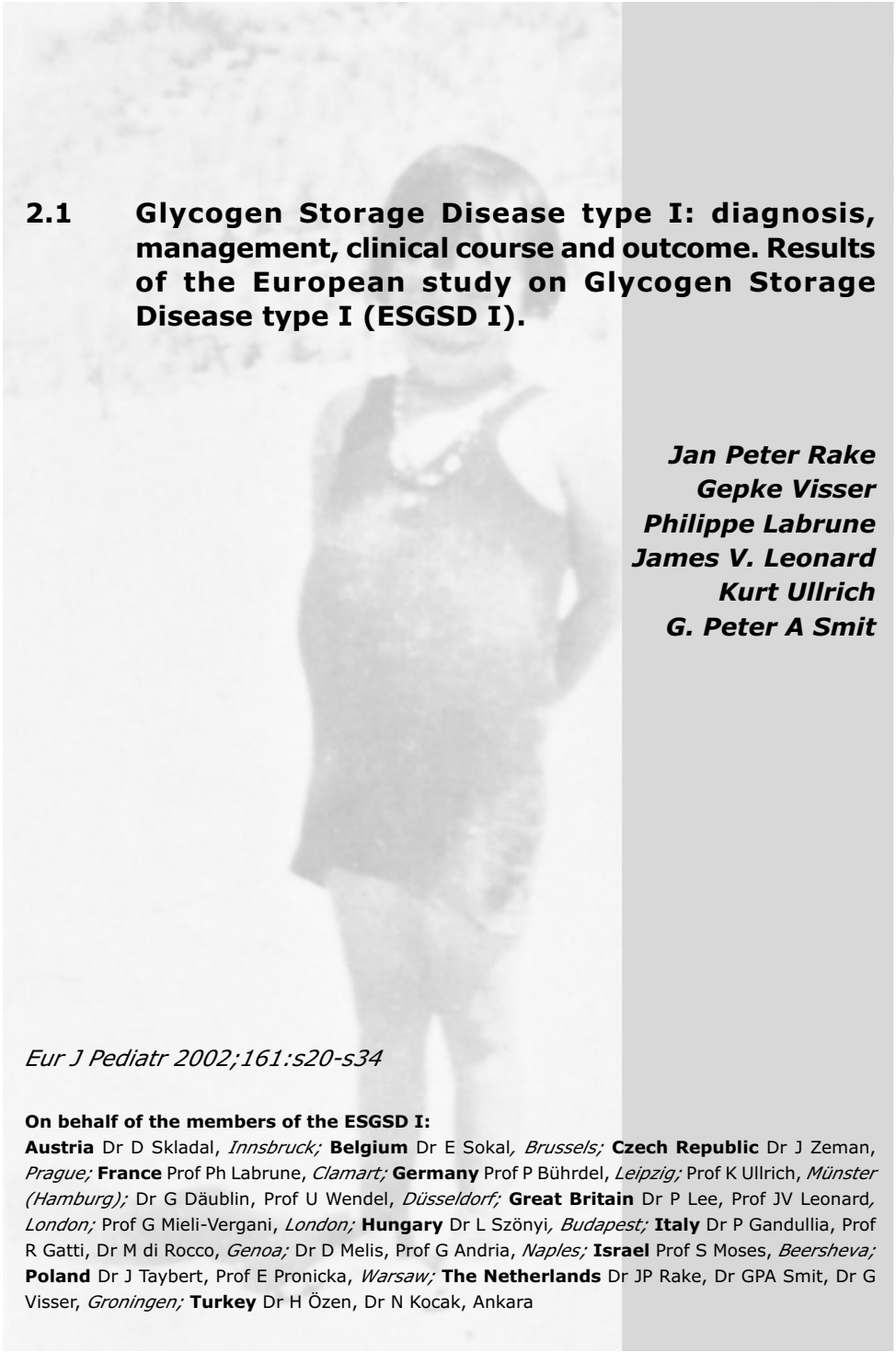
Long-term management and outcome of patients with Glycogen Storage Disease type I

Chapter 2

2.1 Glycogen Storage Disease type I: diagnosis, clinical course, management and outcome. Results of the European study on Glycogen Storage Disease type I (ESGSD I).

2.2 Glycogen Storage Disease type I: long-term outcome of patients born before 1975. Results of the European study on Glycogen Storage Disease type I (ESGSD I).



2.1 Glycogen Storage Disease type I: diagnosis, management, clinical course and outcome. Results of the European study on Glycogen Storage Disease type I (ESGSD I).

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Summary

Glycogen storage disease type I (GSD I) is a relatively rare metabolic disease and therefore no metabolic centre has experience of large series of patients. To document outcome, to develop guidelines about (long-term) management and follow-up, and to develop therapeutic strategies the collaborative European Study on GSD I (ESGSD I) was initiated.

This chapter is an descriptive analysis of data obtained from the retrospective part of the ESGSD I. Included were 231 GSD type Ia and 57 GSD type Ib patients. Median age of data collection was 10.4 years (range 0.4 - 45.4 years) for Ia and 7.1 years (0.4 - 30.6 years) for Ib patients. Data on dietary treatment, pharmacological treatment, and outcome including mental development, hyperlipidaemia and its complications, hyperuricaemia and its complications, bleeding tendency, anaemia, osteopenia, hepatomegaly, liver adenomas and carcinomas, progressive renal disease, height and adult height, pubertal development and bone maturation, school type, employment, and pregnancies are presented. Data on neutropenia, neutrophil dysfunction, infections, inflammatory bowel disease, and the use of granulocyte colony-stimulating factor are presented elsewhere[90,91].

In conclusion, there is a wide variation in methods of dietary and pharmacological treatment of GSD I. Intensive dietary treatment will improve, but not correct completely, clinical and biochemical status and fewer GSD I patients will die as a direct consequence of acute metabolic derangement. With ageing, more complications will develop of which progressive renal disease and the complications related to liver adenomas are likely to be two major causes of morbidity and mortality.

Introduction

Glycogen storage disease type I (GSD I, McKusick 232200) is an autosomal recessive inborn error of carbohydrate metabolism caused by defects of the glucose-6-phosphatase (G6Pase) complex. G6Pase plays a central role in both glycogenolysis and gluconeogenesis, hydrolysing glucose-6-phosphate (G6P) to glucose. Deficiency of G6Pase activity in liver, kidney and intestine results in accumulation of glycogen in these organs. As a result of inadequate glucose production patients have severe fasting hypoglycaemia with secondary biochemical abnormalities: hyperlactacidaemia, hyperuricaemia and hyperlipidaemia. Untreated patients have a protruding abdomen because of marked hepatomegaly (storage of glycogen and fat), short stature, truncal obesity, a rounded doll face, wasted muscles, and bleeding tendency due to impaired platelet function[16,26].

Based on the most plausible molecular model, G6Pase is a multicomponent complex consisting of a catalytic subunit, situated on the luminal side of the endoplasmic reticulum, and one or more membrane transporters[4,5,95]. Deficient activity of the catalytic unit of G6Pase is called GSD Ia. In 1993 the gene encoding this unit was identified in band q21 of chromosome 17 and a steadily growing list of mutations has been reported[59,72,82]. Defects of the putative transporter(s) were named GSD Ib, GSD Ic and GSD Id. Molecular genetic studies have shown that patients diagnosed by enzyme studies as GSD Ib, Ic and the putative Id, all had mutations in the G6P translocase gene identified in band q23 of chromosome 11[3,31,89]. This is consistent with the clinical findings as GSD I can be divided in two clinical phenotypes: GSD Ia patients have 'classical' findings as listed above, whilst those with 'GSD I non-a' have in addition recurrent bacterial infections and inflammatory bowel disease (IBD) associated with neutropenia and neutrophil dysfunction[90]. Recently, however, a GSD Ic patient without mutations in the G6P transporter gene was described suggesting the existence of a distinct GSD Ic locus[63]. In the present study, the term GSD Ib is used for 'GSD I non-a' patients and includes patients formerly diagnosed as GSD Ib, GSD Ic and GSD Id.

The aim of treatment is to prevent hypoglycaemia and suppress secondary metabolic derangements as much as possible. Methods to achieve this are frequent meals (FMs), continuous nocturnal gastric drip feeding (CNGDF) and the administration of uncooked cornstarch (UCCS). If hypoglycaemia can be prevented, the clinical and biochemical abnormalities in most patients will improve[24]. However in older patients numerous complications may still develop[16,26,86].

GSD I has an estimated frequency among newborns of one in 100.000[16]. Thus no single metabolic centre has experience of large series of patients.

Furthermore, in literature there is a relative paucity of data on outcome, and all these reports[15,24,70,84,85,103], except one[86], focus on patients under 18 years. To study the management, clinical course and long-term outcome in both paediatric and adult patients with GSD I, the collaborative European Study on GSD I (ESGSD I) was initiated in 1996. Other objectives of this study-group were to develop therapeutic strategies and to develop guidelines about (long-term) treatment and follow-up.

This chapter is a descriptive analysis of data concerning diagnosis, management, clinical course, and outcome of a large cohort of paediatric and adult GSD I patients obtained from the retrospective part of the ESGSD I. More detailed outcome data of adult GSD I patients is presented in chapter 2.2.

Patients and methods

Patients were identified from hospital records of 16 metabolic centres, in 12 European countries. Patients treated in the centres including patients who had died since 1960 were enlisted. Patients were coded by initials and date of birth to check for duplication. Retrospective case records forms were discussed in a multicenter meeting and filled in by either the treating physician or by one of the investigators (JPR).

The diagnosis of GSD Ia was made either by enzyme studies that showed the combination of deficient G6Pase activity in intact and/or disrupted microsomes and/or by mutation analysis of the G6Pase gene. The diagnosis of GSD Ib was made either by enzyme studies that showed the combination of deficient G6Pase activity in intact microsomes and (sub)normal G6Pase activity in disrupted microsomes and/or by mutation analysis of the G6P transporter gene.

Most of the results are descriptive. Results are expressed as mean (± standard deviation) or as median (minimum - maximum), except otherwise stated. Differences in the number of affected individuals between two subgroups of patients (2x2 contingency table) were analysed using the Fisher exact test (including calculating an odds ratio with 95% confidence interval). Differences in variables with a normal distribution between two subgroups of patients were analysed using unpaired two tailed t-tests. A p value < 0.05 was considered to be significant in all instances.

Results

general results

Retrospective case records were obtained from 301 patients. A further 23 'patients' were mentioned in case record forms of siblings, but not included

because the data were incomplete. Of the 301 patients, another 13 were excluded because they did not meet the diagnostic criteria. Thus, 288 patients were included: of whom 231 had GSD Ia and 57 had GSD Ib. There were 20 families with two affected children and two with three. In 28% of the patients, the parents were consanguineous. Demographic characteristics are shown in Table 2.1.1. The patients were born between 1943 and 1996 (Figure 2.1.1). Median age when the data were collected was 10.4 years (range 0.4 - 45.4 years) for Ia and 7.1 years (range 0.4 - 30.6 years) for Ib patients.

Table 2.1.1 Characteristics of 288 included GSD I patients

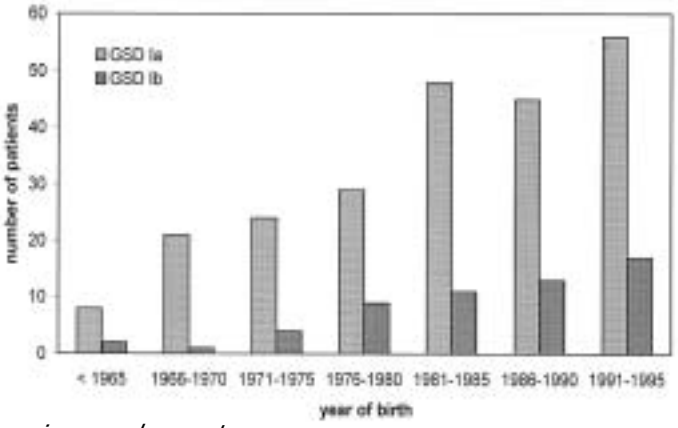
	GSD Ia	GSD Ib	Total
male - female (n)	134 / 97	30 / 27	164 / 124
percentages	(58% / 42%)	(53% / 47%)	(57% / 43%)
race or ethnic group (n)			
Asian	3	5	8
Caucasian	131	33	164
Caucasian - Mediterranean	92	13	105
Negroid	0	0	0
mixed	5	6	11
original country of residence (n)			
France	10	0	10
Germany	54	13	67
Israel	9	4	13
Italy	39	7	46
Poland	10	9	19
Netherlands	17	0	17
Turkey	43	3	46
United Kingdom	25	17	42
other	24	4	28

pregnancy, delivery, additional diseases

Complications of pregnancy and/or delivery were reported infrequently and these did not differ from normal pregnancies and deliveries. Prematurity (gestational age < 37 weeks) was observed in 3%, low birth weight (≤ 2500 g) in 10% and very low birth weight (≤ 1500 g) in 1%.

Congenital heart anomalies were observed in 9 (3%) patients (four ventricular septal defect, two atrial septal defect, one patent foramen ovale, one patent ductus arteriosus and atrial septal defect, and one congenital mitral insufficiency). The prevalence of other congenital disorders did not differ from the normal population.

Figure 2.1.1 ESGSD I cohort: year of birth

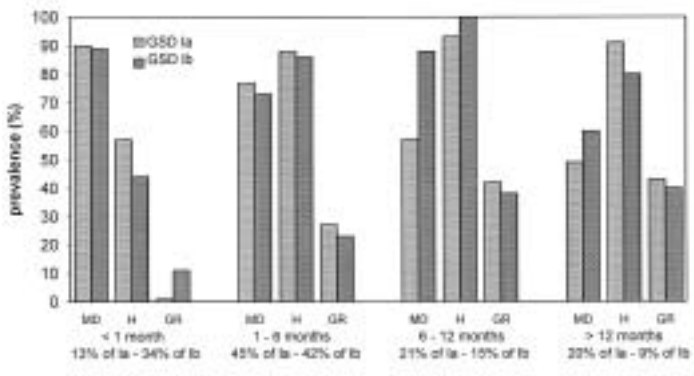


*presenting signs and symptom*s

GSD Ia patients presented at a median age of 6 months (range day 1 - 12 years), GSD Ib patients at a median age of 4 months (range day 1 - 4 years). 80% of the Ia patients and 90% of the Ib patients presented before the age of 1 year.

The dominant presenting features were protruded abdomen (in 83% of the patients), symptoms of acute metabolic derangement (71%), failure to thrive/growth retardation (25%), recurrent infections (3% in GSD Ia; 41% in GSD Ib patients), muscular hypotonia (13%) and delayed psychomotor development (7%). The numbers and percentages of GSD Ia and Ib patients presenting in different age groups and the prevalence of symptoms of metabolic derangement, hepatomegaly and growth retardation among these age groups are shown in Figure 2.1.2.

Figure 2.1.2 Prevalence of the presenting symptoms metabolic derangement (MD), hepatomegaly (H), growt retardation (GR) among GSD Ia an Ib patients presenting at different ages



dietary treatment at present

Dietary treatment during the day and night among different age groups is shown in Figure 2.1.3 and 2.1.4. Six patients are not included in these figures: two patients died before dietary treatment was introduced and in four patients details of dietary treatment were not known. During the daytime, 21% of the patients used FMs only and 70% used FMs and UCCS (1 - 5 times a day) in addition. Overnight, 41% of the patients were on CNGDF (in the majority a glucose-polymer solution, in the minority a complete formula solution) and 45% used UCCS (1 - 3 times a night). In 9% of the patients it was mentioned that dietary compliance was low. Lactose was restricted in 62% of the patients. The use of multi-vitamins supplements was reported in 40%. Furthermore, the use of vitamin B2, vitamin B6, folic acid, vitamin D, and/or vitamin E in different combinations was reported in a minority of patients. (Sodium)bicarbonate treatment was reported in 12% of the patients.

Figure 2.1.3 Dietary treatment during day at latest follow-up

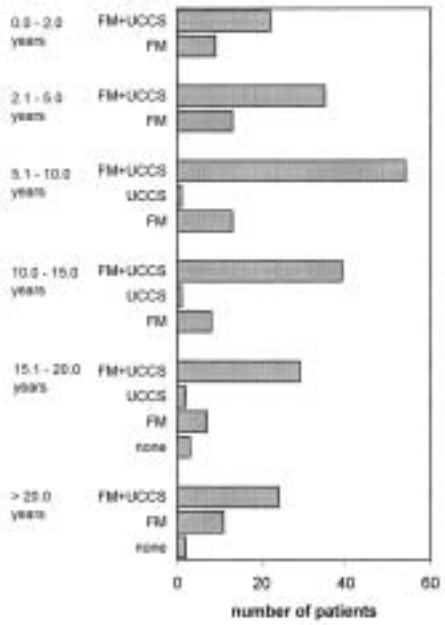
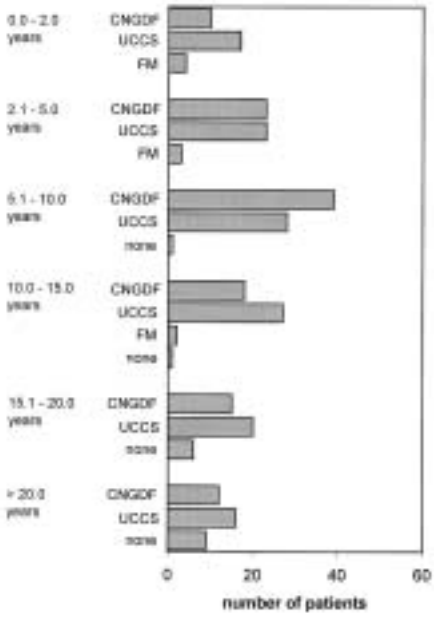


Figure 2.1.4 Dietary treatment during night at latest follow-up



history of dietary treatment

Eight patients had no dietary treatment at all during life. In almost all other patients, FMs during both day and night were started immediately after (the suspicion of) diagnosis. Median age of starting UCCS during daytime

was 2.9 years (range 1 month - 25 years). Median age of starting CNGDF was 1.3 years (range 1 month - 19.5 years) and of starting UCCS overnight 3.2 years (range 2 months - 25 years).

A total of 38 patients had used CNGDF of whom 34 switched to UCCS overnight (median age 13.1 years, range 0.9 - 22.0 years), two to FMs (0.5 and 4.0 years) and two patients had no specific dietary treatment after discontinuation (17.8 and 18.5 years). A total of 18 patients had taken UCCS overnight of whom 11 switched to CNGDF (median age 4.1 years, range 0.9 - 11.5 years) and seven patients had no specific dietary treatment after discontinuation (median age 12.8 years, range 7.0 - 22.0 years).

Three patients discontinued the use of UCCS because of intestinal complaints. Furthermore, three patients had been treated with total parental feeding for a period.

Table 2.1.2 Details of deceased GSD I patients

year of birth		year of death	age at death	cause of death
1943	Ia	1989	46 years	sepsis after 2nd renal transplantation
1965	Ib	1966	< 1 year	metabolic derangement
1966	Ia	1977	11 years	acute renal insufficiency with respiratory insufficiency
1967	Ib	1985	17 years	car accident
1969	Ia	1985	16 years	unknown (probably vitamin B1 deficiency with heart failure)
1974	Ia	1978	4 years	severe epistaxis complicated by aspiration pneumonia
1975	Ib	1978	3 years	metabolic derangement (failure of gastric drip pump)
1975	Ia	1994	18 years	end-stage heart failure by pulmonary hypertension (Osler-Weber-Rendu syndrome)
1976	Ia	1980	4 years	metabolic derangement
1977	Ia	1979	3 years	metabolic derangement
1981	Ib	1989	8 years	metabolic derangement
1984	Ia	1988	4 years	gastroenteritis, metabolic derangement
1984	Ib	1985	< 1 year	metabolic derangement
1985	Ia	1992	7 years	metabolic derangement (connection failure nasogastric tube)
1988	Ib	1995	7 years	sepsis with multi organ failure
1993	Ia	1994	1 year	metabolic derangement

deceased patients

Of the included patients, nine GSD Ia and seven GSD Ib patients had died. Details of these patients are summarised in Table 2.1.2. Furthermore, 17 of the 23 'patients' mentioned in the case records of siblings, had died. Most of them died because of a direct consequence of GSD I, mainly acute metabolic derangement (Table 2.1.3).

Table 2.1.3 Details of deceased 'GSD I patients', not included in the ESGSD I

year of birth		year of death	cause of death	year of birth		year of death	cause of death
1966	Ia	1967	metabolic derangement	1967	Ia	1967	metabolic derangement
1969	Ia	1969	metabolic derangement	1973	Ib	1973	metabolic derangement
1975	Ia	1981	necrotising pancreatitis	1976	Ia	1984	metabolic derangement
<1977	Ia	<1977	metabolic derangement	<1977	Ia	<1978	metabolic derangement
<1979	Ib	<1979	metabolic derangement	<1986	Ia	<1987	metabolic derangement
<1987	Ia	?	unknown	1988	Ia	1988	metabolic derangement
<1990	Ib	?	unknown	<1992	Ia	<1992	metabolic derangement
?	Ia	?	metabolic derangement	?	Ia	?	unknown
?	Ia	?	traffic accident				

metabolic derangement, comas, admissions, mental development, epilepsy

After starting dietary treatment, coma as consequence of metabolic derangement was reported in 34% of the GSD Ia and in 40% of the GSD Ib patients. The number of episodes varied from one (in 19% of the patients), two to four (11%), to five or more (5%).

After starting dietary treatment, metabolic derangement necessitating admission was reported in 55% of the GSD Ia and in 65% of the GSD Ib patients. The number of admissions varied from one to five (in 29% of the patients), six to ten (13%) to more than ten (15%). Metabolic derangements presented with convulsions in 65%, with severe sweating and paleness in 15% and were 'asymptomatic' in 16%. Metabolic derangements were mainly caused by infections (31%), vomiting and/or diarrhoea (21%), a combination of infection and gastrointestinal complaints (30%), and dietary errors (13%).

Mental development was low (IQ < 65) in 3% and borderline (IQ 65 - 85) in 18% of the patients. Of the patients who had experienced coma, 32% had a low or borderline mental development. Of the patients who had never experienced coma 16% had a low or borderline mental development ($p<0.01$; odds ratio 2.43 (95% 1.37 - 4.30). The use of anti-epileptics because of non-hypoglycaemic epilepsy was reported in 6% of the patients.

hyperlipidaemia and complications

Mean serum cholesterol and triglyceride concentrations among different age groups of GSD Ia and GSD Ib patients are summarised in Table 2.1.4.

Complications due to hyperlipidaemia were reported infrequently. Pancreatitis was reported in three patients, and cholelithiasis in two patients. One 46-year-old woman was reported to have atherosclerotic lesions at autopsy, but she died after a second renal transplantation because of end-stage renal disease.

hyperuricaemia and complications

Serum uric acid values ranged from 140 to 890 μmol/l. Use of a xanthine-oxidase (XO)- inhibitor was mentioned in 57% of the patients. It was started at a median age of 4.0 years (range 0.2 – 28 years). In 29% of the patients using XO-inhibitors, serum uric acid concentrations were still elevated (0.0 - 5.0 years: uric acid concentration > 350 μmol/l; 5.1 - 10.0 years: > 390 μmol/l; > 10.0 years: > 450 μmol/l); of the patients not using XO-inhibitors, uric acid concentrations were elevated in 33%.

Complications due to hyperuricaemia were reported in 14% of the patients. Renal calcifications or kidney stones were reported most frequently (median age 4.1 years, range 0.3 - 26.0 years). In 2 patients urolithiasis led to acute renal insufficiency. Other complications due to hyperuricaemia were gouty arthritis and tophi.

bleeding tendency

Complications due to bleeding tendency were reported in 23% of the patients. No difference in prevalence of complications due to bleeding tendency could be demonstrated between GSD Ia and GSD Ib patients. Most frequently reported were severe and/or recurrent epistaxis (19% of the patients), prolonged bleeding after surgery (3%), and gastrointestinal and/or urogenital tract bleeding (2%).

anaemia

Haemoglobin concentrations amongst different age groups of GSD Ia and GSD Ib patients are summarised in Table 2.1.5. Anaemia was asymptomatic in most patients and those who had symptoms, fatigue was the most common complaint. At latest follow-up, iron supplements were used by 11% of the patients; a further 27% had used them.

Table 2.1.4 Serum cholesterol and triglyceride concentrations in GSD Ia and GSD Ib patients

age (years)		cholesterol (mmol/l) n	mean (sd)	hyper-cholesterolaemia		severe hyper-cholesterolaemia		triglycerides (mmol/l) n	mean (sd)	hyper-triglyceridaemia		severe hyper-triglyceridaemia	
0.0 – 2.0	**Ia**	22	5.8 (2.9)	4.7 - 7.1	45%	> 7.1	14%	**Ia** 21	9.1 (6.4)	1.5 - 3.0	10%	> 3.0	90%
	Ib⁰	10	3.8 (1.9)		10%		10%	**Ib*** 9	3.6 (1.9)		56%		44%
2.1 - 5.0	**Ia**	39	5.4 (2.2)	4.7 - 7.1	38%	> 7.1	15%	**Ia** 38	4.4 (2.8)	1.5 - 3.0	29%	> 3.0	61%
	Ib⁰	10	3.9 (1.4)		0		10%	**Ib** 10	3.4 (1.9)		50%		40%
5.1 – 10.0	**Ia**	50	6.3 (2.2)	5.5 - 8.3	50%	> 8.3	10%	**Ia** 50	7.2 (5.9)	1.5 - 3.0	18%	> 3.0	78%
	Ib* **	16	4.1 (2.1)		6%		6%	**Ib**** 16	4.1 (3.0)		25%		50%
10.1 – 15.0	**Ia**	43	6.3 (2.0)	5.5 - 8.3	37%	> 8.3	18%	**Ia** 42	6.0 (4.0)	1.8 - 3.6	12%	> 3.6	71%
	Ib* **	6	3.1 (1.1)		0		0	**Ib*** ** 6	2.3 (1.6)		50%		17%
15.1 - 20.0	**Ia**	29	6.1 (2.6)	5.5 - 8.3	48%	> 8.3	7%	**Ia** 29	6.1 (6.5)	1.8 - 3.6	21%	> 3.6	62%
	Ib*	11	3.9 (1.7)		18%		0	**Ib** 11	4.0 (3.1)		0		64%
> 20.1	**Ia**	40	7.5 (3.9)	6.7-10.0	30%	>10.0	13%	**Ia** 40	9.7 (7.0)	2.1 - 4.2	20%	> 4.2	78%
	Ib	4	4.9 (1.6)		25%		0	**Ib ⁰** 4	3.0 (3.3)		75%		0
total group	**Ia**	223		**41.3%**		**12.1%**		**Ia** 220		**18.6%**		**72.7%**	
	Ib	57		**8.7%**		**5.3%**		**Ib** 56		**35.7%**		**42.9%**	

Differences in mean cholesterol and triglyceride concentrations between GSD Ia and Ib: $^{0}p < 0.07$, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$

Table 2.1.5 Hemoglobin concentration and anaemia in GSD Ia and GSD Ib patients

age (years)		n	hemoglobin (mmol/l) mean (sd)	anaemia		severe anaemia		complaints of anaemia (%)
0.0 - 2.0	**Ia**	23	6.7 (0.9)	5.0 - 6.0	18%	< 5.0	4%	9
	Ib	10	6.6 (0.4)		0%		0%	20
2.1 - 5.0	**Ia**	40	7.3 (0.8)	6.0 - 7.0	20%	< 6.0	13%	5
	Ib	10	6.8 (0.7)		40%		10%	40
5.1 - 10.0	**Ia**	48	7.4 (0.7)	6.0 - 7.0	17%	< 6.0	4%	4
	Ib	16	6.5 (0.8)		56%		25%	27
10.1 - 15.0	**Ia**	41	7.6 (0.7)	6.0 - 7.4	35%	< 6.0	2%	9
	Ib	6	6.3 (1.3)		50%		33%	50
15.1 - 20.0	**Ia**	29	7.5 (0.9)	6.0 - 7.4	38%	< 6.0	7%	20
	Ib	10	7.3 (0.9)		60%		0%	36
> 20.1	**Ia**	41	7.4 (1.0)	6.0 - 7.4	36%	< 6.0	7%	26
	Ib	4	5.4 (0.9)		25%		75%	100

osteopenia

Complications because of osteopenia were infrequent: multiple pathological fractures were mentioned in two patients, single pathological fracture in one patient, and rickets in two patients.

Of the patients, 25% received calcium supplements which were started at a median age of 4.3 years (range 0.4 - 42.0 years) and were used continuously in 80%. The mean dose at latest follow-up was 14 mg/kg/day (range 3.0 - 50.0 mg/kg/day). Of the patients on a lactose-restricted diet, 32% used calcium supplements.

hepatomegaly, splenomegaly, liver adenomas, liver carcinomas

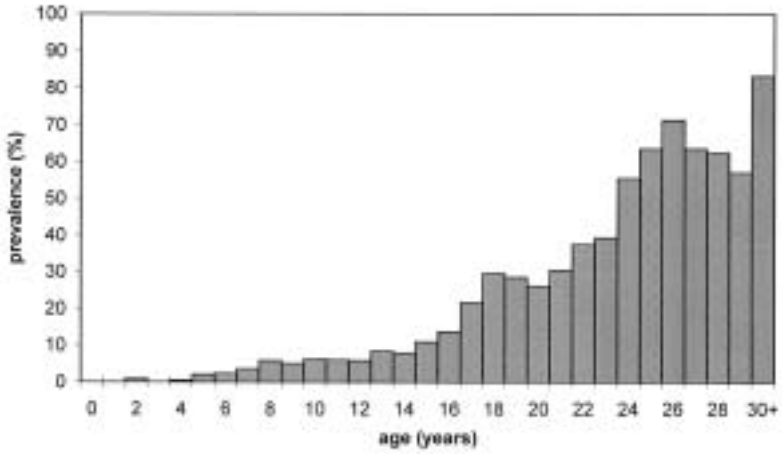
At latest follow-up, the liver was enlarged more than 2 cm below the costal margin in the midclavicular line in 89% of all patients. There was no significant difference in liver size between GSD Ia and GSD Ib patients. Furthermore, no decrease in liver size with ageing could be detected. Splenomegaly was mentioned in 11% of the GSD Ia patients and in 49% of the GSD Ib patients.

Whilst the overall prevalence of liver adenomas was 16% (23 male and 21 female patients), the prevalence increased with age (Figure 2.1.5). Adenomas were detected for the first time at a median age of 15.0 years (range 2.0 - 30.0 years) and two-third of the patients had multiple adenomas. Median follow-up after detection was 4.0 years (range 0.0 - 22.0 years). During this period, in 50% of the patients a progression in size and or number

of adenomas was observed. Six patients developed serious complications: complaints of compression (two patients), bleeding into adenomas (two patients) or a combination of both (two patients). Because of these complications, partial liver resection was performed in three patients, and two patients underwent liver transplantation (LT). In three patients, a remission of adenoma(s) was observed; in one patient after adjusting dietary therapy.

In the ESGSD I cohort, no transformation of adenomas to carcinomas was observed. Three patients showed a transient increase in α-fetoprotein, without evidence of malignant transformation.

Figure 2.1.5 Prevalence of liver adenomas in GSD I at different ages



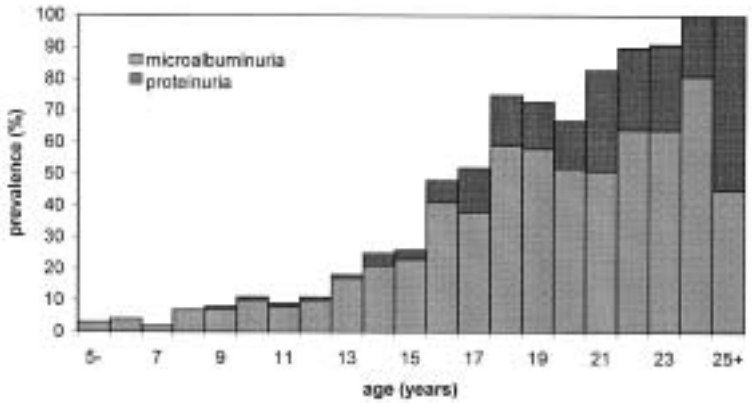
microalbuminuria, proteinuria, hypertension, progressive renal disease

The overall prevalence of proteinuria (urinary protein excretion > 200 μg/min or urinary albumin/creatinine ratio > 20) was 13% and an additional 31% had microalbuminuria (urinary albumin excretion 20 - 200 μg/min or urinary albumin/creatinine ratio 2.5 - 20). Prevalence of proteinuria and microalbuminuria increased with age (Figure 2.1.6). Proteinuria was detected at a median age of 16 years (range 0.5 - 25 years), microalbuminuria at a median age of 13 years (range 0.5 - 22 years).

Hypertension requiring treatment, was observed in 6% of the patients (mainly angiotensin converting enzyme (ACE)-inhibitors, but also β-adrenergic blocking agents and diuretics). Hypertension was detected at a median age of 17 years (range 4.0 - 42.0 years). A further 26 patients started ACE-inhibitors after development of microalbuminuria or proteinuria to prevent or postpone further detoriation of renal function.

Serum creatinine more than two fold above the upper level of normal was reported in six patients. In two patients, this was the consequence of urolithiasis and not of a progressive glomerular disease. Of the four patients with progressive glomerular disease, three required renal replacement therapy. Kidney transplantation was performed in two of these patients.

Figure 2.1.6 Prevalence of micoalbuminuria and proteinuria in GSD I at different ages



height, adult height, pubertal development, bone maturation

Height, in standard deviation score (SDS), calculated by comparing it with sex-, age- and geographical/ethnical matched control values, and body mass index (BMI) at latest follow-up are plotted in Figure 2.1.7 and Figure 2.1.8 respectively and summarised in Table 2.1.6.

Pubertal development was delayed in 56% of the GSD Ia and in 62% of the GSD Ib patients. Delayed bone maturation was observed in 59% of the GSD Ia and in 54% of the GSD Ib patients. Height at latest follow-up was stunted more in patients with delayed pubertal development and in patients with delayed bone maturation (Table 2.1.7).

In total, 54 patients had reached adult heights. Adult height was less stunted in GSD Ia patients (median SDS -1.2, range -4.5 - 2.0) compared to GSD Ib patients (median SDS -2.6, range -8.2 - -0.6; $p<0.05$). Adult height was reached at a median age of 21 years (range 14 - 24 years) in male patients and at a median age of 20 years (range 13 - 23 years) in female patients.

Figure 2.1.7 Height at latest follow-up in GSD I

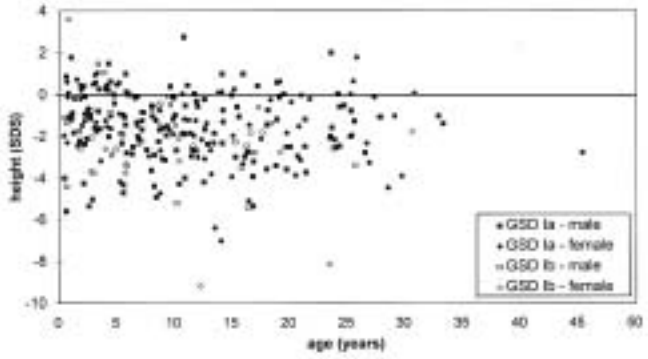
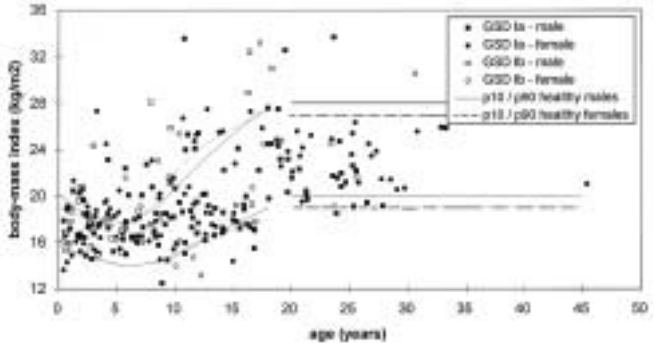


Figure 2.1.8 BMI at latest follow in GSD I



specific complications in patients with GSD Ib

Data about neutropenia, neutrophil dysfunction and IBD in GSD type Ib and the use of granulocyte colony stimulating factor are presented elsewhere[90,91].

Diarrhoea was reported in 35% of the GSD Ia and in 55% of the GSD Ib patients.

school, employment, pregnancy

Of the patients under 15 years of age, 89% were able to follow normal general education. The remaining patients needed special education because of mental disability.

Of the patients above 15 years of age, 44% was still following normal general education and 40% had normal employment. Special education or special work was needed in 11% and 6% were unable to follow any education or have a profession because of mental disability.

Table 2.1.6 Height in SDS and BMI at latest follow-up in GSD Ia and GSD Ib patients

age (years)		n	height SDS median (ranges)	height SDS -2.5 - -2.0 (%)	height SDS < -2.5 (%)	BMI > P90 (%)	BMI <P10 (%)
0.0 - 2.0	**Ia**	23	-0.92 (-5.6 - 1.8)	12	10	22	13
	Ib	8	-1.27 (-4.4 - 3.6)	0	25	25	13
2.1 - 5.0	**Ia**	38	-0.95 (-5.4 - 1.5)	5	11	37	0
	Ib	10	-2.33 (-3.8 - 1.5)*	10	50	40	0
5.1 - 10.0	**Ia**	49	-1.67 (-4.9 - 1.0)	6	33	24	4
	Ib	16	-1.66 (-3.7 - -0.1)	19	19	44	0
10.1 - 15.0	**Ia**	45	-1.85 (-7.0 - 2.7)	11	33	24	11
	Ib	6	-2.82 (-9.2 - -1.5)	33	50	17	50
15.1 - 20.0	**Ia**	29	-1.83 (-5.4 - 1.0)	4	41	10	21
	Ib	11	-2.47 (-5.4 - -0.6)	19	45	36	18
> 20.1	**Ia**	41	-1.53 (-4.5 - 2.0)	14	27	2	12
	Ib	4	-2.99 (-8.2 - -1.8)	0	75	25	0
total	**Ia**	225	**-1.44**	**9.4**	**26.7**	**20.4**	**9.3**
	Ib	55	**-2.08**	**14.5**	**38.2**	**34.5**	**10.9**
	all		**-1.55**	**10.3**	**28.9**	**22.9**	**9.6**

Differences in height SDS between GSD Ia and Ib: *p < 0.05. BMI standards from[37]

Table 2.1.7 Pubertal development, bone maturation and height SDS (median and ranges) in GSD Ia and GSD Ib patients

	pubertal development		bone maturation	
	normal (Ia n = 35; Ib n = 5)	**delayed** (Ia n = 45; Ib n = 8)	**normal** (Ia n = 53; Ib n = 13)	**delayed** (Ia n = 75; Ib n = 15)
Ia	-0.58 (-3.1 - 2.0)	-2.66 (-7.0 - 1.0)***	-0.52 (-3.1 - 2.0)	-2.52 (-7.0 - 0.6)***
Ib	-1.79 (-2.8 - -0.6)	-2.77 (-8.2 - -1.8)#	-1.35 (-3.7 - 1.5)	-2.78 (-8.1 - -0.9)**
Tot	-0.92 (-3.1 - 2.0)	-2.70 (-8.2 - 1.0)***	-0.68 (-3.7 - 2.0)	-2.64 (-8.1 - 0.6)***

differences between normal and delayed pubertal development / bone maturation:
#p = 0.06, **p < 0.01, ***p < 0.001

Three female patients gave birth to three healthy children and two male patients had five healthy offspring.

Although it was not an item in the questionnaire, of five adult patients it was spontaneously mentioned that they suffered from depressive illness needing therapy.

Discussion

We present a descriptive analysis of data of a cohort of 288 patients with GSD I obtained in a retrospective study.

From 1981 until 1996, ca. 50 Ia and 14 Ib patients from each period of 5 years were included, with smaller numbers born before 1981. The smaller numbers before 1981 may be due to loss to follow-up and/or higher mortality in earlier years. Loss to follow-up may have been caused by the fact that the participating clinicians are mainly paediatricians and that adult clinicians are caring for some adult patients. However, in many clinics, adult GSD I patients are still treated by or at least known to the 'paediatric' metabolic doctors. Furthermore, a study among adult nephrologists in the United Kingdom did not identify any adult GSD I patient who was not already known (Dr. Philip Lee, personal communication). It is therefore more likely that these patients have died with or without a diagnosis of GSD I. This is underlined by the fact that in a survey-study in Northrine-Westfalia, Germany (9.5 million inhabitants), among 13 GSD I patients born before 1980, no deceased patients could be identified[47].

This study shows that among GSD I, type Ib is more frequent than formerly stated. In the ESGSD I cohort born after 1980, more than 20% had type Ib. Earlier studies showed a prevalence of type Ib among GSD I patients varying from 10 to 15%[16]. GSD Ib is most likely underestimated in earlier studies because it was not recognised, it was difficult to diagnose (enzymatic pitfalls) and because of higher mortality particularly secondary to infections.

Prevalence of premature birth, (very) low birth weight, complications of pregnancy and delivery and the prevalence of other congenital abnormalities except heart disease did not differ from the normal population. Congenital heart disease occurs in approximately 0.8% of live births[9], whereas in the ESGSD I cohort a prevalence of 3% is observed. It is unlikely that prenatal metabolic abnormalities secondary to GSD I is the underlying cause of these congenital lesions, since the fetal metabolic state is controlled by the asymptomatic heterozygous mother. More stringent surveillance of patients with GSD I probably explains, at least in part, the higher prevalence of otherwise in potential asymptomatic heart anomalies such as ventricular and atrial septal defects.

Generally, GSD I patients present in early infancy. Patients with GSD Ib present at an earlier age than Ia patients. Almost 13% of the GSD Ia and 34% of the GSD Ib patients presented before the age of 1 month and almost 50% of both GSD Ia and Ib patients present between the age of 1 and 6 month during which time the interval between feeds normally is extended and the first common viral infections in childhood occur. In these patients,

coma, seizures, irritability and increased respiratory rate caused by hypoglycaemia and hyperlactacidaemia, and hepatomegaly are the predominant presenting symptoms. Hepatomegaly may have been even underreported since it is easily missed, as the liver is soft. Patients who present at later age may have fewer symptoms of acute metabolic derangement and present more with growth retardation. Hypoglycaemia may be asymptomatic in these patients since lactate may serve as cerebral metabolic fuel[23].

During the day, almost all patients in the ESGSD I cohort used FMs and 70% of the patients used UCCS in addition to prolong the fasting period. Generally, FMs are started immediately after the suspicion of the diagnosis of GSD I. Although it is recommended not to introduce UCCS before the age of 1 year because amylase activity may be immature[39], in a minority of children it was introduced with increasing concentration at earlier age without apparent (intestinal) problems.

At night, an equal number of patients used CNGDF and UCCS: CNGDF is used mostly by patients from Northwestern European countries, whilst UCCS overnight is used mostly by patients from Southern and East European countries. Both, CNGDF and UCCS have been proven to be able to maintain normoglycaemia during night[11,15,25,34,83,100,101,103]. As far as we are aware, there are no studies comparing the use of a glucose polymer solution or a complete formula (sucrose-free, low-lactose) for CNGDF.

A considerable number of patients had a history of CNGDF. CNGDF was discontinued in younger children particularly if the family was unable to cope with the technical and emotional difficulties of this treatment. CNGDF was discontinued in older patients particularly after completing the pubertal growth spurt. After discontinuation of CNGDF, most patients used UCCS overnight. A minority of patients had a history of UCCS overnight. Some younger patients changed to CNGDF to improve metabolic control, whilst especially some adolescent/young adult patients discontinued UCCS overnight and did not have any specific treatment hereafter.

A restriction in lactose and fructose was reported in two-third of the patients. In some patients these sugars are restricted almost completely, whilst in others this restriction is more liberal (up to 0.5 l of milk per day). Lactose and fructose enhance the production of lactate[22]. Some clinics accept somewhat higher lactate concentrations as lactate may serve as an alternative fuel for the brain during hypoglycaemia[23].

The main goal of dietary treatment is to maintain normoglycaemia and to suppress metabolic derangements as much as possible. This study shows that a wide variation in the dietary treatment exists, even for patients of the

same age.

Despite treatment, metabolic derangement is still a major cause of morbidity. Episodes of coma as a consequence of metabolic derangement were recorded in more than one-third of the patients, whilst metabolic derangement necessitating admission were reported in almost two-third. Infections, especially if combined with vomiting and/or diarrhoea are the most common cause of such acute metabolic derangement. Patients with GSD Ib are more prone for such illness because of the neutropenia and neutrophil dysfunction[90].

Mortality, as a consequence of metabolic derangement seems to be less frequent with current treatment. Of the 21 patients (included and not included patients in the ESGSD I, Table 2.1.2 and 2.1.3) who died as a consequence of metabolic derangement, 11 died in the period before 1980 and only three after 1990. Two patients died as a consequence of failure of CNGDF (pump failure and disconnection of the tube system).

With intensive dietary treatment secondary biochemical abnormalities will improve. However, hyperlipidaemia is still observed frequently. On dietary treatment, mild and severe hypercholesterolaemia are observed in 41% and 12% of GSD Ia patients and in 9% and 5% of the Ib patients respectively, whilst mild and severe hypertriglyceridaemia are observed in 19% and 73% of the Ia and 36% and 43% of the Ib patients respectively.

This study shows for the first time a difference in hyperlipidaemia between GSD Ia and GSD Ib patients: the number of GSD Ia patients with hyperlipidaemia is greater and it is more severe. Hyperlipidaemia in GSD I is thought to be a result of both increased synthesis of lipids from excess of acetyl-CoA, and decreased serum lipid clearance[1,6,7,29,35,60,61,81]. The cause of difference in hyperlipidaemia between Ia and Ib patients is still unknown.

In the ESGSD I cohort, complications related to hyperlipidaemia were reported infrequently. Since a history of xanthomas was not recorded it is not possible to estimate the incidence and degree of this complication, but it is known that xanthomas have become rare since the decrease in hyperlipidaemia following the introduction of intensive dietary treatment26. Pancreatitis is associated with severe hypertriglyceridaemia as a consequence of poorly metabolic control[40,46], and its occurrence in GSD I has also become rare.

In familial hypercholesterolaemia or familial combined hyperlipidaemia, a comparable degree of hyperlipidaemia is associated with cardiovascular morbidity and mortality at early age[33,44]. In the ESGSD I cohort however, only one 46-year-old woman who died after a second renal transplantation, had atherosclerotic lesions found at autopsy. It is possible that the

development of atherosclerosis in this patient was mainly due to secondary metabolic changes related to progressive renal failure. Among 37 adult GSD I patients from the United States of America (USA), two 35-year old men were reported to have coronary heart disease[86]. Two in vivo-studies showed no sub-clinical signs of premature atherosclerosis in (young) adult GSD Ia patients[51,88]. Protective factors may be diminished platelet aggregation[18,41], hyperuricaemia since uric acid is a potent radical scavenger[99], increased levels of Apolipoprotein E[87], and decreased susceptibility of low-density lipoproteins to oxidation[6].

On dietary treatment, hyperuricaemia was observed in 29% of the GSD I patients using XO-inhibitors (57% of the patients) and in 33% of the patients not using XO-inhibitors, without a difference between Ia and Ib patients. Complications due to hyperuricaemia were reported in 14% of the ESGSD I cohort: renal calcification or kidney stones have most clinical relevance. Two patients developed end-stage renal failure related to renal calcification. Among the adult GSD I population in the USA, renal calcifications or kidney stones were identified by ultrasound in 17 out of 26 investigated patients[86]. Although a risk factor for the development of renal calcification and kidney stones, it may be advisable to keep uric acid concentrations in the higher normal range, since its possible protective role in the development of atherosclerosis[99]. Besides hyperuricaemia, hypercalciuria is another risk factor for the development of renal calcification and kidney stones. Hypercalciuria is a consequence of renal distal tubular dysfunction[55,78] and is observed in about one-third of the GSD I patients[56]. The administration of citrate in GSD I might be protective[96].

Osteopenia in GSD I has received relatively little attention up to now. Decreased bone mineralisation is found in both young and adult GSD I patients[56,71]. A wide variety of metabolic- and endocrine factors in GSD I may contribute to abnormal bone matrix formation and altered mineralisation. According to the Utah paradigm, control of bone strength and mass depends strongly on muscle strength[30]. Therefore, in GSD I, decreased muscle function caused by increased gluconeogenesis, may also play a role. Among the relatively young ESGSD I cohort, complications due to osteopenia were rare. However, since more and more patients will reach the 5th and 6th decades of life, normal bone formation in childhood and young adulthood becomes important.

Pulmonary hypertension which may be followed by progressive heart failure is a rare fatal complication in GSD I[36,68]. In the ESGSD I cohort, pulmonary hypertension resulting in end-stage heart failure was reported in one female GSD Ia patients who died at the age of 18 years. Since this girl was known

to have Osler-Weber-Rendu syndrome, it is not clear if the pulmonary hypertension was directly related to her GSD I. The pathophysiology of this vasoconstrictive process in GSD I is still unclear. A prospective study showed increased right ventricular pressure in 27% of the investigated GSD I patients, which may be an indication of early pulmonary hypertension[48].

Anaemia, with and without complaints, was observed rather frequently. In the ESGSD I cohort about, about 25% of the prepubertal Ia, 50% of the prepubertal Ib, 40% of the adolescent Ia, 70% of the adolescent Ib, and 45% of the adult Ia and all adult Ib patients had hemoglobin concentrations below the normal range. Among the adult GSD I population in the USA, 81% had hemoglobin concentrations below the normal range[86]. Most GSD I patients seem to have enteral-iron-refractory microcytic anaemia. The pathophysiology is still unclear, but it has been suggested to be associated with decreased intestinal iron absorption due to primary intestinal dysfunction or secondary to UCCS ingestion, with erythropoetin deficiency secondary to renal insufficiency and with chronic blood loss (into hepatic adenomas or intestinal in type Ib)[2,85,93].

Polycystic ovaries (PCOs) have been observed in both prepubertal and postpubertal female GSD I patients. In a study among female GSD I patients in the United Kingdom (UK), all female patients above the age of 5 years had PCOs[53]. Since the existence of PCOs was not recorded in this study, it is not possible to estimate the prevalence and degree of this complication in the female ESGSD I cohort.

Patients with GSD I may suffer from intermittent diarrhoea, which seems to get worse with age[28,93]. Among the ESGSD I cohort diarrhoea was reported in 35% of the GSD Ia patients. No common cause for diarrhoea in GSD Ia has been found[27,32,66,93]. The relation with disturbed enterocyte function due to lack of G6Pase activity remains to be investigated. Diarrhoea was reported in 55% of the GSD Ib patients. In GSD Ib loss of mucosal barrier function due to inflammation seems to be the main cause of diarrhoea[93]. This is most likely related to disturbed neutrophil function[90].

GSD I has been associated with the development of hepatic adenomas, which have the potential to transform into carcinomas[10,67]. The overall prevalence of adenomas in our study is 16%, without a male preponderance as was observed in earlier studies[49]. Striking is the fact that adenomas are observed in 70 to 80 % of the patients above the age of 25 years. Previous reports show a prevalence from 22% to 75% depending on the study population[49,52,70,84,85,86] with a lowest prevalence observed in the youngest population (0.6 - 29 years)[52], and a highest prevalence observed in the oldest GSD I population (18 - 43 years)[86]. Among the ESGSD I cohort, hepatic

adenomas were detected for the first time at a median age of 15 years. Two-third had multiple adenomas. After detection, in 50% there was progression in size and/or number of the adenomas during follow-up.

Hepatic adenomas are not the only focal abnormalities of the liver associated with GSD I. Others include focal fatty infiltration, focal fatty sparing and focal nodular hyperplasia[52,54,57] and ultrasound investigations may erroneously interpret these lesions as adenomas, especially in prepubertal patients. Regression of adenomas after adjusting dietary therapy[69] may be no more than dissolving of focal fatty infiltration and fatty sparring[57].

During follow-up, in our study, six out of the 44 patients with hepatic adenomas developed serious complications as complaints of compression and haemorrhage into the tumour. Among the ESGSD I cohort, no malignant transformation was observed. In two patients LT was performed and in three patients surgical resection of the adenomas. LT should be considered in patients with unresectable and dietary unresponsive multiple adenomas, particularly if associated with serious complaints of compression or haemorrhage, or in case of transformation into carcinoma. However, there is lack of clear-cut criteria to detect malignant transformation early[20]. LT corrects glucose homeostasis[45]. Therefore, it may also be a therapeutic option in (dietary unresponsive) poorly metabolic controlled patients. However, LT may be contra-indicated in these patients since not being able to comply dietary treatment strictly, may implicate poorly compliance to necessary (immuno-suppressive) treatment and follow-up after LT. LT does not prevent for the development of renal failure and does not improve neutrophil function in GSD Ib[64].

A serious complication in the ageing patient is renal disease[12,14,77]: both glomerular and tubular functions are at risk[55].

The first manifestation of glomerular disease is hyperfiltration. Following the onset of hyperfiltration, microalbuminuria and subsequently proteinuria may develop[8,12,14,55,76,77]. In the studied ESGSD I cohort, the prevalence of proteinuria was 13%, microalbuminuria was observed in another 31%. Above 25 years of age, proteinuria was observed in more than 50% of the patients. In addition, all other investigated patients above 25 years of age had microalbuminuria. Hypertension, a subsequent consequence of the progression of renal disease, was observed in 7% of the ESGSD I cohort. Among the adult GSD I population from the USA, 61% had proteinuria and in addition 17% microalbuminuria. Hypertension was reported in 23%[86]. The likelihood of developing end-stage renal failure in GSD I is unclear. In the studied ESGSD I cohort, six patients had increased serum creatinine concentrations. In two (younger) patients however, this was a consequence

of urate nephropathy and not of progressive glomerular disease. Of the four patients with progressive glomerular disease, three required renal replacement therapy, and two had renal transplants. Some evidence exists that stringently maintained metabolic control may improve renal disease[102]. The possible beneficial effect of ACE-inhibitors to prevent progression of renal disease in GSD I is still unclear (unpublished data).

Both proximal and distal renal tubular defects have been described in GSD I[13,55,78]. Since the existence of proximal and/or distal renal tubular dysfunction was not recorded in the ESGSD I, it is not possible to estimate their prevalence among the ESGSD I cohort. Proximal renal tubular dysfunction seems to be related to poor metabolic control and amelioration is observed with dietary therapy[13]. Distal renal tubular dysfunction is frequently associated with hypercalciuria, which may contribute to kidney stones and decreased bone mineralisation[56,71,78].

Short stature is one of the characteristics of patients with GSD I. Among the ESGSD I cohort, height at latest follow-up was below -2.0 SDS in 35% of the Ia and in more than 50% of the Ib patients. A comparable degree of poor growth in height was observed in earlier studies among smaller numbers of prepubertal patients (median SDS –1.35)[56], adolescent and young adult patients (46% < P3[85]; mean SDS –1.27[15]), and among a larger group of adults patients (53% < P3)[86]. GSD Ib patients were shorter compared to GSD Ia patients. Less optimal metabolic control in GSD Ib patients as a consequence of recurrent serious infections and IBD and/or direct consequences of these infections and IBD may explain this observation. GSD Ia patients under 5 years of age have less stunted height compared to the older GSD I patients. It is not clear if this reflects the natural course of height in GSD I or that it is a consequence of better metabolic control. Long-term follow-up of these patients is necessary to answer this. Pubertal development and bone maturation are delayed in more than 50% of both GSD Ia and Ib patients. Patients who had normal pubertal development or bone maturation had less stunted (adult) height compared to those patients who had delayed pubertal development or bone maturation. About one-fourth of the GSD Ia and one-third of the GSD Ib patients under 20 years of age, had a BMI above the p90 of healthy peers. Of the adult GSD I patients, only 2 patients had a BMI above 26.5 kg/m^2 (for females) or 28 kg/m^2 (for males).

Long-term cerebral function in GSD I is normal if hypoglycemic damage is prevented[26]. Among the ESGSD I cohort, mental development was low in 3% and borderline in 18%. However, of the patients who had never been in coma, only 16% had low or borderline mental development, which is

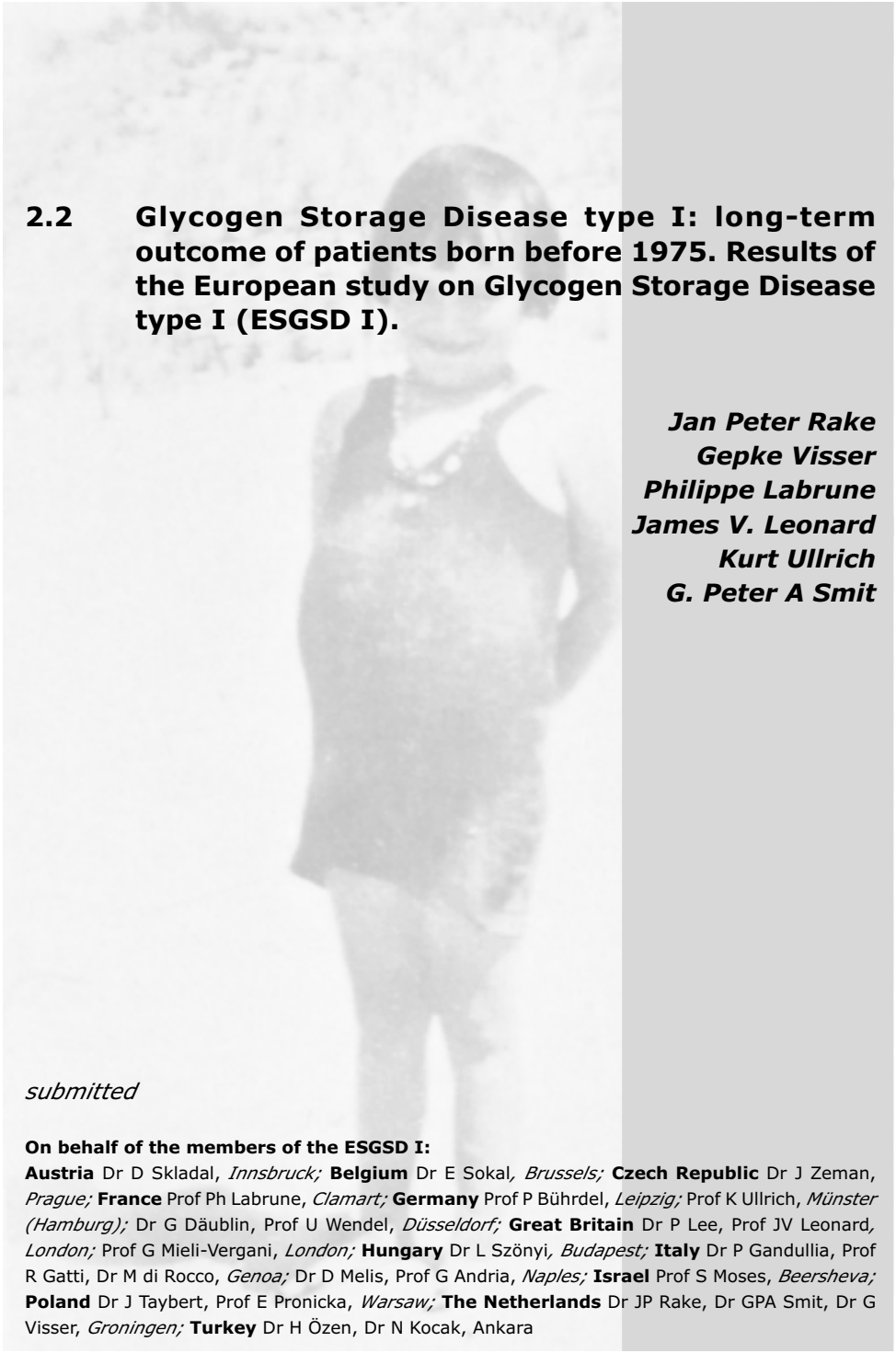
comparable with the normal population. Eleven percent of the younger GSD I patients needed special education, whereas 11% of the older GSD I patients needed special education and/or work, and six percent had no education or profession because of mental disability. Those adults who were employed had jobs comparable to the normal population.

Most of the adult patients were leading fairly normal lives. However, at least five adult patients were suffering from depressive illness needing therapy. In the USA, six out of 42 adult patients were depressed[86]. Lifelong intensive dietary treatment 24 hours a day, in combination with serious medical problems is a major burden for both patients and parents[38].

Reports about pregnancies in female GSD I patients are scare[21,43,79,80]. Among the ESGSD I cohort, three female patients gave birth to three healthy children and two male patients had 5 healthy offspring. Among the adult GSD I population from the USA, two female and five male patients had children[86].

When considering the long-term outcome of the adults it is important to remember that these patients are survivors from a period when dietary treatment was less than optimal. It is hoped that those who have received optimal treatment from an early stage will do better. However, it is possible that a group of patients who previously would not have survived, will now reach adulthood and present with new complications. Close monitoring therefore remains necessary.

In conclusion, the retrospective part of the ESGSD I has added to the understanding of the management, clinical course, and outcome of GSD I. Among GSD I, type Ib is not as rare as formerly thought. There is still wide variation in methods of dietary and pharmacological treatment. With intensive dietary treatment, clinical and biochemical status will improve but cannot be corrected completely in most patients. Fewer GSD I patients, however, will die as a direct consequence of acute metabolic derangement, and, life-expectancy has improved considerably. Nevertheless, with ageing more and more complications will develop. Progressive renal disease and the complications of liver adenomas are likely to be two major causes of morbidity and mortality in these older patients.



2.2 Glycogen Storage Disease type I: long-term outcome of patients born before 1975. Results of the European study on Glycogen Storage Disease type I (ESGSD I).

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Summary

To study long-term outcome in glycogen storage disease type I (GSD I), data of adult patients obtained from the European Study on GSD I (ESGSD I) were elaborated. From hospital records of 16 metabolic centres, in 12 European countries, 60 GSD I patients born before 1975 were identified. Included were 47 patients (43 GSD Ia: median age 25.6 years, range 20.0 - 45.4; 4 GSD Ib: median age 25.0 years, range 23.8 - 30.6) with a follow-up of at least 20 years.

Most of the patients were leading fairly normal lives. Mental development was borderline in 15%, and low in 1 patient. Educational background and employment were comparable with healthy adults. 46% of the GSD Ia and 3 out of 4 GSD Ib patients had an adult height ≤ -2.0 SDS. A history of coma(s) was reported in 29% of the GSD Ia and in one GSD Ib patient. Long-term morbidity included pancreatitis (3 GSD Ia patients), atherosclerotic lesions (1 GSD Ia patient), gouty arthritis (6 GSD Ia patients), nephrolithiasis (57% of the GSD Ia patients; 3 GSD Ib patients), complications related to bleeding tendency (41% of the GSD Ia patients; 3 GSD Ib patients), symptoms of anaemia (29% of the GSD Ia patients; all GSD Ib patients), neutropenia (all GSD Ib patients), intestinal complaints (2 GSD Ia patients), inflammatory bowel disease (2 GSD Ib patients), depressive illness (3 GSD Ia and 1 GSD Ib patients), liver adenomas (55% of the GSD Ia patients; 1 GSD Ib patient), complications related to liver adenomas (5 GSD Ia patients), proteinuria (55% of the GSD Ia patients; 1 GSD Ib patient), microalbuminuria (all others except one GSD Ia patient), and hypertension (31% of the GSD Ia patients; 1 GSD Ib patient). Partial liver resection was performed in 3 GSD Ia patients, liver transplantation in 1 GSD Ia patient. Four GSD Ia and 1 GSD Ib patients needed renal replacement therapy; 2 underwent kidney transplantation.

A large variation in history of dietary treatment was registered. Patients who started stringent dietary treatment before the age of 5 years and continued this life-long, had a lower prevalence of liver adenomas ($p < 0.05$), showed less stunted adult height, a higher prevalence of hypoglycaemic comas, and lower prevalence of delayed pubertal development, gouty arthritis and hypertension (p values between 0.05 - 0.10), compared to those who had no dietary treatment at all or started it after the age of 10 years.

In conclusion, ageing GSD I patients develop complications of different organ systems. Life-long continuation of stringent dietary treatment started in early childhood seems to decrease the prevalence of short-term complications related to secondary metabolic derangements and seems to prevent, or at least postpone the development of long-term complications as liver adenomas and renal disease.

Introduction

Glycogen storage disease type I (GSD I, McKusick 232200) is an autosomal recessive inborn error of carbohydrate metabolism caused by defects of the glucose-6-phosphatase (G6Pase) complex. G6Pase plays a central role in both glycogenolysis and gluconeogenesis, hydrolysing glucose-6-phosphate (G6P) to glucose. Deficiency of G6Pase activity in liver, kidney and intestine results in accumulation of glycogen. As a result of inadequate glucose production patients have severe fasting hypoglycaemia with secondary biochemical abnormalities as hyperlactacidaemia, hyperuricaemia and hyperlipidaemia. Untreated patients have a protruding abdomen because of marked hepatomegaly (storage of glycogen and fat), short stature, truncal obesity, rounded doll face, wasted muscles, and bleeding tendency due to impaired platelet function[16,26].

Based on the most plausible molecular model, G6Pase is a multicomponent complex consisting of a catalytic subunit, situated on the luminal side of the endoplasmic reticulum, and one or more membrane transporters[5,95]. Deficient activity of the catalytic unit of G6Pase is called GSD Ia. In 1993 the gene encoding this unit has been identified in band q21 of chromosome 17 and a steadily growing list of mutations has been reported[59,64,72]. Furthermore, a G6Pase deficient mouse model has been generated and first studies in these mice show that GSD Ia can potentially be corrected by gene therapy[17]. Defects of the putative transporter(s) were named GSD Ib, GSD Ic and GSD Id. Molecular genetic studies have shown however, that patients diagnosed by enzyme studies as GSD Ib, Ic and the putative Id, all had mutations in the G6P translocase gene identified in band q23 of chromosome 11[31,89]. This is consistent with the clinical findings as GSD I can be divided in two clinical phenotypes: GSD Ia patients have 'classical' findings as listed above, whilst those with 'GSD I non-a' have in addition recurrent bacterial infections and inflammatory bowel disease (IBD) associated with neutropenia and neutrophil dysfunction[90]. However, recently a GSD Ic patient without mutations in the G6P transporter gene was described suggesting the existence of a distinct GSD Ic locus[62]. In the present study the term GSD Ib is used for 'GSD I non-a' patients and includes patients formerly diagnosed as GSD Ib, GSD Ic and GSD Id.

GSD I has an estimated frequency among newborns of one in 100.000. Thus no single metabolic centre has experience of large series of patients. Furthermore, in literature there is a relative paucity of data about outcome, and all these reports[15,24,70,84,85,103], except one[86], focus on patients under 18 years.

To share experience and knowledge with regard to GSD I, the collaborative

European Study on GSD I (ESGSD I) was initiated in 1996. Objectives were to study the management, clinical course and long-term outcome of patients with GSD I, to develop therapeutic strategies and to develop guidelines about (long-term) management and follow-up[74,92].

In a previous report, a descriptive analysis of data about diagnosis, management, clinical course, and outcome of 288, both paediatric and adult, GSD I patients obtained from the ESGSD I was presented[73]. In this report detailed outcome data of adult GSD I patients born before 1975 are presented.

Methods

Patients were identified from hospital records of 16 metabolic centres, in 12 European countries. Patients treated in the centres including patients who had died since 1960 were enlisted. Patients were coded by initials and date of birth to check for duplication. Retrospective case records forms were discussed in a multicenter meeting and filled in by either the treating physician or by one of the investigators (JPR).

The diagnosis of GSD Ia was made either by enzyme studies that showed the combination of deficient G6Pase activity in intact and/or disrupted microsomes and/or by mutation analysis of the G6Pase gene. The diagnosis of GSD Ib was made either by enzyme studies that showed the combination of deficient G6Pase activity in intact microsomes and (sub)normal G6Pase activity in disrupted microsomes and/or by mutation analysis of the G6P transporter gene.

Height is expressed in standard deviation score (SDS), which was calculated by comparing height with sex-, age- and geographical/ethnical matched control values.

Proteinuria was defined as urinary protein excretion > 200 μg/min or urinary albumin/creatinine ratio > 20; microalbuminuria as urinary albumin excretion 20 - 200 μg/min or urinary albumin/creatinine ratio 2.5 - 20.

Most of the results are descriptive. Results are expressed as mean (± standard deviation (sd)) or as median (minimum - maximum). Differences in the number of affected individuals between two subgroups of patients (2x2 contingency table) were analysed using the Fisher exact test (including calculating an odds ratio with 95% confidence interval). Differences in variables with a normal distribution between two subgroups of patients were analysed using unpaired two tailed t-tests. P values ≤ 0.10 are expressed in the text or in the tables.

Results

Of the 288 included patients in the ESGSD I[73], 53 GSD Ia and 7 GSD Ib patients were born before 1975. Data about dietary treatment and (long-term) outcome of these patients are presented in Table 2.2.1. 43 GSD Ia patients (median age 25.6 years, range 20.0 - 45.4) and 4 GSD Ib patients (median age 25.0 years, range 23.8 - 30.6) were above 20 years of age at latest follow-up. Except otherwise stated, data of these 47 patients were used to describe management and long-term outcome in GSD I.

Methods of present dietary treatment were known of 40 GSD Ia and 3 GSD Ib patients. During daytime, 11 (26%) patients used frequent meals (FMs), and 24 (56%) FMs and uncooked cornstarch (UCCS) in addition; 11 (26%) patients had continuous nocturnal gastric drip feeding (CNGDF), and 20 (47%) used UCCS overnight.

History of dietary treatment showed a large variation. During their first years of life most patients had FMs only. At the end of the first or in the beginning of the second decade of life, CNGDF was introduced in more than 50% of the patients. More than half of these patients switched to UCCS overnight later in life, especially at the end of the second decade. UCCS overnight was introduced primarily in another one-third of the patients.

Mean adult height was -1.5 SDS (sd 1.44; n=39) in GSD Ia and median adult height -3.0 SDS (range -8.2 - -1.8; n=4) in GSD Ib. 46% of the GSD Ia and 3 out of 4 GSD Ib patients had an adult height below -2.0 SDS. Adult height was reached at the age of 21 (18 - 23.5) in males and 20 (17 - 24) in females. Pubertal development was delayed in 67% of the patients.

Table 2.2.1 (see next page) Dietary treatment and outcome of adult GSD I patients born before 1975

abbreviation *FMs* frequent meals; *UCCS* uncooked cornstarch; *CNGDF* continuous nocturnal gastric drip feeding; *LF* lactose fructose; *SDS* standard deviation score; *RRT* renal replacement therapy; *KT* kidney transplantation; *PLR* partial liver resection; *DI* depressive illness; *(I)BD* (inflammatory) bowel disease; *CMP* cardiomyopathy; *LT* liver transplantation; *LOC* large ovarian cyst; *PHT* pulmonary hypertension; *NP* neutropenia; *ND* neutrophil dysfunction; *n.a.* not applicable; *f* female; *m* male

✞ deceased, causes: [1] sepsis after 2nd renal transplantation; [2] end-stage heart failure caused by pulmonary hypertension (Osler-Weber-Rendu syndrome); [3] unknown (probably vitamin B1 deficiency with heart failure); [4] acute renal insufficiency with respiratory insufficiency; [5] severe epistaxis complicated by aspiration pneumonia and respiratory insufficiency; [6] car accident; [7] metabolic derangement (failure of gastric drip pump); [8] acute metabolic derangement.

+ present; - not present; ? unknown; x not applicable; n normal; ↓ borderline mental development; ↓↓ low mental development

				history dietary treatment (age start- age stop in years)				adult height						complications (age of onset in years)								
	deceased	age (years)	FMs during daytime	UCCS during daytime	UCCS overnight	CNGDF	restricion LF	in cm , between () if adult height not reached	in SDS, between () if adult height not reached	delayed puberty	mental development	employment / education children	hypoglycaemic coma	complic. bleeding tendency	(history of) nephrolithiasis	liver adenomas	(history of) anaemia	microalbuminuria	proteinuria	hypertension	remarks (age in years)
GSD Ia																					
1 f	✞[1]	45.4	+, 14	-	-	-	-	152	-2.8	+	n	housewife, 1	-	-	+	+, 30	+	+	+	+, 42	RRT 40, KT 42,45
2 m		33.8	+	+, 25	+, 25	-	-	166	-1.4	?	n	manager	?	-	+, 23	+, 24	?	+	+	+, 30	gout, cholelithiasis
3 m		33.4	+, 0.4	-	-	-	-	168.7	-1.0	?	n	manager, 2	-	-	-	+, 13	+	+	+	-	
4 f		32.4	?	?	?	?	?	?	?	?	?	?	?	+	+	+	?	+	+	+	RRT 30
5 f		31.3	+	+, 24	+, 24	-, 14-17	-	164	0.1	?	n	nurse	?	?	+	+, 22	?	?	?	+	
6 f		30.2	-, 11-20	-	+, 20	-	-	143	-3.9	+	n	housewife, 1	-	-	-	-	-	?	-	-	
7 f		29.5	+, 1.5	-	+, 16	-, 6-16	+	162	-1.0	+	n	goldsmith, 1	+	+	-	+, 20	+	+, 21	-	-	PLR, gout
8 f		28.9	-, 9-19	-	+, 19	-	-	140.5	-4.5	+	n	housewife	-	+	-	+, 26	-	?	-	-	
9 m		28.3	-	-	-	-	-	168	-1.1	-	n	university	-	-	?	+, 18	-	?	-	-	gout
10 f		28.2	+, 5	+, 16	+, 16	-, 12-16	+	161.5	-1.1	-	n	teacher	-	-	-	+, 17	-	?	-	?	
11 f		27.7	+, 1	+	+, 17	-, 2-17	+	167.5	-0.1	-	n	physiotherapist	-	-	?	-	-	+, 18	-	-	DI
12 f		27.3	+, 0.8	+, 12-26	-	+, 8	+	148	-3.3	+	↓	factory worker	+	+	+	+, 19	+	+, 21	-	-	(I)BD, DI
13 f		27.2	+, 0.8	-	-	+, 9	+	167.1	0.0	+	n	manager	-	-	-	+, 22	-	+	+, 21	+, 22	
14 f		27.1	-	-	-	-	-	155.1	-2.3	+	n	?	-	+	+	+, 25	-	+	+, 25	+, 27	
15 m	?	26.9	+, 5	+, 21	+, 21	-	+	162	-2.8	+	n	salesman	-	-	+, 26	+, 5	-	+	+	+	
16 m		26.4	+	+	+, 13	-	-	157.5	-2.5	?	n	luggage-keeper	+	+	+, 25	+	?	?	?	?	gout
17 f		26.2	+, 0.7	+, 12	+, 16	-, 8-16	+	176.1	1.8	-	n	university	-	-	-	-	-	+, 18	-	-	
18 m		26.0	+	+, 16	-	+, 4	+	171.6	-1.3	-	n	research-fellow	+	-	-	-	-	+, 16	+, 25	-	
19 f		25.9	-	-	-	-	-	167.7	0.6	?	n	midwife	?	-	?	+, 16	-	?	?	?	gout
20 m		25.7	-	-	-	-	-	170.6	-0.8	+	n	farmer, 3	-	+	+	+, 12	-	?	?	-	PLR
21 m		25.7	+, 1.0	+, 17	+, 17	-	-	165	-2.0	+	n	housewife	-	+	+	+, 21	+	+	+, 18	+, 17	cholelithiasis, CMP
22 f		25.6	+, 9	-	-	-, 16-18	-	150.7	-2.0	+	↓	sheltered workshop	-	+	+	-	+	+	+, 17	+, 18	RRT 25
23 m		25.1	+, 0.6	-	-	+, 8	-	176.5	-0.5	-	n	tertiary education	+	-	+	-	-	?	?	?	
24 m		24.7	+, 1.3	+	-	+, 4	+	164.0	-2.5	+	↓	factory worker	+	-	-	-	-	+	+, 18	-	
25 m		24.7	+, 1.3	+	-, 15-19	+, 6-15, 19	+	176.1	-0.6	-	n	employee	+	-	+	+, 24	-	+, 19	-	-	
26 m		24.5	+, 0.3	-, 16-23	-	-, 11-?	-	176.6	0	?	n	university	?	-	+, 0.5	-	?	?	?	?	gout

27	m	24.4	?	?	?	?	?	166	-2.2	?	n	?	?	?	?	+	?	?	?	?	LT 24
28	m	24.2	+	+, 16	-	+	+	167.0	-2.0	?	?	?	?	?	?	-	-	+, 22	-	-	
29	m	24.0	+, 0.2	+, 20	-	+, 20	+	169.7	-1.6	+	↓	?	+	-	+	-	-	+	+, 23	-	pancreatitis
30	m	23.9	+, 1.0	+, 12-23	-	+, 4	+	195.4	2.0	-	n	manager	+	-	-	-	-	-	-	-	(I)BD
31	m	23.8	+, 1.0	+, 13	+, 13	-, 10-13	+	156.4	-2.1	?	n	gym-teacher	-	+	-	-	-	?	?	-	pancreatitis
32	f ?	22.0	+, 12	-	-, 17-22	-, 12-17	-	165.9	-0.2	+	n	?	-	-	-	+, 18	-	+	+, 22	-	
33	m	21.8	+, 0.5	+, 9	+, 9	-, 6-9	-	150	-3.7	+	↓	technician	?	+	+, 15	-	+	+	+, 21	-	
34	m	21.6	+, 17	+, 17	-	+, 17	+	170	-1.2	+	n	tertiary education	-	-	+	-	-	+, 17	+, 21	+, 19	
35	m	21.6	+, 11	-	+, 14	-, 11-14	+	164	-2.5	-	n	university	-	+	-	-	-	+	+, 21	-	
36	f	21.3	-	-	-	-	-	163.4	0	+	↓	army RAF	-	-	-	-	-	?	?	-	DI
37	f	21.2	+, 0.9	-	-	+, 5	+	151	-3.1	+	↓	sales woman	-	+	-	-	+	?	?	-	
38	f	21.1	+, 0.4	+, 10	+, 10	-	-	151	-1.5	+	n	tertiary education	+	-	+, 20	-	-	?	-	-	pancreatitis
39	m	21.0	?	?	?	?	?	154.5	-3.0	?	n	nurse	?	?	?	?	?	?	?	?	
40	f	20.8	+, 16	-	-	-, 17-19	-	(147)	(-3.9)	+	n	?	-	+	+	+, 17	+	+	+, 16	+, 16	RRT 17
41	m	20.3	+, 10	+, 10	+, 16	-	+	162	-2.5	-	n	university	-	-	-	+, 11	+	?	-	-	PLR
42	m	20.0	+, 5	+, 8	+, 16	-, 6-16	-	(151	(-3.6)	+	n	librarian	-	+	+, 18	+, 13	-	?	?	-	
43	f	20.0	+, 0.7	+, 11	+, 11	-, 4-11	-	(154)	(-1.8)	?	n	taylor	-	+	+	-	?	?	-	-	
44	m	19.4	+, 1.5	+	+, 17	-, 8-17	+	179	-0.1	+	n	tertiary education	+	+	-	+, 15	+	+	+, 17	-	
45	f ✙[2]	18.6	+, 1.5	+, 5	+, 7	-, 5-7	+	162.1	-0.3	-	↓	?	+	+	-	+, 4	+	+, 13	-	-	LOC, PHT
46	m ?	18.4	+, 14	+, 15	+, 15	-	+	172	-0.8	-	n	?	?	-	-	?	-	+	-	-	severe scoliosis
47	f ✙[3]	16.7	+, 0.5	+	+, 15	-, 4-15	+	(136)	(-5.1)	+	n	?	+	+	-	-	+	+, 16	-	-	DI
48	f ?	15.2	+	-	-	-	-	(134	(-3.9)	+	n	?	?	?	-	-	-	-	-	-	
49	f	14.9	+, 5	+, 12	+, 12	-	+	(116	(-6.4)	?	↓	?	-	+	?	?	+	?	-	-	
50	m ?	12.7	+, 2	-	-	-	-	(121)	(-4.2)	x	↓	?	-	-	-	-	-	?	?	-	
51	m ✙[4]	11.1	-	-	-	-	-	(120)	(-4.0)	x	n	elementary school	-	+	+	?	+	+	+	+	
52	f ✙[5]	4.6	+, 0.3	+, 0.3	+, 0.3	-	-	?	?	x	?	n.a	+	+	-	-	-	?	?	-	
53	f ?	4.5	+, 0.9	-	-	-	-	(101)	(-1.6)	x	n	n.a.	?	?	?	?	?	?	?	?	
GSD Ib																					
54	f	30.6	+	+	-	-	-	154.2	-1.8	-	n	nurse	-	-	+	-	+	?	?	?	NP
55	m	26.0	?	?	?	?	?	157	-3.4	?	n	car-mechanic	?	+	?	+, 21	+	?	?	?	NP, IBD
56	f	24.0	+, 8	+, 13	+, 13	-	+	150	-2.6	+	n	employee	-	+	+, 1.5	-	+	?	-	-	NP, ND, IBD
57	f	23.8	+, 0.2	+, 16	+, 16	-	+	125	-8.2	+	↓↓	mentally disabled	+	+	+, 3	-	+	+, 8	+, 14	+	RRT 14, KT 24, NP
58	f ✙[6]	17.9	+, 0.5	-	-	+, 12	-	(152)	(-1.8)	+	n	tertiary education	+	+	-	-	+	+	+	-	NP, rickets
59	m ✙[7]	1.9	+, 0.3	-	-	+, 1.5	-	(77.2)	(-2.6)	x	↓	n.a.	+	-	-	-	-	?	?	-	NP
60	f ✙[8]	1.1	-	-	-	-	-	?		x	↓	n.a.	+	+	-	?	-	?	-	-	NP

A history of coma(s) as consequence of acute metabolic derangement was reported in 10 (29%) GSD Ia patients and in one out of three GSD Ib patients. Mental development was low (IQ < 65) in 1 GSD Ib patient (#57), and borderline (IQ 65 - 85) in 7 (15%) GSD Ia patients.

Complications related to hyperlipidaemia were reported infrequently. Three patients suffered from pancreatitis (#29, #31 and #38; serum triglycerides at the onset of pancreatitis 28.3, 22.1 and 9.9 mmol/l respectively). One 46-year-old woman (# 1) had atherosclerotic lesions at autopsy; she died after a second kidney transplantation (KT) because of end-stage renal disease. Concentrations of plasma cholesterol and triglycerides at latest follow-up are summarised in Table 2.2.2.

Complications related to hyperuricaemia were reported more frequently. Gouty arthritis was reported in 6 GSD Ia patients. Furthermore, nephrolithiasis was reported in 21 (57%) GSD Ia patients and in 3 GSD Ib patients. It led tot renal insufficiency in two patients (#51 and #57). One died (#51) as a consequence of secondary complications and the other (#57) underwent KT after a period of renal replacement therapy (RRT). Plasma uric acid concentrations at latest follow-up are summarised in Table 2.2.2. No difference in uric acid concentrations could be observed between patients using a xanthine oxidase (XO) inhibitor and those who did not.

Complications related to bleeding tendency were reported in 16 (41%) GSD Ia patients and in 3 GSD Ib patients. Most frequently epistaxis was mentioned.

Symptoms of anaemia were mentioned in 10 (29%) GSD Ia patients and in all 4 GSD Ib patients. Fatigue was the common complaint. Concentrations of hemoglobin at latest follow-up are summarised in Table 2.2.2. Patients with liver adenomas had significantly lower hemoglobin concentrations compared to those without liver adenomas.

Liver adenomas were reported in 23 (55%, 12 female and 11 male) GSD Ia patients and in one male GSD Ib patient. Adenomas were detected for the first time at a median age of 19 years (5 - 30). Two-third had multiple adenomas. Five patients developed serious complications as complaints of compression and bleeding into adenomas. Partial liver resection (PLR) was performed in three patients, and one patient underwent liver transplantation (LT). No transformation of adenomas to carcinomas was observed.

Proteinuria was reported in 17 (55%) GSD Ia and in one GSD Ib patient, and was detected at a median age of 21 years (14-25). All others patients tested, except one (#30), had microalbuminuria. Hypertension requiring treatment was observed in 11 (31%) GSD Ia patients and in one GSD Ib patient. Hypertension was detected at a median age of 20.5 years (16 - 42).

Table 2.2.2 Blood concentrations of cholesterol, triglycerides, uric acid and hemoglobin at latest follow-up among adult GSD Ia and GSD Ib patients

		GSD Ia					GSD Ib		
		n	mean	sd		% of total	n	median	range
cholesterol (mmol/l)		40	**7.5**	3.9	6.7 – 10.0 > 10.0	**30%** **13%**	4	**4.2**	3.8 – 4.7
triglycerides (mmol/l)		40	**9.7**	7.0	4.3 – 11.3 > 11.3	**55%** **23%**	4	**3.3**	1.3 – 5.3
uric acid (mmol/l)	XOi + XOi -	34 4	**0.38** **0.44** (0.31-0.53)[1]	0.09	> 0.45 > 0.45	**24%** **2/4**	2 2	**0.37; 0.32**[2] **0.55; 0.89**[2]	
hemoglobin (mmol/l)	liver adenomas + liver adenomas -	22 19	**7.1** **7.8** [#]	0.8 1.1	6.0 – 7.4 < 6.0 6.0 – 7.4 < 6.0	**50%** **9%** **26%** **5%**	1 3	**4.7** **6.7; 5.3; 5.0**[2]	

XOi + / - : patients using / not using a xanthine oxidase inhibitor;
liver adenomas + / - : patients with / without liver adenomas;
[1] median (ranges); [2] individual values
[#] difference between patients with and without liver adenomas: $p < 0.05$

Five patients needed RRT. In one patient (#57) this was the consequence of urolithiasis. This patient and patient #1 with progressive glomerular disease underwent KT.

To study differences in long-term outcome between patients who started stringent dietary treatment (FMs with or without UCCS during the day, and CNGDF or UCCS overnight) at different ages, three groups were distinguished: a group of 6 adult GSD Ia patients who started stringent dietary treatment before the age of 5 years and continued it till latest follow-up, a group of 10 adult GSD Ia patients who started stringent dietary treatment between the age of 5 and 10 years and continued it till latest follow-up, and a group of 24 adult GSD Ia patients who started stringent dietary treatment after the age of 10 years or who had no stringent dietary treatment at all. Outcome data of these three groups are summarised in Table 2.2.3. Patients who started stringent dietary treatment before the age of 5 years and continued this life-long, had a lower prevalence of liver adenomas ($p < 0.05$), showed less stunted adult height, a higher prevalence of hypoglycaemic comas, and lower prevalence of delayed pubertal development, gouty arthritis and hypertension (p values between 0.05 - 0.10), compared to those who started dietary treatment after the age of 10 years or had no dietary treatment at all.

Table 2.2.3 Differences in outcome between adult GSD Ia patients who started stringent dietary treatment (SDT) before the age of 5 years, who started SDT between the age of 5 and 10 years, and who started SDT after the age of 10 years or had no intensive dietary treatment at all

	SDT started < 5 years of age	SDT started 5-10 years of age	no SDT or started > 10 years of age
number of patients	6	10	24
age at latest follow-up (median (ranges))	24.3 (20.0-27.7)	24.9 (20.0-29.5)	25.8 (20.3-45.4)
adult height SDS (mean (sd))	-1.13 (1.68)	-1.45 (1.67)	-1.88 (1.26)
normal mental development	4/6 67%	8/10 80%	21/23 91%
normal pubertal development	3/5 60%*	3/9 34%	4/17 24%
hypoglycaemic coma	3/6 50%*	5/9 56%##	2/19 11%
compl.bleeding tendency	2/6 34%	5/10 50%	8/22 36%
history pancreatitis	0/6 0%	2/9 22%	1/22 5%
history gouty arthritis	0/6 0%*	1/9 11%	5/22 23%
history nephrolithiasis	1/5 20%	6/10 60%	13/21 62%
liver adenomas	0/6 0%**	5/10 50%	16/24 67%
microalbuminuria	3/4 75%	6/6 100%	13/13 100%
proteinuria	2/5 40%	2/7 29%	12/18 67%
hypertension	0/6 0%*	1/9 11%	9/20 45%

* differences between SDT started < 5 years and no SDT or started > 10 years: p between 0.05-0.10
** differences between SDT started < 5 years and no SDT or started > 10 years:p < 0.05
differences between SDT started 5-10 years and no SDT or started > 10 years: p < 0.05

Discussion

In addition to our previous reports[73,90,91], a detailed descriptive analysis of long-term outcome data of GSD I patients born before 1975 obtained from the ESGSD I was presented. A follow-up of at least 20 years was available of 43 GSD Ia and 4 GSD Ib patients. Only one other report is available of such a large group of adult GSD I patient[86]. The age distribution of this group of 37 adult GSD Ia (mean age 27.9 years, range 18 - 43) and 5 adult GSD Ib patients (mean age 21.8 years, range 19 - 25) from the United States of America (USA) is comparable with our study.

Our study represents incompletely GSD I patients treated in the participating centres since 1960 and who are born before 1975. In the ESGSD I, from 1981 till 1996, around 50 Ia and 14 Ib patients from each birth period of 5 years were included[73]. The smaller numbers born before 1975 may be due to loss to follow-up and/or higher mortality in earlier years. Loss to follow-up may have been caused by the fact that the participating clinicians were mainly paediatricians and that adult clinicians are caring for some adult patients. However, in many clinics adult GSD I patients are still treated by,

or at least known to, the 'paediatric' metabolic doctors. Furthermore, a study among adult nephrologists in the United Kingdom did not identify any adult GSD I patient who was not already known (Dr. Philip Lee, personal communication). It is therefore more likely that these patients have died with or without a diagnosis of GSD I and are therefore not included in the ESGSD I.

The prevalence of type Ib among paediatric GSD I patients is more than 20%[73]. Among the adult ESGSD I cohort, GSD Ib has a prevalence of 12%, comparable to the adult population from the USA[86]. This lower prevalence among adult GSD I patients is most likely because of higher mortality particularly secondary to infections, but also because of shortcoming of recognition and difficulties with diagnosing (enzymatic pitfalls). All four adult GSD Ib patients in the ESGSD I had episodes of neutropenia. Neutrophil dysfunction was demonstrated in the only patient tested. Two adult GSD Ib patients had symptoms of IBD. Data about neutropenia, neutrophil dysfunction and IBD among the ESGSD I cohort and the use of granulocyte colony stimulating factor in these patients are presented elsewhere[90,91].

Short stature is one of the characteristics of patients with GSD I. Almost half of the GSD Ia patients had an adult height ≤ -2.0 SDS. This is comparable with the adult group from the USA, of which 53% had a (adult) height below P5[86]. Patients who started stringent dietary treatment before the age of 5 years showed a trend to less stunted adult height. Furthermore, lower prevalence of delayed pubertal development was observed in this group. In GSD I, normal pubertal development is associated with less stunted height[73]. GSD Ib patients showed more stunted adult height compared to adult GSD Ia patients. Less well metabolic control in GSD Ib patients as a consequence of recurrent serious infections and IBD, and/or direct or indirect consequences of these infections and IBD may explain this observation. Height is also more stunted in paediatric GSD Ib patients compared to paediatric GSD Ia patients[73].

Despite dietary treatment, hyperlipidaemia was observed frequently. Hypercholesterolaemia was observed in almost 50% of the GSD Ia patients and hypertriglyceridaemia in almost all. Hyperlipidaemia was less pronounced in GSD Ib patients. Hyperlipidaemia is thought to be a result of both increased synthesis from excess of acetyl-CoA, and decreased serum clearance [1,6,34,60,61,81]. Differences in hepatic compartmentalisation of G6P may explain the difference in hyperlipidaemia between GSD Ia and GSD Ib patients, as G6P might play a regulatory role in lipid synthesis via activation of transcription of lipogenic genes[7].

Complications related to hyperlipidaemia were reported infrequently. A

history of pancreatitis was mentioned in 3 patients with severe hypertriglyceridaemia. Data about the degree of acidosis at the time of onset of pancreatitis were not available. It is still not fully elucidated whether the hyperlipidaemia in GSD I is atherogenic: in familial hypercholesterolaemia or familial combined hyperlipidaemia, a comparable degree of hyperlipidaemia is associated with cardiovascular morbidity and mortality at early age[33,44]. Among the ESGSD I cohort however, only one 46-year-old woman, who died after a second KT, had atherosclerotic lesions found at autopsy and among the 37 adult GSD I patients from the USA, only two 35-year old men had coronary heart disease[86]. It is very well possible that the development of atherosclerosis in these patients was mainly due to secondary metabolic changes in lipid metabolism related to progressive renal failure. Two in vivo-studies showed no sub-clinical signs of premature atherosclerosis in (young) adult GSD Ia patients[51,88]. Protective factors may be diminished platelet aggregation[18,41], hyperuricaemia as uric acid is a potent radical scavenger[99], increased levels of Apolipoprotein E[87], and decreased susceptibility of low-density lipoproteins to oxidation[6,7].

Complications related to hyperuricaemia were reported frequently: one-sixth of the adult GSD Ia patients had a history of gouty arthritis and more than 50% a history of nephrolithiasis. Two patients developed end-stage renal failure related to nephrolithiasis. Among the adult GSD I population from the USA, only one patient had a history gouty arthritis and renal calcifications or kidney stones were identified in 17 out of 26 patients[86]. Both complications can occur at every age, however the prevalence of nephrolithiasis is lower among patients born after 1975[73]. Improved metabolic control as a result of more intensive and stringent dietary therapy and the use of XO-inhibitors have resulted in less patients with hyperuricaemia. Despite the fact that most adult patients use a XO-inhibitor, hyperuricaemia is still observed in one-quarter of these patients. Although hyperuricaemia is a risk factor for the development of renal calcification and kidney stones, it is advisable to keep uric acid concentrations in the higher normal range, since its possible protective role in the development of atherosclerosis[99]. Hypercalciuria, a consequence of renal distal tubular dysfunction and chronic lactacidemia[55,78], which is observed in about one-third of the GSD I patients[56,75], and hypocitraturia, which is observed in almost all adult GSD I patients[96] are another risk factors for the development of renal calcifications and kidney stones. The administration of citrate in GSD I might be protective[96].

Decreased bone mineralisation is found in both young and adult GSD I patients[56,71,75]. Complications related to osteopenia were mentioned infrequently among the ESGSD I cohort. Among the adult patients from the

USA, one-third of the patients had osteonecrosis, osteopenia, frequent fractures, vertebral fractures, or a combination of these[86]. Since more and more patients will reach 5th and 6th decades, achieving adequate peak bone in childhood and young adulthood is becoming more important. To minimise the metabolic and endocrine factors in GSD I that contribute to abnormal bone matrix formation and altered mineralisation[75], dietary treatment should be optimised in both paediatric and (young) adult patients[74].

Symptoms of anaemia are mentioned rather frequently in adult GSD I patients. Anaemia in GSD I has been suggested to be associated with decreased intestinal iron absorption due to primary intestinal dysfunction or secondary to UCCS ingestion, with erythropoetin deficiency secondary to renal insufficiency and with chronic blood loss (into hepatic adenomas or intestinal in type Ib)[2,85,93]. Recently, an association with liver adenomas has been suggested. Liver adenomas produce inappropriately high levels of hepcidin mRNA. Hepcidin is a peptide hormone that inhibits the release of iron from macrophages, thereby decreasing serum transferine saturation and impairing erythropoiesis[98]. This association is confirmed by the fact that a lower hemoglobin concentration along with a trend to a higher prevalence of anaemia was demonstrated in adult GSD Ia patients with liver adenomas compared to those without liver adenomas.

Two adult patients with GSD Ia without neutropenia had episodes of bloody stools, diarrhoea and associated symptoms as abdominal pain, cramps and bloating. In both patients, faecal α1-antitrypsine was normal and colon biopsies showed little to no inflammation. IBD is a known complication in GSD Ib associated with neutropenia and neutrophil dysfunction[90]. Although 35% of the GSD Ia patients have episodes of diarrhoea[73] for which no common cause is known[93], symptoms of IBD have not been described in GSD Ia before. Maybe there is a relation with life-long use of UCCS, since in both patients symptoms vanished after discontinuation of UCCS.

More than 50% of the adult GSD I patients had one or more liver adenomas. Previous reports showed a prevalence of liver adenomas from 22% to 75% depending on the study population, with a highest prevalence observed in the adult GSD I population from the USA[49,70,84,85,86]. Liver adenomas were detected for the first time at the end of the second decade or at the beginning of the third decade. Five patients developed serious complications as complaints of compression and haemorrhage into the tumor. Adenomas are thought to have an approximately 10% risk of undergoing malignant transformation[10,58,67]. Among the adult ESGSD I cohort no malignant transformation was described. Among the adult GSD I population from the USA, one patient developed hepatocellular carcinoma[86]. The aetiology of

liver adenomas is unclear[58]. The prevalence of adenomas was lower in patients who started dietary treatment before the age of 5 years, indicating that improved metabolic control as a result of lifelong intensive dietary treatment decreases the risk or at least postpones the development of liver adenomas. This is confirmed by the observation that no adenomas were observed among a cohort of adolescent / young adult GSD I patients in Germany who started stringent dietary treatment in young childhood and continued this lifelong[19]. Furthermore, among a group of GSD Ia patients in the USA, patients with liver adenomas had started intensive dietary treatment at older age, had more stunted height and higher blood lactate concentrations compared to patients without liver adenomas[97]. If serious complications of liver adenomas develop, the subsequent therapy is surgery (partial hepatectomy or orthotopic LT)[50]. The timing of this intervention is difficult and it is not without its own hazards[58]. Especially, the lack of early clear-cut criteria to detect malignant transformation makes timing of surgery difficult[20]. LT corrects glucose homeostasis[45]. Therefore, it may also be an option in (dietary unresponsive) poorly metabolic controlled patients. However LT may be contra-indicated in these patients since not being able to comply dietary treatment strictly, may implicate poor compliance to necessary (immunosuppressive) treatment and follow-up after LT. LT does not prevent for the development of renal failure and does not improve neutrophil function in GSD Ib[64].

Another serious complication in the ageing patient is progressive renal disease[12]. The first manifestation of this glomerular disease is hyperfiltration. Following the onset of hyperfiltration, microalbuminuria and subsequently proteinuria may develop[8,14,55,76,77]. More than half of the adult GSD I patients had proteinuria, all others except one had microalbuminuria. One-third had hypertension, a subsequent consequence of the progression of renal disease. Among the adult GSD I population from the USA, 61% had proteinuria and in addition 17% microalbuminuria. Hypertension was reported in 23%[86]. The likelihood of developing end-stage renal failure and its pathogenesis are still unclear; striking is the fact of similarity in the course of renal disease with renal disease in insulin dependent diabetes mellitus. Our study suggests that stringently maintained metabolic control started in early childhood may postpone or at least slow down the progression of renal disease. This is underlined by other observations. Urinary albumin excretion is higher and more common in patients with less optimal biochemical control compared to those with optimal metabolic control[102]. Furthermore, GSD I patients with microalbuminuria had started intensive dietary treatment at an older age, and had more stunted height and higher blood lactate concentrations compared to patients without microalbuminuria[97]. The possible beneficial

effects of angiotensin converting enzyme inhibitors to prevent for the progression of renal disease in GSD I are still unclear (unpublished data). KT is a therapeutic option for GSD I patients with end-stage renal disease[50].

Among adult GSD I patients, a large variation in (history of) dietary treatment exists. In adulthood, susceptibility to hypoglycemia is less pronounced[16] and most adult patients have less stringent dietary treatment compared with younger patients[73]. However, starting stringent dietary treatment in early childhood and continuing this throughout life, hereby maintaining normoglycemia and suppressing secondary metabolic abnormalities and endocrine derangements as much as possible, is important to prevent for the short-term complications and may also prevent for, or at least postpone, the development of long-term complications. One should keep in mind however, that especially some of the long-term complications are not directly related with metabolic and endocrine abnormalities, and are therefore not, or only partial, affected by dietary treatment. Our study showed however, that patients who started stringent dietary treatment before the age of 5 years and continued this lifelong, showed a lower prevalence of liver adenomas, and a trend to lower prevalence of delayed pubertal development, gouty arthritis and hypertension, and less stunted adult height compared to those who started dietary treatment after the age of 10 years or had no dietary treatment at all. This is confirmed by Daublin et al[19] showing favourable outcome in a group GSD I patients in their late 2nd decade, early 3rd decade of life who started stringent dietary treatment in early childhood. However, stringent metabolic control may be associated with increased prevalence of hypoglycaemic comas: stringent dietary treatment makes patients more prone to develop cerebral symptoms as a result of earlier development of low blood glucose concentration during fasting as a consequence of normalised concentrations of post-prandial hormones as insulin, and as a result of loss of capability to use lactate as alternate brain fuel[23]. Recurrent hypoglycaemic comas may compromise long-term cerebral function in GSD I[73].

Most of the patients were leading fairly normal lives. Mental development, educational background and employment were comparable with healthy adults. Three female patients gave birth to three healthy children and two male patients had 5 healthy offspring. Among the adult GSD I population from the USA, two female and five male patients had children[86]. Other reports about pregnancies in female GSD I patients are scare[63]. Of four adult patients it was mentioned that they were suffering from depressive illness needing therapy, although it was not an item in our study-questionnaire. In the USA study, six out of 42 adult patients were depressed[86]. Lifelong intensive dietary

treatment 24 hours a day, in combination with serious medical problems and an unpredictable medical future seems to be a major burden for both patients and parents[38].

When considering the long-term outcome of patients with GSD I it is important to keep in mind that these patients are survivors from a period when both dietary and pharmacological treatment were less than optimal. It may be that these survivors have a 'mild' GSD I. Therefore, it is possible that a group of patients who previously would not have survived, will now reach adulthood and present with new complications, for example pulmonary hypertension[42]. It is more likely however, that patients who receive lifelong optimal treatment from early childhood on, will do better. Close monitoring remains necessary[74,92].

In conclusion, ageing GSD I patients develop complications of different organ systems. Lifelong continuation of stringent dietary treatment started in early childhood decreases the prevalence of short-term complications related to secondary metabolic derangements (gouty arthritis, nephrolithiasis, pancreatitis) and seems to prevent, or at least postpone, the development of long-term complications as liver adenomas and renal disease. However, as lifelong stringent dietary therapy is a burden for both patients and parents, further follow-up studies are warranted to confirm this.

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