Gastric Drip Feeding in Patients with Glycogen Storage Disease Type I: Its Effects on Growth and Plasma Lipids and Apolipoproteins

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ABSTRACT. In 19 patients with a deficiency of glucose-6-phosphatase and 1 patient with a deficiency of glucose-6-phosphate translocase, the effect of nocturnal gastric drip feeding (GDF) on growth and plasma lipids and apolipoproteins was studied. The effect on growth was estimated by determining the height standard deviation score (SDS) of the patients and comparing its changes (Δ SDS) over 4-, 2-, and 1-y periods before and 1-, 2-, 5-, and 8-y periods after the institution of GDF. The effect of GDF on plasma lipids and apolipoproteins was investigated by following the concentrations of triglycerides, cholesterol, and apolipoproteins A-I, A-II, B, C-I, C-II, C-III, and E. Growth caught up significantly or remained in the normal range in 14 patients. They were defined as responders to GDF. In the other six patients, growth caught up insufficiently or showed a further deceleration. They were defined as nonresponders to GDF. GDF had only a temporary and marginal effect on plasma lipids and apolipoproteins, but after 5–8 y, the levels of plasma triglycerides, cholesterol, apolipoprotein, B, C-I, C-II, C-III, and E increased further in both responders and nonresponders, whereas apolipoproteins A-I and A-II decreased in nonresponders. There were minor differences in the levels of lipids and apolipoproteins between responders and nonresponders without any discernible trends during the first years of GDF. After 5–8 y, the levels of cholesterol, triglycerides and apolipoproteins B, C-I, C-II, C-III, and E seemed to be higher, and apolipoproteins A-I and A-II lower, in nonresponders than in responders, but the differences were not significant. (*Pediatr Res* 25:327–331, 1989)

Abbreviations

GSD-IA, glycogen storage disease caused by deficiency of glucose-6-phosphatase
GSD-IB, glycogen storage disease caused by deficiency of glucose-6-phosphate translocase
GDF, gastric drip feeding
height SDS, height standard deviation score

The administration of nocturnal GDF to patients with GSD-IA or GSD-IB has markedly improved their growth (1, 2). With GDF such main metabolic abnormalities as hyperlactacidemia,

hyperuricemia, and hyperlipidemia also improve initially, but the long-term effects vary (3).

We treated 20 patients (19 with GSD-IA and 1 with GSD-IB) with GDF during 2 to 12 y, and the majority showed catch-up growth. However, some patients continued to grow at or below the lowest percentiles of the height references or lagged further behind. The height SDS was found to correlate inversely with the urinary excretion of some important metabolites of glycogenolysis (lactate) and the citric acid cycle (2-oxoglutarate) (4). Assuming that a similar relation might exist between growth and other metabolic abnormalities, we studied the concentrations of plasma lipids and apolipoproteins before and during GDF. Hyperlipidemia and hyperlipoproteinemia are well-known abnormalities in GSD-I (2, 5), and the plasma apolipoprotein profile shows a characteristic pattern (6). It is not known whether the abnormal apolipoprotein profile persists during GDF irrespective of the condition of the patient or improves in concert with an improved growth. Therefore, we studied this issue in 20 GSD-I patients with a large range of ages and height SDS from the beginning of GDF until adolescence.

PATIENTS

The study included 20 patients, aged 0.03 to 8.51 y at the institution of GDF. Glucose-6-phosphatase deficiency was diagnosed in 19 patients by enzyme assay of a liver biopsy, except for one patient who is a brother of a biopsy-documented case. Glucose-6-phosphate translocase deficiency was diagnosed in the liver biopsy of one patient (case 9). The patients were free from other diseases, but had the usual abnormalities due to their primary disorder, such as marked hepatomegaly, tendency to hypoglycemia, hyperlactacidemia, hyperuricemia, hyperlipidemia, and hyperlipoproteinemia. The diet before the institution of GDF consisted of frequent meals around the clock. The average composition of the diet was: carbohydrates, 60–70 energy% (lactose- and sucrose-restricted), protein 10–15 energy%, fat 20–25 energy% with a polyunsaturated/saturated (P/S) fatty acid ratio of 1:3. After the institution of GDF, the amount of carbohydrates decreased slightly to 60–65 energy% with more emphasis on starch. The amount of fat increased reciprocally, and the P/S ratio increased to 1:1. The GDF was a low-lactose adapted cow's milk formula with extra maltodextrin, amounting to 4–8 mg glucose·kg⁻¹·min⁻¹, administered during 10–12 h/night. The GDF provided approximately 35% of the total energy intake/d.

MATERIALS AND METHODS

Growth analysis. Data on statural growth before the start of GDF were collected from the referring pediatricians and from

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our own clinic. Our measurements of height were performed on a Harpenden stadiometer. All heights were expressed as SDS, according to Tanner *et al.* (7). The SDS is defined as the patient's height minus the mean for the actual age, divided by the SD at that age. For this purpose, the 1980 nation-wide Dutch references (8) were used. In addition, the SDS corrected for parental height was calculated by subtracting the mean parental SDS from the child's SDS value. The parental SDS was calculated using the mean and SD of adult men's and women's heights in the 1965 nation-wide Dutch references (9). Normally, the height SDS of a child remains stable after the age of approximately 4 y, which signifies that heights tend to keep their track on the percentile charts. Deviation from the normal track, *i.e.* a change in height SDS, is the growth parameter of interest when the effect of a disease or of a possibly growth-promoting treatment is investigated. We therefore calculated the change of height SDS over periods of 1, 2, and 4 y before and 1, 2, 5, and 8 y during GDF treatment. These values were all estimated by interpolation of the available height measurements. The values obtained over 1, 2, 4, and 5-y periods were compared with the 95% confidence intervals in a Finnish healthy child population (10). Wt-for-height was expressed as a percentage of the median wt-for-height from the recent Dutch growth study (8).

Laboratory methods. Venipuncture was performed for routine assay of electrolytes, urate, and liver and kidney function. Additional blood was taken for the lipoprotein studies with the consent of the parents and/or the patients. The venipuncture was performed in the nonfasting state because of the risk of fasting hypoglycemia. The preceding breakfast consisted of 1–2 slices of bread with margarine, jam, or marmalade, and tea with low-fat milk. EDTA blood samples were centrifuged at low speed, and the plasma was used for the determination of triglycerides and cholesterol by routine procedures (11, 12). The remaining plasma was shipped immediately by airmail at ambient temperature from Groningen to Oklahoma City, OK, for apolipoproteins analyses. Plasma apolipoproteins were measured by electroimmunoassays as described earlier (6).

Statistical methods. As a result of skewed distributions of lipid

and apolipoprotein values in some patients, the significance of differences was estimated by the Wilcoxon rank sum test. The level of significance was taken as $p \leq 0.05$.

RESULTS

Growth analysis. The height SDS at the start of GDF and its changes before and after the institution of GDF are shown in Table 1. Before treatment, a negative growth deviation is seen in almost all children, and in many cases the height SDS is below the 2.5 percentile. After the institution of GDF, catch-up growth, indicated by positive SDS changes, is seen in most children. The SDS changes are above the $p = 95$ value in many cases. When the data are analyzed on an individual basis, several patterns emerge. The most common pattern is growth retardation before the onset of treatment, followed by catch-up growth for a few years, and subsequently stable growth parallel to the percentile curves. This pattern is seen in cases 1–9, except that case 2 already showed accelerated growth before the start of GDF, probably because of more frequent feeding. These cases showed a normal distribution of height SDS (corrected for parental height SDS) from -1.14 to $+2.86$ after 5 y of GDF. Two patients, cases 10 and 11, had a normal growth before GDF, which did not substantially change subsequently,

Cases 1–11 all have a growth pattern that can be considered as a satisfactory response to GDF. Two patients, cases 12 and 13, with significant catch-up growth can be expected to attain ultimately normal height SDS, although their height SDS at 5 y still were subnormal.

Case 14 showed catch-up growth after the start of GDF, but the period of observation was not long enough to be certain that this catch-up growth will be adequate.

Cases 15 and 16 had an early growth acceleration, followed by a lag. After 5 y of GDF they, and case 17, still showed a low height SDS (corrected for parental height SDS). This may be considered an insufficient response.

Finally, three cases, 18–20, had a continued deceleration of growth, resulting in lower height SDS values during GDF than

Table 1. Height SDS and its changes among 20 patients with GSD-IA and GSD-IB before and during GDF

Case	Initials	Age	At start of GDF		After 5 y GDF	Before GDF: Δ SDS over			During GDF: Δ SDS over			
			Height (SDS)	Height SDS (corr)*	Height SDS (corr)*	4 y	2 y	1 yr	1 y	2 y	5 y	8 y
1	MB	6.57	-3.65	-4.09	-0.96	-2.38†	-0.82†	-0.07	+1.70†	+2.48†	+3.13†	+3.26
2	DD	7.52	-1.45	-1.85	-0.57	+0.89	+0.38	+1.02†	+0.98†	+1.40†	+1.28†	+2.38
3	RS	5.30	-4.22	-2.87	-0.97	-2.32†	-0.93†	-0.79†	+1.12†	+1.89†	+1.90†	+2.25
4	PS	8.51	-2.94	-2.14	-1.14	-0.77	-0.09	-0.18	+0.56†	+0.94†	+1.00†	+1.71
5	TD	5.18	-2.49	-0.79	+2.16	-0.80	-0.20	-0.34	+1.85†	+2.21†	+2.95†	
6	MG	3.68	-0.98	-2.12	-0.67		-0.95	-0.07	+0.39	-0.01	+1.45†	+1.13
7	ME	1.59	+0.42	+0.32	+2.86			-0.35‡	+1.90†	+2.11†	+2.54†	+1.61
8	LA	0.59	-1.32	-1.56	+0.84			-1.85‡		+1.64	+2.40†	
9	RP	4.57	-3.43	-2.19	+0.01§		-0.18	-0.19		+1.40†	+2.20†§	
10	DS	4.77	-1.11	-0.31	-0.86	+0.26	-0.28	+0.32	-0.29	-0.08	-0.55	-0.75
11	ID	4.69	-1.89	-1.17		+0.96	+0.10	-0.10	+0.17	-0.06		
12	HM	8.33	-3.50	-4.25	-2.44	-1.55†	-1.08†	-0.34	+0.29	+0.60†	+1.81†	
13	MR	5.19	-4.03	-4.51	-2.63	-1.32	-0.03	+0.22	+0.99†	+0.98†	+1.88†	
14	EO	0.20	-1.53	-2.39					+0.82	+0.59		
15	ER	4.81	-4.85	-2.68	-2.41	-3.78†	-0.51	-0.50	+1.47†	+1.58†	+0.27	-0.38
16	MD	4.98	-3.43	-3.23	-3.97	-3.58†	-0.69	-0.29	+0.34	+0.52	-0.74	-1.62
17	CG	4.48	-2.17	-3.31	-2.67	-0.17	-0.45	-0.16	+0.46	+0.69	+0.64	
18	SN	5.95	-0.91	-1.20		-0.26	0.00	+0.05	-0.49	-1.04†		
19	AN	1.61	-0.64	-0.93	-1.79			+0.25	-0.34	-0.73	-0.86	
20	NS	0.03	+0.55	+1.34					-0.57	-1.80		

* Patient's height SDS corrected for parental height SDS.

† Height SDS changes exceeding the 95% confidence intervals.

‡ SDS over 6–7 mo.

§ SDS over 4 y after start of GDF because data after 5 y were unavailable.

at its start. The first two must be considered as total nonresponders. The last patient is still very young, and the decrease of her height SDS may be the normal crossing of percentiles seen in genetically short children in the first years of life.

The weight (mean $\pm$ SD) of the patients was $107 \pm 7\%$ of the median wt-for-height. Wt-for-height increased slightly but not significantly ($113 \pm 12\%$) after 4 y of GDF.

Plasma lipids and apolipoproteins. Plasma lipid and apolipoprotein concentrations of patients responding to the GDF treatment (cases 1–14, see "Discussion") are shown in Table 2. As previously demonstrated (6), the patients' lipid and apolipoprotein profiles were abnormal before initiation of GDF. Triglycerides and apolipoproteins B, C-I, C-II, C-III, and E were all increased, A-I decreased, in comparison with normolipidemic, asymptomatic children of similar age (6). After the beginning of treatment with GDF fluctuations and changes in the concentrations of plasma triglycerides, cholesterol and all apolipoproteins were observed. The changes never reached statistical significance at any of the time intervals. After 1–2 y of GDF, the concentrations of triglycerides and cholesterol tended to decrease slightly, but after prolonged treatment, both triglyceride and cholesterol values were higher than at the beginning of GDF treatment. Concentrations of apolipoproteins A-I and A-II remained unchanged throughout the entire treatment period. There was some initial decrease in the apolipoprotein B concentrations, but after 5–8 y of GDF the apolipoprotein B levels were as high or higher than before the treatment. The initially high levels of apolipoprotein C peptides and apolipoprotein E remained unchanged, or increased further, after 5–8 y of GDF.

Similar trends, but without any transient decrease of some

apolipoproteins, were also observed in lipid and apolipoprotein profiles of patients not responding to the GDF treatment (cases 15–20, Table 3). However, the increase in the concentration of cholesterol after 5–8 y was statistically significant when compared to that at the beginning of GDF. The increase of triglyceride levels after prolonged treatment with GDF was not statistically significant because of the small number of samples available for analysis and the relatively wide range of values. The same argument applies to the markedly increased levels of apolipoproteins B, C-I, C-II, C-III, and E after 5–8 y of GDF. The concentrations of apolipoprotein A-I and apolipoprotein A-II decreased steadily.

A comparison of lipid and apolipoprotein profiles estimated at different time intervals between responders and nonresponders to GDF therapy shows that both groups of patients were characterized by abnormal concentrations of plasma triglycerides and all apolipoproteins with the possible exception of apolipoprotein A-II. Small differences in the levels of these constituents were statistically insignificant. During prolonged treatment with GDF, the elevated levels of triglycerides, cholesterol, and most apolipoproteins were maintained in both responders and nonresponders. However, from 1–2 y of treatment onward, the concentrations of triglycerides, cholesterol, apolipoproteins B, C-III, and E of nonresponders tended to be higher than those of responders, especially at the interval of 5–8 y, whereas apolipoprotein A-I levels behaved reversely. As already stated, the lack of statistical significance of the differences between responders and nonresponders at these later intervals is most probably due to the relatively small number of samples available for analysis and wide variations in the lipid and apolipoprotein values of individual patients. However, the mean values for lipids and apolipo-

Table 2. Plasma lipid and apolipoprotein concentrations (in mg/dL) (mean $\pm$ SD) in patients with GSD-IA and GSD-IB responding to GDF treatment (cases 1–14) and in control subjects (Ref. 6)

Treatment	Lipids		Apolipoproteins						
	TG*	TC†	A-I	A-II	B	C-I	C-II	C-III	E
Before GDF (–1–0 y)	434 $\pm$ 343	195 $\pm$ 84	104 $\pm$ 27	64 $\pm$ 22	135 $\pm$ 48	11.6 $\pm$ 5.7	5.7 $\pm$ 1.4	18.6 $\pm$ 9.9	17.2 $\pm$ 14
After GDF (0–1 y)	568 $\pm$ 372	227 $\pm$ 61	96 $\pm$ 27	57 $\pm$ 18	155 $\pm$ 45	9.0 $\pm$ 3.1	6.0 $\pm$ 1.8	19.3 $\pm$ 9.0	18.9 $\pm$ 7.7
After GDF (1–2 y)	400 $\pm$ 410	185 $\pm$ 79	103 $\pm$ 27	60 $\pm$ 16	130 $\pm$ 63	6.2‡	5.0‡	19.0 $\pm$ 17.5	14.8 $\pm$ 6.9
After GDF (2–5 y)	398 $\pm$ 314	201 $\pm$ 73	102 $\pm$ 34	53 $\pm$ 11	109 $\pm$ 47	11.2 $\pm$ 1.2	6.1 $\pm$ 1.6	20.7 $\pm$ 11.9	17.8 $\pm$ 6.5
After GDF (5–8 y)	601 $\pm$ 557	246 $\pm$ 101	107 $\pm$ 25	57 $\pm$ 10	158 $\pm$ 79	12.0 $\pm$ 6.7	7.7 $\pm$ 2.5	27.6 $\pm$ 18	21.6 $\pm$ 10.7
Control subjects	92 $\pm$ 40	181 $\pm$ 30	104 $\pm$ 22	15 $\pm$ 11	92 $\pm$ 21	9.0 $\pm$ 2.6	3.2 $\pm$ 1.2	7.2 $\pm$ 1.6	8.5 $\pm$ 3.2

* TG, triglycerides.

† TC, total cholesterol.

‡ Single measurement.

Table 3. Plasma lipid and apolipoprotein concentrations (in mg/dL) (mean $\pm$ SD) in patients with GSD-IA and GSD-IB, not responding to GDF treatment (cases 15–20) and in control subjects (Ref. 6)

Treatment	Lipids		Apolipoproteins						
	TG*	TC†	A-I	A-II	B	C-I	C-II	C-III	E
Before GDF (–1–0 y)	479 $\pm$ 389	143 $\pm$ 59	113 $\pm$ 43	59 $\pm$ 17	137 $\pm$ 58	15.4‡	5.0‡	23.0 $\pm$ 11	16.2 $\pm$ 8.0
After GDF (0–1 y)	447 $\pm$ 133	155 $\pm$ 35	82 $\pm$ 19	41 $\pm$ 8.7	121 $\pm$ 24	13.0‡	5.0‡	25.7 $\pm$ 9.0	12.6 $\pm$ 8.2
After GDF (1–2 y)	485 $\pm$ 297	218 $\pm$ 36	87 $\pm$ 28	54 $\pm$ 22	162 $\pm$ 41	10.6 $\pm$ 2.1	4.6‡	26.5 $\pm$ 9.3	21.1 $\pm$ 18.5
After GDF (2–5 y)	692 $\pm$ 314	236 $\pm$ 58	77 $\pm$ 31	51 $\pm$ 17	155 $\pm$ 67	9.4 $\pm$ 3.3	11.6‡	21.5 $\pm$ 6.7	17.7 $\pm$ 9.7
After GDF (5–8 y)	1625 $\pm$ 1360	390 $\pm$ 163	71 $\pm$ 22	45 $\pm$ 6.3	260 $\pm$ 72	17.2 $\pm$ 15	8.4 $\pm$ 1.8	33.8 $\pm$ 11.2	39.0 $\pm$ 27
		$p < 0.05$							
Control	92 $\pm$ 40	181 $\pm$ 30	104 $\pm$ 22	55 $\pm$ 11	92 $\pm$ 21	9.0 $\pm$ 2.6	3.2 $\pm$ 1.2	7.2 $\pm$ 1.6	8.5 $\pm$ 3.2

* TG, triglycerides.

† TC, total cholesterol.

‡ Single measurement.

§ Significantly different from the mean cholesterol value for patients before GDF.

proteins of both responders and nonresponders were significantly different from those of normolipidemic, asymptomatic children (6).

DISCUSSION

Improvement of growth in GSD-I patients, due to treatment with nocturnal GDF in conjunction with frequent feedings during the day, has been reported by many authors (1–3, 13). The favorable effects of GDF have been attributed to the constant provision of fuel to peripheral tissues (14). This is associated with a decrease of plasma glucagon and an increase of plasma insulin and growth hormone (1, 13). These hormonal changes as well as an amelioration of the tendency toward lactic acidosis (3) and a normalization of the sleep pattern (2) may be factors contributing to the improvement of growth.

We used two criteria to substantiate a favorable response of the patients' growth to long-term GDF treatment. First, a significant upward deviation of height SDS from the track of growth before the institution of GDF. The calculation of significance was obtained by comparing the Δ SDS over 1-, 2-, and 5-y periods with the 95% confidence intervals of Δ SDS of a healthy Finnish child population (10). This is applicable to growth-retarded patients showing catch-up growth, but not to patients who maintained a normal track before and during GDF. We defined the latter patients also as responders to GDF as long as their SDS remained above -2 and Δ SDS did not show a significant downward deviation. Using these two criteria, we consider our patients 1–11 to be definite responders, and cases 12–14 as probable responders.

Unlike these 14 responders, the other six patients reacted less favorably to GDF. Two patients (cases 15 and 16) showed only a temporary catch-up growth followed by deceleration. Three patients (cases 18–20) had a clearly downward deviation of height SDS.

Such a division of patients into responders and nonresponders might suggest the existence of two distinct groups of patients. However, this is obviously not the case because a transition zone exists between patients who respond conspicuously favorably to GDF and those who did improve with respect to vitality, appetite, excessive sweating, and sleep pattern but not with respect to growth. Yet, having defined some patients as nonresponders, we increased our efforts to search for dietary imperfections, endocrinologic abnormalities, and environmental interferences, but we failed to find any explanation for their insufficient growth during GDF. Thus, the decelerated growth could not be due to advanced glomerular sclerosis (15), because of 14 patients in whom glomerular filtration rate and renal plasma flow were determined, increased values were found in nine and 12 patients, respectively; none of the patients showed decreased values. Tubular function, as estimated by the urinary excretion of β_2 microglobulin and lysozyme, was normal. The abnormalities of renal function were not related to the growth rate of the patient, to the age at which GDF had been instituted, or to the age of the patient when tested.

With respect to the abnormalities of plasma lipids and apolipoproteins, which closely resembled those of Levy *et al.* (16), no statistically significant differences existed between responders and nonresponders before the initiation of GDF treatment. GDF had a marginal effect on plasma lipids and apolipoprotein profiles after 1–2 y, but only in those patients whose growth responded favorably. These effects wore off after continued treatment, and ultimately plasma triglycerides, cholesterol, apolipoproteins B, C-III, and E increased to higher concentrations, and, conversely, apolipoproteins A-I and A-II decreased to lower concentrations than those characteristic of the pretreatment period, particularly in nonresponders. Therefore, neither the pre-GDF profile of plasma lipids and apolipoproteins, nor the post-GDF changes of the profile allowed one to predict if a patient's growth would respond favorably to GDF treatment, whereas a good correlation

appears to exist between growth and such other metabolic abnormalities as 2-oxoglutarate and lactate (4).

The atherogenic character of the apolipoprotein profile (17) was not reflected in clinical symptoms of premature atherosclerosis in our patients. In four patients, aged 10, 14, 15, and 16 y, ultrasound study of the heart and ECG during exercise did not reveal abnormalities.

Probably the increased tendency to atherosclerosis that might be expected from the apolipoprotein profile is offset by the decreased adhesiveness of the platelets, characteristic of GSD I (18). This would tally with the resistance to atherosclerosis in pigs with Von Willebrand's disease (19) and with the antiatherogenic effect of such platelet-inhibiting drugs as aspirin in the human.

The absence of atherosclerotic symptoms in our patients does not mean that the abnormalities of plasma lipids and apolipoproteins do not have pathologic implications. Although no etiologic mechanism is known, the elevated lipid and apolipoprotein levels may be involved in the development of glomerular disease (20), the initial phase of which was found in 10 of our 20 patients. We have previously suggested (6) that the molar ratio of apolipoproteins B/C-III/E of 1:4–5:1 might reflect mainly the overproduction of some triglyceride-rich lipoprotein particles (21). The increased liponeogenesis may be the consequence of an enhanced glycogenolytic flux through an enlarged glucose-6-phosphate pool (22), resulting not only in increased pyruvate and lactate formation (4) but in increased production of malonyl-CoA as well. The latter is the main substrate of fatty acid synthesis from pyruvate (23). Thus, lactate overproduction, which has been shown to be very sensitive to insufficient glucose availability (4), may be the first outlet of excessive glycogenolysis; endogenous triglyceride overproduction reflected in hyperlipoproteinemia would be a relatively insensitive and quantitatively larger second outlet (3). This abnormality appears to be less easily corrected by GDF than growth, the latter being usually, though not always, responsive to dietary manipulation.

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