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Cholesterol
familial hypertriglyceridemia
triglyceride

type IV diet
type IV hyperlipoproteinemia

Familial Hypertriglyceridemia in Children: Dietary Management

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Summary

This study was designed to evaluate prospectively the continuing effects of dietary management in 44 children with familial hypertriglyceridemia. For obese children, weight reduction programs were instituted by metabolic dietitians. For nonobese children, for obese children with successful weight reduction (or for those who could not lose weight but would follow an altered diet), a modification of the National Institutes of Health (NIH) type IV diet was provided. Adherence to the diet program was monitored by monthly reassessment for 6 months in the outpatient clinic. In 43 children whose average age was 13 years at the time of diagnosis, mean ± SE plasma triglycerides were reduced after 6 months of weight reduction-NIH type IV diet from 253 ± 33 to 116 ± 8 mg/dl, $P < 0.01$. After 6 months on diet, the group mean decrement in weight (1 ± 1 kg) was not significant, and decrements in weight failed to correlate with decrements in plasma triglycerides, $r = 0.131$. Despite this failure to reduce weight appreciably, after 6 months on diet plasma triglyceride levels were reduced to normal (< 140 mg/dl) in 32 of the 43 children. At 8 months' follow-up in 13 children, mean plasma triglyceride was 170 ± 31 mg/dl, having been 290 ± 86 at time of diagnosis, $P < 0.01$. Plasma triglyceride levels at 8 months were normal in 5 of the 13 children. Plasma triglycerides were normal in 4 of 5 children with evaluation at 1 year, in 3 of 7 at 18 months, and in 4 of 14 at 22–26 months. When weight gain was proportionately greater than accretion of height, and where no attention to either caloric intake or composition was given, triglycerides remained elevated, whereas dietary adherence was generally accompanied by reduced or normal triglycerides. Amelioration of familial hypertriglyceridemia on the NIH type IV diet is a realizable goal in children, but requires persistent, repetitive reexamination and reinstruction.

Speculation

Dietary management of pediatric familial hypertriglyceridemia may be important as a primary, longitudinal approach to reduction of the increased atherosclerotic risk attendant to familial hypertriglyceridemia.

Primary hypertriglyceridemia occurs in 20% of children (under age 21) born to parents with familial hypertriglyceridemia (10). Substantial obesity is associated with the pediatric expression of familial hypertriglyceridemia in 30–60% of affected children (9, 10). Unlike pediatric familial hypercholesterolemia (7, 11), where dietary intervention provides only limited lipid lowering, most children with familial hypertriglyceridemia will normalize their triglycerides on a weight reducing/type IV (5) diet (9, 10). Amelioration of pediatric hypertriglyceridemia on diet may be important as a primary, longitudinal approach to reduction of increased atherosclerotic risk reported in some (2, 3), but not all adults (1) with famial hypertriglyceridemia.

In children with familial hypercholesterolemia the initial moderate reductions in plasma cholesterol on diet are less marked with passage of time (7, 8, 11). This study was designed to evaluate prospectively the continuing effects of dietary management in 44 children with familial hypertriglyceridemia.

MATERIALS AND METHODS

PATIENTS: HYPERTRIGLYCERIDEMIC CHILDREN AND YOUNG ADULTS

Diagnoses of pediatric familial hypertriglyceridemia were made using previously described criteria (9, 10). Of the 44 hypertriglyceridemic children in the current report, basal kindred information has previously been published in one study for 23 (10) and in another study for 16 patients (9). All of the 44 hypertriglyceridemic children came from kindreds where one propositus parent and at least one additional first or second degree relative had primary endogenous hypertriglyceridemia (9, 10). Three children (two with type III hyperlipoproteinemia, patients *14* and *15)* and one with type IV (patient *16)* came from kindreds with familial type III (6). All children thus came from kindreds with documented familial hypertriglyceridemia, predominantly type IV hyperlipoproteinemia (4, 8–10). These kindreds were probably biased toward those with the more severe forms of familial hypertriglyceridemia (4, 8–10). The primary nature of the hypertriglyceridemia was defined by the exclusion of other disorders known to produce secondary hypertriglyceridemia (4, 8–10).

ANALYTIC METHODS

Blood samples were obtained after a 12-hr overnight fast. All plasmas were visually inspected (after sitting overnight at 4°) to evaluate for the presence of chylomicrons floating as a "cream layer" at the plasma surface. In *subjects 37* and *41* (Table 1) with initial plasma triglycerides 1320 and 968 mg/dl, heavy tailing of chylomicron-triglyceride into the electrophoretic origin made it difficult to distinguish between type IV and type V lipoprotein patterns (4, 8–10). Plasma cholesterol and triglyceride were quantitated following the Lipid Research Clinics methodology (12).

STUDY PROTOCOL

After identification of primary hypertriglyceridemia by two separate measurements while on *ad libitum* diet, individualized dietary programs were devised for each child. For obese children (9, 10), weight reduction programs were instituted by metabolic dietitians. For nonobese children, obese children with successful weight reduction (or for those who could not lose weight but would follow an altered diet), a modification of the NIH type IV diet was provided (5, 9). This diet included 20% of the calories as protein, 40% as fat, 40% as carbohydrate, with a polyunsaturate/saturate ratio of 1.5/1. Adherence to the diet program was monitored by monthly reassessment for 6 months in the outpatient clinic.

For continued evaluation past 6 months, each subject was urged to return every 2–4 months. Follow-up studies past 6 months were carried out in 19 of the 44 children (Table 2). In the 25 children with no studies reported beyond month 6, 8 are scheduled for future resampling, 9 are being cared for by private pediatricians, 6 have moved out of town, and 2 are at out of town colleges. At each follow-up visit, adherence to the suggested dietary regimen was assessed after obtaining a 24-hr diet recall. Because of the highly limited, semiquantitative to qualitative nature of the assessment of dietary adherence, children in the continuing evaluation program could only be identified as: (*1*) following none of the suggested dietary recommendations, (*2*) having satisfactory dietary adherence, (*3*) unable to provide sufficient information to allow any judgement in regard to adherence (Table 2).

STATISTICAL ANALYSES

Relationships between the prediet baseline triglyceride levels and those during follow-up were studied using the paired Wilcoxon nonparametric test for differences (13). Relationships between changes in weight and changes in triglyceride levels were evaluated using regression analysis (14) or nonparametric regression analyses (15).

RESULTS

EFFECTS OF DIET ON PLASMA TRIGLYCERIDES AT 6 AND 8 MONTHS' FOLLOW-UP

Mean (±SE) age at the time of diagnosis was 13.3 ± 0.6 years (Table 1). Forty-three children were available for follow-up 6 months after initial diagnosis, having followed the weight reduction/type IV diet program. Mean (±SE) fasting plasma triglycerides for the group fell from 253 ± 33 mg/dl to 116 ± 8, $P < 0.01$ (Table 1). Mean plasma cholesterol was moderately reduced from 194 ± 6 mg/dl to 181 ± 5 at 6 months, $P < 0.05$. Plasma triglyceride levels were reduced to normal (< 140 mg/dl) (4) at 6 months in 32 of the 43 children (Table 1).

At 6 months' follow-up for the 43 children, mean ± SE weight loss was 1 ± 1.09 kg, $P > 0.1$ (Table 1). The decrements in weight failed to correlate significantly with decrements in triglyceride, $r = 0.131$.

At 8 months follow-up (Table 2), 13 children were available for study. Mean ± SE plasma triglyceride in this group, 290 ± 86 mg/dl prior to diet, was 170 ± 31 mg/dl at 8 months, $P < 0.01$. At 8 months, plasma triglyceride levels were normal in 5 of 13 children. At 8 months, mean weight in the 13 children had increased 2.7 ± 1 kg from baseline levels, $P > 0.1$.

EFFECTS OF DIET ON PLASMA TRIGLYCERIDE, 1-2-YEAR FOLLOW-UP

Follow-up data on plasma triglyceride levels for 1–2-year periods following diagnosis are summarized in Table 2. Of the five children seen at 1 year, plasma triglycerides were normal in the four who adhered to the diet. In *subject 15*, weight increased 3 kg over baseline, height was unchanged, and triglycerides increased. Of the seven children seen at 18 months, plasma triglycerides were normal in three, had risen above baseline-prediet levels in two, and were slightly below baseline levels in two. In the two children with recrudescent hypertriglyceridemia, 24-hr dietary recall revealed no efforts to follow the suggested diet in one (*subject 7)*, whereas in the other (*subject 44)*, there was a 12-kg increase in weight over baseline.

Fourteen children were studied for 22–26 months following initial diagnosis (Table 2). Four (*subjects 6, 8, 28, 44)* retained normal triglyceride levels. Although not reduced to normal levels, triglycerides fell 15%, 24%, 45%, and 88% in four additional children, respectively, and rose 10%, 16%, 19%, 21%, and 46% above baseline in five children. In the six children whose triglycerides rose or remained at baseline (*subjects 9, 11, 31, 34, 38, 55)*, five followed no suggested diet.

For those children studied at 12, 18, and 22–26 months, the ratio of the change (Δ) in weight to the change in height (ΔWt/ΔHt) failed to correlate with the change in triglyceride (ΔTG), $r = 0.20$. For those children during these periods whose triglyceride increased above baseline, ΔWt/ΔHt and ΔTG correlated significantly (15), $r = 0.68$, $P < 0.05$, indicating the influence of disproportionate weight gain on plasma triglycerides.

DISCUSSION

Approximately 20% of children (under age 21) at genetic risk for familial hypertriglyceridemia have primary elevations of fasting plasma triglycerides (10), and many are considerably overweight at the time of initial diagnosis (9, 10). Their obesity and their excessive intake of calories, saturated fatty acids, and

Table 1. *Baseline cholesterol and triglyceride, and levels after 6 months of diet (milligrams per ml)*

Subject no.	Age	Sex	Baseline		At 6 months		Weight	
			Cholesterol	Triglyceride	Cholesterol	Triglyceride	Baseline	At 6 months
1 (RH)	9	F	244	146	225	114	47	43
2 (MB)	17	M	198	300	147	180	99	93.7
3 (MJ)	15	F	199	197	158	98	61	63
4 (AE)	14	F	206	222	203	140	100	99.5
5 (GH)	12	M	134	188	187	120	66.8	64.6
6 (JC)	13	F	231	34	220	128	47	49
7 (PS)	11	F	213	332	205	107	58.6	56.6
8 (JR)	13	M	218	400	182	172	79.2	79.8
9 (RC)	11	M	190	202	193	60	61.8	60
10 (JC)	8	F	144	154	112	23	25.4	26.8
11 (LH)	11	F	199	148	185	149	61	63.7
12 (FB)	15	M	156	253	253	106	103.5	89.5
13 (TR)	7	F	178	213	195	170	54	55
14 (SE)	17	F	139	221	176	232	104	105
15 (CH)	21	M	343	217	208	102	66	64
16 (CH)	17	F	188	160	178	74	56	55.1
17 (JJ)	17	M	202	272	129	102	113	73
21 (LA)	12	F	156	181	171	125	68	66
22 (RA)	13	F	248	308	226	134	85	84
23 (BA)	19	F	280	201	271	154	82	80
24 (LW)	12	F	152	194	150	89	50.2	53
25 (CS)	3	M	170	158	174	64	17	18
26 (DN)	14	M	193	220	201	138	68	68
28 (LI)	13	F	200	210	200	90	48	47
30 (EW)	16	F	169	340	140	210	66.2	66
31 (DS)	21	M	189	187	129	158	75	74
32 (TU)	14	F	197	176	153	43	50	48
33 (JH)	18	M	196	210	198	230	77.3	77.6
34 (TY)	17	M	186	400	199	122	81	85
35 (MY)	22	M	224	154	203	116	88	91
36 (KW)	14	F	165	192	152	92	59.1	58.6
37 (ES)	17	F	246	1320	159	185	66.4	63
38 (MS)	13	M	186	196	188	81	55	53
39 (KB)	13	M	128	158	120	118	55	54.2
40 (BU)	12	F	164	158	148	74	46.2	47
41 (TU)	9	M	255	968	172	141	26	24
42 (JN)	9	F	189	147	174	69	29	36.8
44 (GH)	11	M	237	142	253	56	56	56.4
47 (DJ)	7	F	137	144	162	120	21	22.2
50 (BV)	11	F	195	149	212	63	45	46
51 (RV)	13	M	179	140	164	69	47	47.1
52 (MM)	6	F	168	145	138	30	205.	20.8
54 (RD)	14	M	168	170	168	118	91	90
$\bar{X}$	13.3		194.4	2534.	1809[1]	115.5[2]	62.2	60.9
SE	.6		6.4	32.6	5.4	7.5	3.6	3.3

[1] $P < 0.05$, 6-month levels vs. baseline.
[2] $P < 0.01$, 6-month levels vs. baseline.

carbohydrates may facilitate early expression of the genetic trait (9, 10). In this study, mean plasma triglyceride in 43 children with familial hypertriglyceridemia fell after 6 months of weight reduction-NIH type IV diet (5) from 253 ± 32 to 116 ± 8 mg/dl, $P < 0.01$. The mean decrement in weight (1 ± 1 kg) was not significant, and decrements in weight failed to correlate with decrements in plasma triglycerides, $r = 0.131$. Despite this failure to appreciably reduce weight, after 6 months on diet, plasma triglyceride levels were reduced to normal (< 140 mg/dl) in 32 of the 43 children.

On subsequent follow-up for 8–26 months (in 19 subjects) most of the children were in a rapid pubertal growth phase and separation of the effects of caloric restriction and the compositional restrictions of the type IV diet cannot be made. Dietary effect is an amalgamation of caloric restriction (where indicated) and modification of dietary constituents. At 8 months' follow-up in 13 children, mean plasma triglyceride was 170 + 31, compared to baseline levels of 290 ± 86 mg/dl, $P < 0.01$, and 5 of the 13 had normal triglyceride levels. Plasma triglycerides were normal in 4 of 5 children at evaluation at 1 year, in 3 of 7 at 18 months, and in 4 of 14 at 22–26 months. When weight gain was proportionately greater than accretion of height, and where no attention to either caloric intake or composition was given, triglycerides remained elevated, whereas dietary adherence was generally accompanied by reduced or normal triglycerides.

Although we urged all of the 46 children in the initial intensive 6-month study group to continue with routine 2–4-month evaluations over time, only a minority continued in the re-evaluation program. The sharp reductions in plasma triglyceride after 6 months follow-up apparently misled many parents-children-physicians that the levels would remain normal without repetitive reexamination, caution as to total caloric intake, and dietary re-

Table 2. *Plasma triglyceride (TG), baseline, and on diet (milligrams per dl)*

Subject no.	Baseline	Months of follow-up 8	10	12	14	16	18	20	22	24	26
3 Ht/Wt[1]	165/61									166.5/69.8	
TG	197									(149)	
4 Ht/Wt	169/100	172/103	173/110				174/104				
TG	222	(228)[2]	(90)				(123)				
6 Ht/Wt	145/47	148/52		150/54			150/57.5			152/58	
TG	304	(119)		(95)			(104)			(118)	
7 Ht/Wt	157.5/58.6					161/69	162/73		162.5/78		
TG	332					298[3]	414[3]		184[3]		
8 Ht/Wt	168/79.2									190.5/108.6	
TG	400									(81)	
9 Ht/Wt	152/61.8	159/64								164/74	
TG	202	(130)								241[3]	
10 Ht/Wt	130/25.4				135/28.6						
TG	154				(12)						
11 Ht/Wt	155/61									165.5/74.5	
TG	148									216[3]	
14 Ht/Wt	175/104.5	175/113.4									
TG	221	212[3]									
15 Ht/Wt	167.7/66	167.7/69		167.7/69			167.7/68.7				
TG	217	(154)		320[3]			(211)				
16 Ht/Wt	160/56	161/56		161/57.4			161/57.4				
TG	160	(48)		(97)			(96)				
26 Ht/Wt	175.3/68.2	179/68.8									
TG	220	(156)									
28 Ht/Wt	163/48	170/56								172.7/56.1	
TG	210	(75)								(56)	
31 Ht/Wt	177.8/75	180/74					180/75.5			180.5/76.5	
TG	187	(116)					(181)			(206)	
34 Ht/Wt	183/81									183/89	
TG	400									464[3]	
37 Ht/Wt	158/66.4	158/62				158/70.4				158/64.5	
TG	1320	5-2[3]				606[3]				(162)	
38 Ht/Wt	168/55	169/53		170/52		173/58		174/59		174/65.2	
TG	196	(154)		(98)		(182)		(124)		238[3]	
44 Ht/Wt	149/56	155/62	155/60.2	156/60	157/62		157/68		158.5/64.3		
TG	142	(170)	(148)	(109)	(105)		218[3]		(126)		
54 Ht/Wt	177/91	177/88.2								183/97	
TG	170	(149)								(145)	
55 Ht/Wt	156/45									158/46.1	
TG	144									144[3]	

[1] Height (Ht) in centimeters; weight (Wt) in kilograms.

[2] Satisfactory dietary adherence is shown within parentheses.

[3] Following none of the suggested dietary recommendations.

[4] Unable to provide sufficient information to allow any judgment in regard to adherence.

instruction. As shown in Table 2 this was not the case, although plasma triglycerides were generally normal in those children who followed a consistent long range diet program.

CONCLUSION

Amelioration of familial hypertriglyceridemia on the NIH type IV diet is a realizable goal in children, but requires persistent, repetitive reexamination and re-instruction. Normalization of triglyceride levels in children may be important as a primary, longitudinal approach to reduction of the increased atherosclerotic risk attendant to familial hypertriglyceridemia in some (2, 3), but not all adults with familial hypertriglyceridemia (1).

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High density lipoprotein cholesterol (C-LDL)
low density lipoprotein cholesterol (C-HDL)
neonate

Low and High Density Lipoprotein Cholesterol Interrelationships in Neonates with Low Density Lipoprotein Cholesterol ≤ the 10th Percentile and in Neonates with High Density Lipoprotein Cholesterol ≥ the 90th Percentile

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Summary

Since the inverse relationship between high density lipoprotein cholesterol (C-HDL) and low density lipoprotein cholesterol (C-LDL) is generally recognized in school children and in adults, but not at birth, the current study was focused on neonates having C-HDL ≥ the 90th percentile and neonates with C-LDL ≤ the 10th percentile to determine whether any distinctive relationships existed at the extreme limits of the frequency distribution among C-HDL, C-LDL, and total plasma cholesterol. Sixty-three neonates with C-LDL ≤ the 10th percentile (20 mg/dl), and 58 with C-HDL ≥ the 90th percentile (50 mg/dl) were selected in the consecutive order of their birth as part of an ongoing cord blood lipid and lipoprotein survey. Comparisons of the hypobeta- and hyperalphalipoproteinemic neonates with 117 previously described unselected neonates were made. In the 117 unselected neonate controls, both C-HDL and C-LDL levels were closely correlated with total cord blood cholesterol ($r = 0.63, 0.76, P < 0.01$), whereas C-HDL was not significantly related to C-LDL ($r = 0.002$). In the 63 hypobetalipoproteinemic neonates, C-HDL correlated closely with total plasma cholesterol concentrations ($r = 0.98, P < 0.01$). C-LDL failed to correlate with total plasma cholesterol ($r = 0.07$). In the face of low cord blood C-LDL, nearly all of the total plasma cholesterol variation was accounted for by C-HDL. C-HDL was not significantly related to C-LDL ($r = -0.15$). In 58 hyperalphalipoproteinemic neonates, C-HDL did not significantly correlate with total cholesterol concentrations ($r = 0.22$), whereas C-LDL was closely related ($r = 0.88, P < 0.01$), with nearly all of the total plasma cholesterol variation accounted for by C-LDL. The inverse C-HDL to C-LDL relationship was not significant ($r = -0.18$)

Speculation

Whatever factors contribute to both the overall and to the extremes of the C-HDL and C-LDL frequency distributions at birth, C-HDL and C-LDL in neonates appear to be under independent metabolic control.

Plasma high density lipoprotein cholesterol levels in adults are often inversely correlated with low density lipoprotein cholesterol levels (1, 3, 7, 8). In the Bogalusa lipoprotein study in white and black school children, total plasma cholesterol and C-LDL levels were closely correlated ($r = 0.745, 0.727$) (12). Total plasma cholesterol also correlated with C-HDL concentrations in whites and blacks ($r = 0.441$, $r = 0.595$) (12). The Bogalusa study (12) revealed significant inverse relationships between C-HDL and C-LDL levels in 1174 black children ($r = -0.09$), and in 2009 white children ($r = -0.231$). The correlation in black children ($r = -0.09$) between C-HDL and C-LDL, although statistically significant, is low, and perhaps of doubtful biologic import. Rhoads *et al.* (9) found no significant correlation between C-HDL and C-LDL ($r = 0.01$) and concluded that "the inverse relation of alpha cholesterol to prevalence of coronary heart disease was independent of beta cholesterol . . . ." (9).