16, 26, 33). Furthermore, the changes in the serum triglyceride levels observed in patients with GFR below 40 ml/min/ 1.73 m^2 did not significantly correlate with age (correlation coefficient, 0.0). Similarly, the marked decrease in the alpha lipoproteins observed in patients in groups C and D did not significantly correlate with age (correlation coefficient, 0.3 with a P value $<$ 0.16).

Elevated fasting triglyceride levels have been reported in adult uremic and dialyzed patients (3, 6, 7, 29, 32, 39). The lipid increment has been shown to be primarily in the pre-beta fraction (VLDL) which is triglyceride-rich (9, 13, 22, 24, 32, 36). Similarly, decreased levels in the alpha lipoproteins (HDL) have been described in adult uremic patients and are attributed to abnormally low levels of alpha lipoprotein cholesterol content (5, 22, 32, 36). Serum total cholesterol levels, on the other hand, have been shown to remain within normal range by all of these investigators. Thus, the nonnephrotic, chronically uremic state affects lipoprotein metabolism in such a way that triglyceride levels in the whole plasma as well as in the VLDL class (pre-beta lipoprotein) are elevated, cholesterol levels in whole plasma and in the LDL class (beta lipoproteins) are normal, and HDL levels (pre-beta lipoproteins) are markedly reduced. Furthermore, hyperlipidemia has been shown to persist after renal transplantation in children (35, 37) and adults (8, 12, 18, 22, 27, 30). Evidence has been accumulating over the past few years that chronic hemodialysis and renal transplant patients have shortened survival because of accelerated atherosclerotic cardiovascular disease (28, 30) for which hyperlipidemia could be one of several etiologic factors (27, 28, 30). Similar epidemiologic studies have not been performed in children. Low levels of HDL (alpha lipoprotein) cholesterol has been shown to be also present in renal transplant adult patients (5) resulting in a high ratio of LDL to HDL cholesterol. It has been speculated by Bagdade *et al.* (5) that these lipid disturbances may play some role in the development of accelerated vascular disease in these patients. Whether such correlations indicate a causal relationship remains unclear however.

Few studies have been conducted in nonnephrotic patients with various degrees of renal function to document whether hyperlip-

idemia occurs early in the course of renal insufficiency or whether it is a sole feature of end stage renal disease. Frank *et al.* (15), in a study of adult uremic patients on hemodialysis and in patients with normal to severely compromised renal function, found that hypertriglyceridemia developed as the creatinine clearance fell below 40 ml/min. However, lipoprotein fractionation was not determined. Similar results have been reported by McCosh *et al.* (31). In our studies, although the triglyceride levels increased significantly when the GFR fell below 40 ml/min/1.73 m^2, the pre-beta lipoproteins (VLDL) did not significantly increase until after the onset of hemodialysis. However, three children in group C with GFRs of 33, 27, and 17 ml/min/1.73 m^2, respectively (patients 16, 19, and 22) did demonstrate a significant elevation of the pre-beta lipoproteins. The failure of patients in group C as a whole to demonstrate a significant elevation in the pre-beta lipoproteins cannot be explained as yet.

Dietary and hormonal factors did not appear to play a significant role in the pathogenesis of hyperlipidemia in our patients. Although a significant relationship between dietary carbohydrate and triglyceride concentration has been demonstrated by several investigators (10, 14, 35), the alterations in lipid metabolism which were observed in patients in group C were unrelated to dietary factors since these children were in a stable nutritional state and receiving a normal diet. In addition, the diet in group D patients was carefully regulated so that they all received an adequate caloric, protein, and carbohydrate intake. In addition, absolute PTH levels did not significantly correlate with serum triglyceride levels. A negative correlation was also demonstrated by Amend *et al.*(1) who studied adult uremic patients before and after parathyroidectomy and found no significant change in carbohydrate metabolism, in triglyceride levels, or in the incidence of type IV hyperlipidemia.

We have demonstrated that in children, the onset of hypertriglyceridemia and reduced levels of alpha lipoproteins (HDL) occur early in renal insufficiency when the GFR decreases below 40 ml/min/1.73 m^2. These lipid abnormalities, which are believed to accelerate altherosclerotic cardiovascular disease, become further aggravated with the onset of hemodialysis. If pediatric renal transplant patients show similar lipid abnormalities, then the potential for cardiovascular complications will be of importance in the early management of these children.

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