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The Effect of Growth Hormone Administration on Lipids and Lipoproteins in Growth Hormone-Deficient Patients (41610)

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Abstract. Plasma lipids, lipoproteins, and lipoprotein cholesterol levels were studied in a group ($n = 8$) of prepubertal growth hormone-deficient patients before and after growth hormone (GH) administration. Determination of plasma lipoproteins by a sensitive agarose gel electrophoretic technique demonstrated: (a) in the patients with two prebeta bands an intensification of the fast prebeta lipoprotein fraction after growth hormone administration; and (b) in the patients with one prebeta band the appearance of a second prebeta band after growth hormone administration. The mean (±SD) plasma triglyceride level before GH was 86 ± 60 mg/dl and 158 ± 95 mg/dl after GH ($P < 0.01$). Mean (±SD) plasma cholesterol level before GH was 196 ± 25 mg/dl and 174 ± 28 mg/dl after GH ($P < 0.05$). High-density lipoprotein cholesterol concentrations decreased significantly ($P < 0.001$) from mean (±SD) 55 ± 12 mg/dl before GH to 37 ± 10 mg/dl after GH. Very-low-density lipoprotein cholesterol concentrations increased significantly ($P < 0.05$) from mean (±SD) 13 ± 12 mg/dl before GH to 23 ± 15 mg/dl after GH. Low-density lipoprotein cholesterol concentrations decreased (N.S.) from mean (±SD) 123 ± 15 mg/dl before GH to 114 ± 15 mg/dl after GH. These lipid and lipoprotein changes could be mediated through the insulin antagonism, hyperinsulinemia, and a decrease in lipoprotein lipase activity caused by growth hormone.

The purpose of this study was to investigate the variations in plasma lipids and lipoproteins in growth hormone (GH)-deficient patients before and after GH treatment. Merimee (1) in his follow-up report of GH deficient dwarfs suggested that the GH deficient state protected these patients from the pathogenesis of vascular disease associated with their hyperlipidemia and glucose intolerance. In a more recent report (2) further evidence was presented suggesting that GH administration did not alter lipid patterns in GH-deficient patients.

In this report evidence is presented which demonstrates the effect of GH administration on plasma cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol concentrations as well as on lipoprotein patterns in GH-deficient patients.

Materials and Methods. *Patients.* Eight GH-deficient patients were investigated in the study; informed consent was obtained prior to study. The patients' diagnoses, ages, sex, and hormone therapy are listed in Table 1. GH deficiency was diagnosed by subnormal GH responses during at least two provocative tests (arginine, insulin, or L-Dopa). Pubertal status was assessed by clinical and biochemical criteria. All male patients had testicular lengths less than 2.5 cm; the female patient did not have breast budding; all patients had bone ages less than 12.5 yr; all patients had subnormal testosterone and estradiol levels and failed to have a LH and FSH response to LHRH infusion. Patients on replacement therapy were euthyroid and adrenal sufficient as judged biochemically and by a linear response to growth hormone while not on protocol (GH 2 U im, three times per week). All patients not on replacement therapy were euthyroid and had a normal cortisol response to insulin-induced hypoglycemia. At least 1 month prior to admission to the Clinical Center, National Institutes of Health, GH treatment was stopped. After an overnight fast (12–14 hr), blood was collected from the patients for lipid and lipoprotein determinations. Human GH, 2.5 U im every 12 hr, was administered for 7 days. Twelve hours after the last growth hormone injection, fasting blood samples were collected again for lipid and lipoprotein determinations. Human GH was pro-

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TABLE I

Patient	Diagnosis	Sex	Age	Hormone replacement
1	Idiopathic hypopituitarism	F	9	GH T_4
2	Craniopharyngioma	M	14-11/12	GH T_4 Cortisol Vasopressin
3	Pinealoma	M	17-1/2	GH T_4 Cortisol Vasopressin
4	Idiopathic hypopituitarism	M	25-4/12	GH T_4
5	Idiopathic GH deficiency	M	8-8/12	GH
6	Craniopharyngioma	M	12-6/12	GH
7	X-linked GH deficiency, hypogammaglobulinemia	M	5-2/12	GH
8	X-linked GH deficiency, hypogammaglobulinemia	M	3-9/12	GH

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Agarose gel electrophoresis. Blood samples were drawn before and after GH administration. They were allowed to clot and the serum separated by centrifugation. Lipoprotein determinations were performed by an agarose gel electrophoretic technique which sharply resolves the lipoprotein fractions and demonstrates additional subfractions as previously described (3, 4).

Plasma lipid and lipoprotein cholesterol determinations. Blood samples were collected in 0.1% EDTA test tubes and plasma was separated by centrifugation at 4°C. Plasma cholesterol and triglycerides were measured with an AutoAnalyzer II (5, 6). HDL cholesterol was measured after heparin–manganese precipitation of plasma (7). The plasma was ultracentrifuged at its own density (1.006 g/ml) for 18 hr at 39,000 rpm (4°C) in a Beckman 40.3 rotor (Beckman Instruments, Fullerton, Calif.) and the very-low-density lipoproteins (VLDL) were separated from the other plasma-lipoproteins by tube slicing (8). The cholesterol concentration in the 1.006 g/ml infranate fraction was determined by these methods, and VLDL and low-density lipoprotein (LDL) cholesterol were calculated (7). These latter measurements were carried out in five patients.

Statistics. Statistical comparisons were performed using Student's paired *t* test. Lipid values were expressed as mean ± standard deviation.

Results. *Serum lipoprotein electrophoresis.* Typical examples of serum lipoprotein electrophoretic patterns from normal subjects and patients are shown in Fig. 1. Normal patterns from normolipidemic subjects are represented by N and N′ with one and two prebeta lipoprotein fractions, respectively. The lipoprotein patterns A and B are from the same patient. Pattern A demonstrates one prebeta

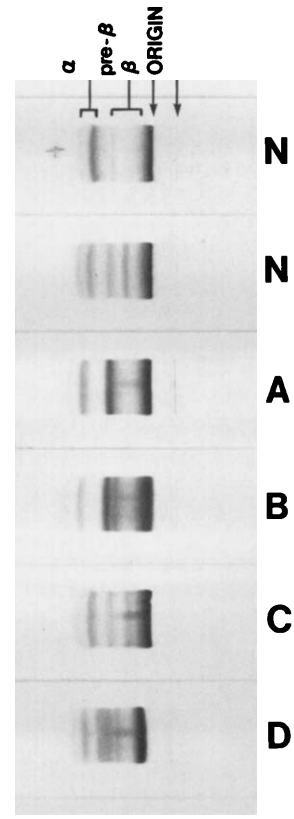

FIG. 1. Lipoprotein electrophoretic patterns of serum from a normolipidemic subject (N) with one prebeta band, a normolipidemic subject (N′) with two prebeta bands. Patterns A and B are from the same patient originally with one prebeta band (A), and demonstrating the appearance of a second prebeta band after GH administration (B). Patterns C and D are from the same patient originally with two prebeta bands (C), and demonstrating increased intensity of the fast prebeta band after GH (D).

band before GH treatment; pattern B demonstrates the appearance of a second prebeta after administration of GH. The lipoprotein patterns C and D are from a patient with two prebeta bands of equal intensity before GH; after GH treatment a change in the intensity of the two prebeta bands is evident in pattern D. The intensity of the slow prebeta band decreased while the intensity of the fast prebeta band increased considerably. It is also apparent that the second, slow, prebeta band in the patients after GH administration is migrating faster than the second band noted in N′.

Plasma lipid and lipoprotein cholesterol levels in GH-deficient patients before and after GH administration. Plasma lipid and lipoprotein cholesterol levels for the patients studied are shown in Table II. Values obtained in normal controls of appropriate age are given for each sex.

After replacement with human GH, patients had repeat lipid studies. Six of the eight patients studied had reductions in plasma cholesterol levels after GH treatment; as a group there was a modest 11.2% reduction ($P < 0.05$) in cholesterol in contrast to previous reports (1, 2). Plasma triglyceride levels increased significantly ($P < 0.01$) after GH administration in the patients studied; as a group there was an 83.2% increase in plasma triglyceride levels. This increase in triglycerides is consistent with the increase in prebeta lipoproteins after GH administration that we have demonstrated here and reported by others (9). Furthermore, HDL cholesterol levels fell by 32.7% after GH administration. This reduction in HDL cholesterol after GH treatment was significant ($P < 0.001$). Measurement of VLDL cholesterol in five patients and by calculation in three patients by the Friedewald formula (10) revealed an increase after therapy of 77% ($P < 0.05$) and measurement of LDL cholesterol revealed a decrease after therapy of 7% (N.S.).

Discussion. We studied a heterogeneous group of GH-deficient patients. All patients were normolipidemic except for one (patient 3) who had significant hypertriglyceridemia. All patients were normoglycemic and not glucose intolerant in the basal state (data not shown). The patients with other pituitary deficiencies were on replacement therapy before and during the study. Our patients were prepubertal thus eliminating known effects of estrogens (11) and androgens (12) on lipid metabolism and different than the mature patients studied by Merimee (2).

We then performed studies with sera and plasma obtained from GH-deficient patients before and after GH treatment. Lipids are known to circulate in blood as lipoproteins (4). Agarose gel electrophoresis of patient sera before and after GH therapy revealed that GH either intensifies the prebeta lipoprotein band or it caused the appearance of a second, prebeta lipoprotein band. These lipoprotein patterns demonstrate changes in the circulating native lipoprotein in response to GH.

Prebeta lipoprotein alterations have been reported after GH administration in normocholesterolemic subjects (9), but identification of a second prebeta lipoprotein has not been described. The appearance of the second, prebeta lipoprotein in patients originally having only one prebeta is of particular interest because the new band migrates faster than the slow prebeta band shown in Fig. 1 (N′). This latter band which is present in 30% of normal subjects (13) has been found in a higher frequency (over 90%) in patients with atherosclerotic cardiovascular disease (14, 15). However, the significance and relevance of this abnormal band in the context of GH-deficient patients on replacement therapy is unclear.

Plasma lipid determinations supported the electrophoretic patterns. Plasma triglycerides significantly increased in our patients after GH therapy associated with an increase in the prebeta lipoprotein bands, as well as in VLDL cholesterol levels. HDL cholesterol significantly decreased following GH therapy in our patients as would be expected due to the negative correlation of HDL cholesterol with plasma triglyceride (16).

We would speculate that the effects seen in our patients post GH replacement are secondary to the known diabetogenic effects of GH (17). GH causes insulin antagonism (18). The resulting insulin resistance (19) and/or GH excess (20) would cause a decrease in lipoprotein lipase (21). When triglyceride-rich lipoproteins are catabolized in plasma, some of their lipid and protein constituents are transferred to LDL and HDL (22, 23). Reduced lipoprotein lipase impairs the periph-

TABLE II. LIPID DETERMINATIONS BEFORE AND AFTER GROWTH HORMONE TREATMENT

	Cholesterol (mg/dl)		Triglyceride (mg/dl)		HDL cholesterol (mg/dl)		VLDL cholesterol* (mg/dl)		LDL cholesterol* (mg/dl)	
Patient No.	Before	After	Before	After	Before	After	Before	After	Before	After
1	206	148	75	161	52	34	6	29	148	85
2	178	147	58	166	50	35	1	20	127	92
3	253	228	231	372	69	38	39	48	145	142
4	189	153	44	70	60	49	7	6	122	98
5	185	198	60	97	51	38	11	1	123	159
6	179	166	57	181	47	24	11	36	121	106
7	186	168	92	123	36	26	18	25	132	117
8	188	184	70	90	73	51	14	18	101	115
Mean	196	174	86	158	55	37	13	23	123	114
±SD	25	28	60	95	12	10	12	15	15	25
P†	<0.05		<0.01		<0.001		<0.05		NS	
Controls										
Males										
Age 0–14 (n = 132)	174 ± 33		63 ± 31		56 ± 12		13 ± 8		106 ± 30	
Age 15–24 (n = 140)	171 ± 30		80 ± 31		49 ± 9		14 ± 9		108 ± 26	
Females										
Age 0–14 (n = 116)	167 ± 32		65 ± 29		52 ± 12		13 ± 9		102 ± 28	
Age 15–24 (n = 136)	173 ± 28		75 ± 31		57 ± 12		14 ± 7		103 ± 26	

* In patients 6, 7, and 8 insufficient plasma was obtained for complete study. This necessitated calculation of LDL and VLDL by the Friedewald formula (10). In patients with triglycerides less than 400 mg/dl this is a highly reliable method for calculation of VLDL and LDL.

† Determined by Student's paired t test.

eral catabolism of triglyceride-rich lipoproteins, resulting in increases in triglyceride-carrying lipoprotein as well as decreases in LDL and HDL (16). In this study GH administration caused increases in plasma triglycerides and VLDL cholesterol as well as decreases in LDL and HDL cholesterol levels. Alternatively, GH causes basal hyperinsulinemia (19). This manifests itself with increased triglyceride synthesis and a subsequent increase in triglyceride-carrying lipoproteins (24). Future studies measuring insulin levels and lipoprotein lipase activity will better elucidate the mechanism of GH's effect on lipids and lipoproteins.

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