0031-3998/08/6306-0702
PEDIATRIC RESEARCH

Vol. 63, No. 6, 2008
Printed in U.S.A.

Increased *de novo* Lipogenesis and Delayed Conversion of Large VLDL into Intermediate Density Lipoprotein Particles Contribute to Hyperlipidemia in Glycogen Storage Disease Type 1a

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ABSTRACT: Glycogen storage disease type 1a (GSD-1a) is a metabolic disorder characterized by fasting-induced hypoglycemia, hepatic steatosis, and hyperlipidemia. The mechanisms underlying the lipid abnormalities are largely unknown. To investigate these mechanisms seven GSD-1a patients and four healthy control subjects received an infusion of [1-^{13}C]acetate to quantify cholesterogenesis and lipogenesis. In a subset of patients, [1-^{13}C]valine was given to assess lipoprotein metabolism and [2-^{13}C]glycerol to determine whole body lipolysis. Cholesterogenesis was 274 ± 112 mg/d in controls and 641 ± 201 mg/d in GSD-1a patients ($p < 0.01$). Plasma triglyceride-palmitate derived from *de novo* lipogenesis was 7.1 ± 9.4 and 86.3 ± 42.5 μmol/h in controls and patients, respectively ($p < 0.01$). Production of VLDL did not show a consistent difference between the groups, but conversion of VLDL into intermediate density lipoproteins was relatively retarded in all patients (0.6 ± 0.5 pools/d) compared with controls (4.3 ± 1.8 pools/d). Fractional catabolic rate of intermediate density lipoproteins was lower in patients (0.8 ± 0.6 pools/d) compared with controls (3.1 ± 1.5 pools/d). Whole body lipolysis was similar, *i.e.*, 4.5 ± 1.9 μmol/kg/min in patients and 3.8 ± 1.9 μmol/kg/min in controls. Hyperlipidemia in GSD-1a is associated with strongly increased lipid production and a slower relative conversion of VLDL to LDL. **(*Pediatr Res* 63: 702–707, 2008)**

Glycogen storage disease type 1a (GSD-1a, von Gierke Disease, OMIM#232200) is caused by deficiency of glucose-6-phosphatase α (G6Pase-α), which catalyzes the terminal steps in gluconeogenesis and glycogenolysis by converting glucose-6-phosphate to glucose and phosphate. G6Pase-α deficiency results in an inability to release glucose from liver, kidney, and possibly intestine. Phenotypical, G6Pase-α deficiency is characterized by growth retardation, hypoglycemia, hepatomegaly (massive hepatic steatosis) and lactic acidemia, as well as hypertriglyceridemia and hypercholesterolemia (1). Increased concentrations of cholesterol are found in both very LDL (VLDL) and LDL fractions whereas HDL cholesterol and apolipoprotein A-I concentrations are usually decreased (2,3). To control hypoglycemia in GSD-1a, patients often receive uncooked cornstarch which is accompanied by reductions in plasma lipid levels in GSD-1a (4,5). The underlying mechanisms responsible for disturbed lipid metabolism in GSD-1a are largely unknown. We have previously reported increased rates of hepatic *de novo* lipogenesis and cholesterogenesis in two patients with GSD-1a (6), which may drive VLDL production by the liver. Lipogenesis and cholesterogenesis have both been implicated in regulation of VLDL secretion (7–9). In addition, insulin is known to suppress hepatic VLDL production (10): prevailing low insulin concentrations in GSD-1a patients may contribute to increased VLDL production in these subjects, but quantitative data are not available. Furthermore, defective lipoprotein lipolysis might also contribute to hypertriglyceridemia, because lipoprotein lipase activities have been reported to be low in GSD-1a (11). This may lead to delayed clearance of VLDL-triglycerides as was shown in a single patient with GSD-1a (12). To date, no reports simultaneously assessing lipid synthesis and lipoprotein kinetics in GSD-1a patients are available. Therefore, we addressed the question whether hyperlipidemia in GSD-1a is related to increased *de novo* lipogenesis/cholesterogenesis leading to increased VLDL production or to a disturbance in lipolysis. Insight in the processes responsible for lipid abnormalities in GSD-1a may allow development of tailored therapies to reduce atherogenic lipid levels in these patients.

METHODS

Subjects and infusion protocol. Seven GSD-1a patients and four age-matched healthy control subjects were studied. GSD-1a in patients was diagnosed by appropriate clinical tests (13) and confirmed by mutation analysis. Subject characteristics are summarized in Table 1. All GSD-1a patients were treated with allopurinol and an ACE inhibitor, which was continued during the study. None of the control subjects received any medication. Informed written consent from all subjects was obtained in accordance with the policy of the University Medical Center Groningen Ethical Committee. The study was approved by the institutional review board.

Received September 24, 2007; accepted January 4, 2008.

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This work was supported by a grant from the Dutch Foundation for Scientific Research (NWO 920-03-123) and a grant from the Netherlands Diabetes Research Foundation (DFN 96.604).

Abbreviations: CHREBP, carbohydrate-response element binding protein; **G6Pase-α,** glucose-6-phosphatase α; **GSD,** glycogen storage disease; **IDL,** intermediate density lipoprotein; **LXR,** liver-X receptor; **SREBP,** sterol regulatory element-binding protein

Table 1. *Basic characteristics of GSD-1a patients and healthy control subjects*

	Sex	Age (y)	BMI (kg/m^2)	Glucose (mM)	Lactate (mM)	Insulin (ng/mL)	ASAT	ALAT	Uric acid	Mutations
Controls										
1	F	23	27	5.5	1.4	19	ND	ND	ND	
2	F	23	28	5.4	1.5	40	ND	ND	ND	
3	M	24	22	4.5	1.8	15	ND	ND	ND	
4	M	22	23	4.9	1.0	11	ND	ND	ND	
Mean ± SD		23 ± 1	25 ± 3	5.1 ± 0.4	1.4 ± 0.3	21 ± 13				
GSD-1a										
1	M	25	21	4.5	3.9	21	27	25	0.19	G270V; Q347X
2	M	25	22	4.9	2.8	28	32	29	0.16	G270V; Q347X
3	F	13	25	4.2	2.9	33	59	59	0.10	R170X; F327del
4	F	17	24	4.2	0.7	11	67	28	0.17	W63X; V338F
5	M	31	20	4.5	3.5	6	30	24	0.31	Unknown
6	F	22	27	4.6	2.3	7	29	27	0.38	Unknown
7	M	21	20	4.0	5.0	7	62	96	0.33	G266V; F327del
Mean ± SD		22 ± 6	23 ± 3	4.4 ± 0.3	3.0 ± 1.3	16 ± 11	44 ± 18	41 ± 27	0.23 ± 0.10	

All concentrations represent mean value of multiple samples taken throughout experimental protocol.

All studies were performed in the metabolic ward of the University Medical Center Groningen. Subjects were admitted to the metabolic unit the evening before start of the isotope study. All subjects stopped consuming food or energy-containing drinks from 22:00 h onwards. At this time, a glucose infusion (3.5 mg/kg/min) was started to maintain normoglycemia in the GSD-1a patients and to produce a semi-fasted steady state. Glucose was infused during the same period during the day and at an identical rate in control subjects and in patients. At 09.00 ($t = 0$), a [1-^{13}C]acetate infusion (0.20 mmol/kg/h for 10 h) was initiated in all subjects. In the control subjects and in a subset of patients ($n = 4$), a [1-^{13}C]valine infusion (15 μmol/kg priming dose + 15 μmol/kg/h for 8 h) was also started. At 17.00, a [2-^{13}C]glycerol infusion (3.0 μmol/kg priming dose + 12.0 μmol/kg/h for 2 h) was initiated in the control subjects and a subset of patients ($n = 3$). Blood samples were taken hourly and after $t = 8$ h every 30 min in all subjects studied. Concentrations of glucose, lactate, and insulin were determined at $t = 0$, 5 and 8 h of the experimental protocol. Because these concentrations remained constant throughout the study, results were averaged. Indirect calorimetry was performed on two different occasions, between $t = 1$–3 h and between $t = 5$–7 h.

Biochemical analysis. Concentrations of cholesterol, cholesteryl ester, and triglycerides in plasma were determined using commercially available kits (Boehringer Mannheim, Germany). Fatty acid composition in VLDL fractions was analyzed by gas-chromatography as described earlier (14). Insulin concentrations were measured using a radio-immunoassay (Diagnostic Systems Laboratories, Webster, TX).

Stable isotope analysis. Cholesterol was extracted from total plasma and derivatized according to Neese *et al.* (15). VLDL1, VLDL2, intermediate density lipoproteins (IDL) and LDL fractions were isolated from plasma by ultracentrifugation according to de Sain-van der Velden *et al.* (16). Palmitate from VLDL fractions was methylated as described elsewhere (6). Cholesterol and fatty acids were analyzed by gas chromatography/mass spectrometry as described in detail earlier (17). Apolipoproteins from lipoproteins were precipitated using isopropanol (18), extracted as described previously (19) and subsequently hydrolyzed with 0.5 mL of 6 N HCl for 24 h at 110°C. Derivatization of the isolated amino acids from apoB100 to their corresponding *N*(*O*)-methoxycarbonyl methyl ester was done according to the method of Hušek (20). Analysis of isotopic enrichment of plasma [^{13}C]valine was carried out by gas chromatography-mass spectroscopy on a Hewlett Packard 5890 Plus gas chromatograph coupled to a Finnigan SSQ 7000 quadruple mass spectrometer using methane positive-ion chemical ionization. The mass spectrometer was operated in the selected ion-monitoring mode at fragments with a mass-to-charge ratio (m/z) 190/191. Glycerol was isolated from plasma after precipitation of proteins with ice cold ethanol and derivatized to its tri-acetylated form, after addition of d5-glycerol as internal standard (21). Gas chromatography-mass spectroscopy analysis was performed, essentially as described by Ackermans *et al.* (21). The ions at m/z 159, 160, and 164, representing unlabeled, [2-^{13}C]- and [1,2,3-^{2}H$_5$]-glycerol, were measured using selected ion recording.

Calculations. The fractions of newly synthesized cholesterol and palmitate molecules in plasma and VLDL, respectively, were quantified by mass isotopomer distribution analysis, as described in detail previously (22,23). Absolute cholesterol synthesis rates were then calculated using a nonsteady state equation, applying an estimate of body free cholesterol pool size (15). Palmitate synthesis rates were calculated by multiplying plasma triglyceride-palmitate concentration with the fraction of newly synthesized palmitate at the end of the 10-h label infusion period. Lipoprotein kinetics were determined using SAAM II modeling (16). The model used was described earlier (24) and is shown in Figure 1. Plasma glycerol turnover was used as an indicator of whole body lipolysis and was calculated according to Ackermans *et al.* (21). Basically, the formula $R_a = F/E_p$ was used, where F is the tracer infusion rate and E_p is the isotopic enrichment at steady state. Furthermore, a correction was made for the overlap in mass spectra caused by the introduction of the two stable isotopes.

Statistical analysis. All values reported are mean ± SD. Significance was determined using the nonparametric Mann–Whitney U test. Furthermore, bivariate correlation analyses were performed and tested using Spearman's rank correlation. Differences were considered significant at $p < 0.05$.

RESULTS

Basal lipid parameters in controls and GSD-1a patients are shown in Figure 2. GSD-1a patients showed strongly elevated triglyceride concentrations and significantly higher concentrations of total cholesterol and apoB100. No significant differences in plasma HDL cholesterol, LDL-cholesterol and apoA-I concentrations between both groups were observed. FFA levels were

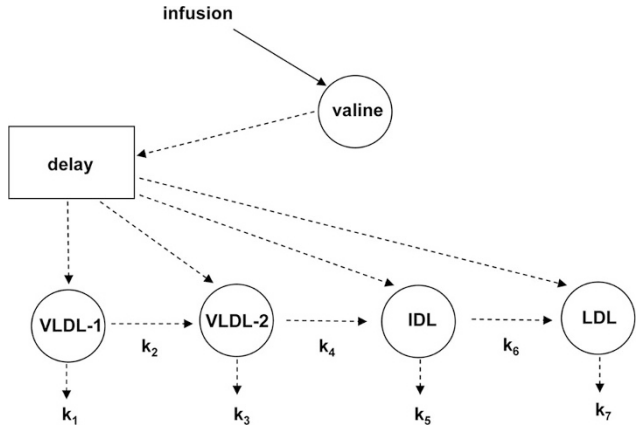

Figure 1. Multicompartmental model for apoB100 metabolism. The "valine" compartment represents plasma valine into which the tracer was injected. The "delay" compartment represents a delay compartment. Valine is incorporated in the lipoproteins via the other compartments. The k-values represent the rate constants.

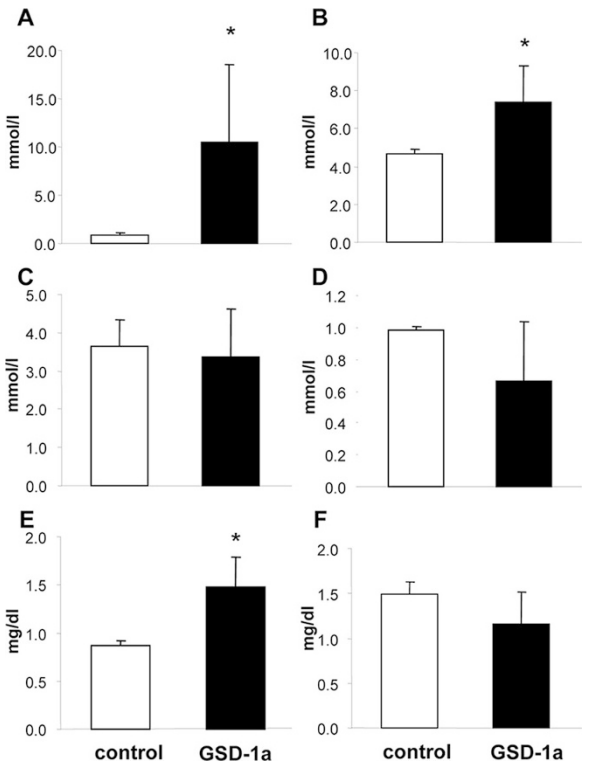

Figure 2. Plasma concentrations of triglyceride (*A*), total cholesterol (*B*), LDL-cholesterol (*C*), HDL-cholesterol (*D*), apoB (*E*) and apoA-1 (*F*) in GSD-1a patients ($n = 7$) and healthy control subjects ($n = 4$). Values are means ± SD. *$p < 0.05$.

similar in both groups, *i.e.*, 0.11 ± 0.01 mM in controls and 0.14 ± 0.05 mM in GSD-1a patients.

Hepatic *de novo* lipogenesis was strongly induced in patients as revealed by a strongly increased contribution of newly synthesized palmitate in VLDL (86.3 ± 42.5 μmol/h) compared with controls (7.1 ± 9.4 μmol/h), as depicted in Figure 3*A*. Cholesterol synthesis rates were three-fold increased in GSD-1a patients compared with control subjects (Fig. 3*B*). Increased cholesterogenesis and *de novo* lipogenesis were associated with lower enrichments of the acetyl-CoA precursor pool, calculated from cholesterol spectra (Fig. 3*C*), indicating an increased acetyl-CoA production (Fig. 3*C*). There was no significant difference between acetyl-CoA precursor pool enrichments calculated from cholesterol spectra and palmitate spectra.

Lipoprotein kinetic data in controls and GSD-1a patients are shown in Table 2. In one patient (no. 1), a thick solid layer containing triglycerides was formed in the VLDL fractions, preventing further accurate lipoprotein analysis. ApoB pool sizes were increased in the GSD-1a patients in the larger VLDL-1 and smaller VLDL-2 fractions. There seemed to be a large variability in VLDL metabolism in the GSD-1a patients and in controls. In two patients (nos. 2 and 7), GSD-1a was associated with a relatively low absolute synthesis rate of VLDL-1 and VLDL-2, but a much higher synthesis rate in another patient (no. 6). This last patient also showed a fractional catabolic rate of VLDL-1 (k1 + k2 in Fig. 1) and VLDL-2 (k3 + k4) that was higher than in the other two patients and more comparable with the controls. The transfer of VLDL-2 into IDL (k4) was lower in all patients (0.6 ± 0.5 pools/d) compared with controls (4.3 ± 1.8 pools/d). The fractional catabolic rate of IDL (k5 + k6) was lower in all patients than in the control subjects. No clear differences in LDL metabolism were found between patients and controls. VLDL-1 particles were significantly larger in diameter in the GSD-1a patients compared with the control subjects, *i.e.*, 86.7 ± 9.2 nm and 57.3 ± 7.7 nm, respectively ($p < 0.01$).

Rates of appearance of glycerol were 3.8 ± 1.9 μmol/kg/min in controls and 4.5 ± 1.9 μmol/kg/min in GSD-1a patients, indicating similar whole body lipolysis rates, at least in the semi-fasted state used in this study. Metabolic clearance of glycerol was lower in all three GSD patients (0.06 ± 0.01 L/min/kg) compared with controls (0.10 ± 0.03 L/min/kg). Furthermore, values for respiratory quotients were similar in both groups under these conditions, *i.e.*, 0.81 ± 0.08 in controls and 0.84 ± 0.07 in GSD-1a patients, indicating undisturbed whole body fat-oxidation in the GSD-1a patients.

DISCUSSION

GSD-1a is an inborn error of metabolism, the phenotypical characteristics of which underscore the important (patho)physiologic interactions that exist between carbohydrate and lipid metabolism. To the best of our knowledge, this is the first study to address lipoprotein kinetics, lipogenesis/cholesterogenesis and whole body lipolysis simultaneously in GSD-1a patients. Control subjects with high BMI were selected to match the GSD-1a patients some of whom also showed relatively high BMI values. A great variability existed between the patients with respect to the

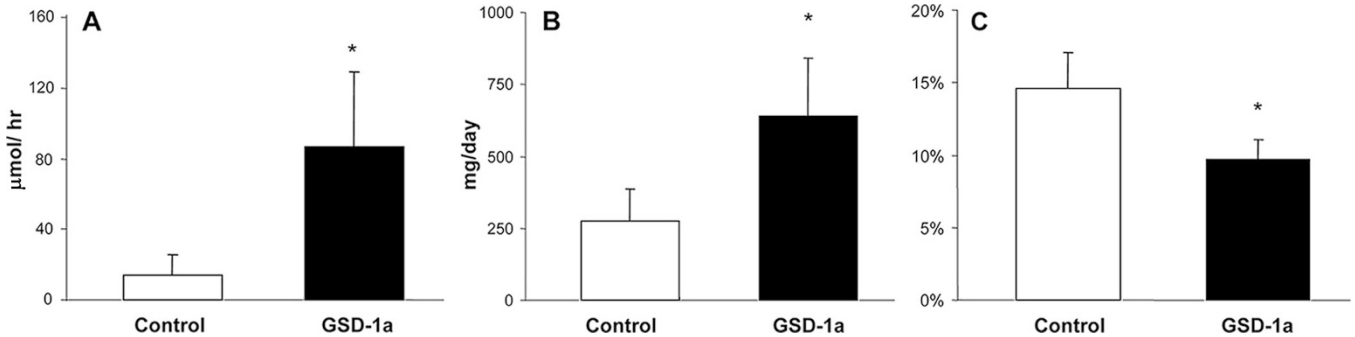

Figure 3. Total newly synthesized triglyceride-palmitate (*A*) Cholesterol synthesis rates (*B*) and acetyl-CoA pool enrichments (*C*) in control subjects and GSD-1a patients. *$p < 0.05$.

Table 2. *Lipoprotein metabolism in control subjects and GSD-1a patients*

	Controls				GSD-1a		
	1	2	3	4	2	6	7
VLDL-1							
Pool size (mg)	68	27	45	83	357	150	170
Synthesis rate (mg/kg/d)	3.2	0.8	2.1	6.7	1.2	17.4	1.8
Transfer (pools/d)	3.1	2.3	3.8	4.2	0.1	5.2	0.6
Direct catabolism (pools/d)	0.7	0	0	2.9	0.2	2.9	0
Total FCR (pools/d)	3.8	2.3	3.8	7.1	0.2	8.1	0.6
VLDL-2							
Pool size (mg)	156	116	85	78	187	362	277
Synthesis rate (mg/kg/d)	9.0	1.6	3.8	2.7	0.4	9.8	1.5
Transfer (pools/d)	5.3	1.6	5.6	4.6	0.1	1.1	0.6
Direct catabolism (pools/d)	0.7	0	0	2.9	0.2	2.9	0
Total FCR (pools/d)	6.0	1.6	5.6	7.5	0.2	4.0	0.6
IDL							
Pool size (mg)	161	134	205	179	115	494	206
Synthesis rate (mg/kg/d)	0.0	0.3	1.4	1.7	0.1	3.4	0.6
Transfer (pools/d)	3.9	1.6	2.0	0	0	1.3	1
Direct catabolism (pools/d)	1.2	0	0.8	2.9	0.2	0	0
Total FCR (pools/d)	5.1	1.6	2.9	2.9	0.2	1.3	1.0
LDL							
Pool size (mg)	1686	1830	1544	1248	472	2387	1380
Synthesis rate (mg/kg/d)	0.0	2.1	0.8	1.1	0.2	1.7	1.3
Total FCR (pools/d)	0.4	0.2	0.3	0.1	0.0	0.3	0.2

FCR indicates fractional catabolic rate.

severity of the hyperlipidemia, insulin concentrations and to a lesser extent also BMI. It is widely known that a high BMI is associated with insulin resistance, which, in turn, has been to shown to greatly affect lipid metabolism. In this study, no correlation could be found between BMI or insulin levels and the degree of hyperlipidemia (data not shown), indicating that the underlying metabolic disorder has a much greater effect on lipid metabolism in GSD-1a patients than obesity or insulin resistance.

De novo lipogenesis was strongly increased in the GSD-1a patients, compared with the healthy control subjects. Increased *de novo* lipogenesis was noted earlier by us in a case report (6) and in an animal model of GSD-1 (17). Hepatic *de novo* lipogenesis is under control of sterol regulatory element-binding protein-1 (SREBP-1) (25,26), Liver-X receptor (LXR) (27) and the carbohydrate-response element binding protein (CHREBP) (28,29). SREBP1c, which is the subtype mostly responsible for activation of *de novo* lipogenesis, is under control of insulin. Insulin concentrations during the study were low in some GSD-1a patients and relatively high in other patients. A clear role of SREBP in the induction of *de novo* lipogenesis is therefore not likely in GSD-1a. LXR is activated by oxysterols, oxygenated derivatives of cholesterol. In GSD-1a with strongly increased plasma cholesterol concentrations, *de novo* lipogenesis stimulation through activation of LXR represents a possible pathway. Xylulose-5-phosphate is the activator of CHREBP, by stimulating its translocation to the nucleus and increasing its expression (30). Strongly increased hepatic glucose-6-phosphate levels in GSD-1a are expected to lead to an increased flux through the pentose-phosphate cycle through which xylulose-5-phosphate is formed. *De novo* lipogenesis is therefore likely to be activated through induction of CHREBP in GSD-1a. Furthermore, GSD-1a was associated with a decrease in acetyl-CoA precursor pool enrichments, indicating an increased flux through this pool. This increased flux, leading to increased production of acetyl-CoA, which is the precursor for cholesterogenesis and *de novo* lipogenesis, could possibly stimulate *de novo* lipogenesis directly, although no evidence is present to support this. However, in an acute animal model of GSD-1, cholesterol synthesis was not stimulated despite an increased production acetyl-CoA (17).

Increased cholesterol synthesis found in this study and an earlier case report (6) could very well be a major contributor to the hypercholesterolemia in GSD-1a. Cellular cholesterol synthesis is under control of SREBP-2, which becomes inactivated by increased intracellular sterol contents (31). However, we did not find an increase in cholesterol synthesis rates in an acute animal model of GSD-1 (17). This might indicate that increased cholesterol synthesis in GSD-1a patients might be caused by indirect mechanisms, although a role of SREBP-2 cannot be excluded. In the present study, no difference in LDL catabolism was observed *in vivo* in the patients. Older studies found increased LDL-cholesterol concentrations (2,3) and Levy *et al.* (32) showed a decreased *in vitro* uptake of LDL particles by fibroblasts isolated from GSD-1 patients. It could be that these differences in LDL metabolism between studies are related to the degree of dietary control in GSD-1a patients.

Limited data exists with respect to lipoprotein kinetics in GSD-1. A case report in one GSD-1a patient noted similar VLDL production rates but strongly decreased VLDL clearance rates compared with control subjects (12). Indirect evidence suggestive of decreased VLDL clearance, related to decreased activity of lipoprotein lipase, has been reported previously (2,11,33). In this study, low rates of VLDL particle production were found in two GSD-1a patients, but a very high rate in another patient. In an acute animal model of

GSD-1, VLDL production was not altered (17), despite massive induction of lipogenesis and severe hepatic steatosis. These data indicate that other factors are responsible for determining VLDL production rates than metabolic consequences of G6Pase-α deficiency alone. It is generally assessed that hepatic fat content correlates with VLDL production (34) and that GSD-1a is associated with hepatic steatosis (35). In this study, the degree of hepatic steatosis was not determined and thus its effect on number or size of the VLDL produced could not be determined. One must take into account that the patients in whom we studied lipoprotein kinetics had less severe hypertriglyceridemia and lower insulin concentrations than the group as a whole. So, it cannot be ruled out that in patients with more severe hypertriglyceridemia and hyperinsulinemia, effects on lipoprotein kinetics might be more pronounced. Furthermore, patient (no. 6) with high production of VLDL, was also the patient with a much larger BMI, which could be related to a relative insulin resistance leading to less effective suppression of VLDL production by insulin in this patient. Finally, the variability in lipoprotein kinetics between the various patients could in theory be related to different patient compliance to the dietary treatment, although no clear indications for different treatment compliance were present. Conversion of VLDL-1 into VLDL-2 and onwards to LDL was relatively slow in the GSD-1a patients, although patient 6 showed a high conversion rate. The increased VLDL-apoB content is thus more likely to be related to decreased activity of lipoprotein lipase than to differences in VLDL production. In association with increased VLDL particle size, this could account for much of the observed hyperlipidemia. Lipogenesis induction by LXR leads to steatosis and formation of large VLDL particles, but not more particles (apoB) (36). Whether LXR plays a role in the development of steatosis and hypertriglyceridemia in GSD-1a remains to be determined.

Whole body lipolysis was similar in GSD-1a and control subjects, implicating that release of FFA and glycerol from adipose tissue is not altered in GSD-1a at least under "glucose clamped conditions." We therefore have no data to indicate that increased lipolysis, leading to more FFA delivery to the liver, contributes to the hyperlipidemia in GSD-1a patients. However, if some degree of insulin resistance is present in GSD-1a, this might be associated with increased activity of hormone sensitive lipase leading to increased lipolysis under postprandial conditions. The patients in whom we studied glycerol turnover had lower insulin concentrations than the other patients, which could lead to higher glycerol turnover rates in the patients we studied compared with the remaining patients. Finally, one must take into account that this study was performed under semi-fasted conditions, with relatively low insulin levels. Therefore, potential effects of insulin resistance could have remained unnoticed. Apart from an absence in differences in lipolysis, whole body fat oxidation was also not impaired, as indicated by similar RQ values. Of course, hepatic lipid oxidation might still be impaired as low ketone body concentration in plasma and severe hepatic steatosis are characteristic features in GSD-1a. Interestingly, metabolic clearance of glycerol was lower in all GSD-1a patients compared with the control subjects. Decreased glycerol clearance has been shown in alcoholic liver disease (37) and cirrhosis (38). Whether metabolic clearance of glycerol is related to the hepatic steatosis or general hepatic damage is not known.

The findings of these studies in combination with earlier studies could have implications for the treatment of the hyperlipidemia of GSD-1a patients. Fibrates have been shown, through activation of PPARα, to increase lipoprotein lipase activity (39) and hepatic β-oxidation. Case reports have indeed shown that fibrates decrease plasma triglyceride concentrations in GSD-1a patients (12,40). Use of statins to lower cholesterol synthesis rates would likely have a strong effect on plasma cholesterol levels, although data supporting this hypothesis in GSD-1a patients is currently not available. Furthermore, use of statins has been shown to have strong effects on lipoprotein concentrations in multiple studies, mainly by lowering VLDL remnants through increased uptake by the LDL receptors (41). This study shows that GSD-1a is mainly associated with increased VLDL levels and statins could potentially substantially lower these levels. However, premature atherosclerosis has rarely been reported in GSD-1a patients, which suggests the existence of a protective mechanism in these patients. Potential benefits of lowering lipid concentrations in GSD-1a patients might therefore be limited. Treatments aimed at reducing hepatic steatosis might be of more clinical benefit, because it is associated with hepatic insulin resistance and development of fibrosis. Recent trials have addressed the use of thiazolinediones, which act as agonists of the nuclear hormone receptor peroxisome proliferator-activated receptor-γ, for the treatment of hepatic steatosis and have shown promising results (42). It would be worthwhile to study the effects of both statins and thiazolinediones in GSD-1a patients.

In conclusion, GSD-1a is associated with increased levels of *de novo* lipogenesis and cholesterogenesis, possibly contributing to the observed increased VLDL particle size without a clear effect on VLDL-apoB production rates. A relative defect in lipoprotein-triglyceride clearance might contribute to the strongly elevated hyperlipidemia in GSD-1a.

Acknowledgments. We thank Anke ter Harmsel and Theo van Dijk for excellent technical support.

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