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ORIGINAL PAPER

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Guidelines for management of glycogen storage disease type I – European Study on Glycogen Storage Disease Type I (ESGSD I)

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Abstract Life-expectancy in glycogen storage disease type I (GSD I) has improved considerably. Its relative rarity implies that no metabolic centre has experience of large series of patients and experience with long-term management and follow-up at each centre is limited. There is wide variation in methods of dietary and pharmacological treatment. Based on the data of the European Study on Glycogen Storage Disease Type I, discussions within this study group, discussions with the participants of the international SHS-symposium 'Glycogen Storage Disease Type I and II: Recent Developments, Management and Outcome' (Fulda, Germany; 22–25th November 2000) and on data from the literature, guidelines are presented concerning: (1) diagnosis, prenatal diagnosis and carrier detection; (2) (biomedical) targets; (3) recommendations for dietary treatment; (4) recommendations for pharmacological treatment; (5) metabolic derangement/intercurrent infections/emergency treatment/preparation elective surgery; and (6) management of complications (directly) related to metabolic disturbances and complications which may develop with ageing and their follow-up. *Conclusion:* In this paper guidelines for the management of GSD I are presented.

Keywords Collaborative European Study on GSD I · Complications · Dietary and pharmacological treatment · Glycogen storage disease type I · Guidelines, management and follow-up

Abbreviations *ACE* angiotensin converting enzyme · *CNGDF* continuous nocturnal gastric drip feeding · *ESGSD I* European Study on Glycogen Storage Disease Type I · *G6Pase* glucose-6-phosphatase · *GSD* glycogen storage disease · *IBD* inflammatory bowel disease · *PCCS* precooked cornstarch · *PCOs* polycystic ovaries · *UCCS* uncooked cornstarch

Introduction

Life-expectancy in glycogen storage disease type I (GSD I) has improved considerably. However, its relative rarity implies that experience with long-term management and follow-up at each referral medical centre is limited. In 1996, the European Study on Glycogen Storage Disease Type I (ESGSD I) was established. One of the objectives of this collaborative study was to develop guidelines for long-term management and follow-up. The necessity of such guidelines is underlined by the statement of a father of a GSD I patient: "hey doctors, we need you to meet all together and define a protocol that would be the best for everybody, if that is possible. I do not know two families who do the same thing!" (gsdnet@maelstrom.stjohns.edu; 7th August 1999). This was indeed confirmed as the ESGSD I has found that

On behalf of the participating members of the ESGSD I. Members of the ESGSD I are: Austria (W Endres, D Skladal, Innsbruck), Belgium (E Sokal, Brussels), Czech Republic (J Zeman, Prague), France (P Labrune, Clamart), Germany (P Bührdel, Leipzig, K Ullrich, Hamburg, G Däublin, U Wendel, Düsseldorf), Great Britain (P Lee, JV Leonard, G Mieli-Vergani, London), Hungary (L Szönyi, Budapest), Italy (P Gandullia, R Gatti, M di Rocco, Genoa, D Melis, G Andria, Naples), Israel (S Moses, Beersheva), Poland (J Taybert, E Pronicka, Warsaw), The Netherlands (JP Rake, GPA Smit, G Visser, Groningen), Turkey (H Özen, N Kocak, Ankara)

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there is a wide variation in long-term management and follow-up [32, 41, 42].

In this paper, guidelines are presented based on the data of the ESGSD I [32], discussions with the members of the ESGSD I group and participants of the international SHS symposium 'Glycogen Storage Disease Type I and II: Recent Developments, Management and Outcome' (Fulda, Germany; 22–25th November 2000) and on data from the literature. However, only very little evidence on long-term management exists and most of the guidelines are so called 'best practice'. Furthermore, in the management of patients with GSD I, both children and adults, one must take in account individual differences and circumstances.

In the present guidelines, deficient activity of the catalytic unit is called GSD Ia and defects of the transporter(s) GSD Ib. The management of the specific GSD Ib complications such as neutropenia, neutrophil dysfunction, recurrent infections and inflammatory bowel disease (IBD) will be discussed in a separate paper [43].

Guidelines concerning the following subjects are presented: (1) diagnosis, prenatal diagnosis and carrier detection; (2) (biomedical) targets; (3) recommendations for dietary treatment; (4) recommendations for pharmacological treatment; (5) metabolic derangement/intercurrent infections/emergency treatment/preparation elective surgery; and (6) management of complications (directly) related to metabolic disturbances and those which may develop with ageing and their follow-up.

Diagnosis, prenatal diagnosis, carrier detection

With increased knowledge of the genetic basis of GSD I, the diagnosis GSD Ia and GSD Ib can be based on clinical and biochemical findings (Table 1) combined with mutation analysis. A flowchart for the diagnosis of GSD I is presented elsewhere [31]. If patients have neutropenia, recurrent infections or IBD, mutation analysis of the glucose-6-phosphate translocase gene (G6PT, 11q23) should be performed first. Otherwise analysis of the glucose-6-phosphatase (G6Pase) gene (*G6PC*, 17q21) should be performed. If one or two mutations in *G6PC* or *G6PT* are identified, enzyme assays in liver tissue obtained by biopsy are no longer necessary to establish the diagnosis. Only if no mutations in neither *G6PC* nor in *G6PT* are identified, a glucose tolerance test should be performed. In GSD I, a marked decrease in blood lactate concentration from an elevated level at zero time is observed. This pattern is also observed in fructose-1,6-biphosphatase deficiency. An increase in blood lactate concentration is observed in other glycogen storage diseases [12]. If after a glucose tolerance test the suspicion of GSD I remains, enzyme assays in fresh liver tissue should be performed. In the case of GSD Ia, G6Pase activity is deficient in both intact and disrupted microsomes; in that of GSD Ib, a combination of deficient G6Pase activity in intact microsomes and (sub)normal G6Pase activity in disrupted microsomes is observed [29].

Biomedical targets

The following main targets for the management of GSD I should be held in mind: prevention of acute metabolic derangement, prevention of acute and long-term complications, attainment of normal psychomotor development, and good quality of life. The biomedical targets for patients with GSD I are summarised in Table 2. Biomedical targets are based on evidence of what levels of abnormality constitute an added health risk. One should attempt to approach these targets as much as closely, without deterioration in quality of life.

Table 1. Findings and complications in GSD I. Identification of mutations on both *G6PC* or *G6PT* alleles of a GSD I index case allows reliable prenatal DNA-based diagnosis in chorionic villi samples. Carrier detection in partners of a known mutation carrier is a reliable option, since a high detection rate of mutations is observed for both *G6PC* and *G6PT* [31, 40]

A	**Findings/complications (directly) related to metabolic disturbances**
Hypoglycaemia	Paleness, sweating, irritability, convulsions, coma, death, cerebral dysfunction, impaired platelet function
G6Pase deficiency (liver)	Hepatomegaly (glycogen – and fat storage)
G6Pase deficiency (kidneys)	Renomegaly, proximal tubular dysfunction
G6Pase deficiency (intestine)	Impaired intestinal function: diarrhoea/loose stools
Hyperlactacidaemia	Hyperventilation
Hyperuricaemia	Gout, urolithiasis
Hyperlipidaemia	Xanthomas, pancreatitis, cholelithiasis
Combination/unknown	Stunted growth, rounded 'doll face', truncal obesity, hypotrophic muscles
B	**Complications in the ageing patient:**
Hepatic tumours	Liver adenomas (mechanical complaints, haemorrhage), liver carcinomas
Progressive renal disease	Glomerular hyperfiltration, (micro)albuminuria, proteinuria, hypertension, decreased renal function, end-stage renal disease
Renal distal tubular dysfunction	Hypercalciuria, hypocitraturia (urolithiasis)
Osteopenia	Increased risk of fractures
Anaemia	Fatigue
Ovarian cysts	Decreased fertility, mechanical/vascular complaints
Vascular abnormalities	(Atherosclerosis), pulmonary hypertension
Type Ib: neutropenia/neutrophil dysfunction	Recurrent infections, IBD

Table 2. Biomedical targets in GSD type I

Target	Parameter
1	Preprandial blood glucose > 3.5–4.0 mmol/l (adjusted to target 2)
2	Urine lactate/creatinine ratio < 0.06 mmol/mmol
3	Serum uric acid concentration in high normal range for age and laboratory
4	Venous blood base excess > −5 mmol/l and venous blood bicarbonate > 20 mmol/l
5	Serum triglyceride concentration < 6.0 mmol/l
6	Normal faecal alpha-1-antitrypsin concentration for GSD Ib
7	Body mass index between 0.0 and + 2.0 SDS

Table 3. Recommendations for dietary therapy GSD I patients

Age	Day	Night	Glucose requirement
0–12 months	Breast feeding/formula feeding (lactose-free + maltodextrin) 2–3 h interval From 6 months: maltodextrin in formula feeding replaced by rice/corn (up to 6%)	CNGDF if possible during 12 h (50% → 35% energy), otherwise frequent feedings	7–9 mg/kg per min
1–3 years	3 meals with PCCS and 2 snacks (preferable PCCS) UCCS (4 h interval; 1.0–1.5 g/kg)	CNGDF during 12 h (35% energy), otherwise UCCS (4 h interval; 1.0–1.5 g/kg)	6–8 mg/kg per min
3–6 years	3 meals with PCCS and 2 snacks (preferable PCCS) UCCS (4–6 h interval; 1.5–2.0 g/kg)	CNGDF during 12 h (35% energy), otherwise UCCS (4–6 h interval; 1.5–2.0 g/kg)	6–7 mg/kg per min
6–12 years	3 meals with PCCS and 2 snacks (preferable PCCS) UCCS (6 h interval; 1.5–2.0 g/kg)	CNGDF during 10 h (30% energy), otherwise UCCS (6 h interval; 1.5–2.0 g/kg)	5–6 mg/kg per min
Adolescents	3 meals with PCCS and 2 snacks (preferably PCCS) UCCS (6 h interval; 1.5–2.0 g/kg)	CNGDF during 10 h (30% energy), otherwise UCCS (6 h interval; 1.5–2.0 g/kg)	5 mg/kg per min
Adults	3 meals with PCCS and 2 snacks (preferably PCCS) UCCS (6 h interval; 1.5–2.0 g/kg)	CNGDF during 8–10 h (25%–30% energy), otherwise UCCS (6–8 h interval; 2.0 g/kg). CNGDF and UCCS during night exchangeable (weekends/holidays)	3–4 mg/kg per min

Single (clinic) blood glucose estimations are not very useful because of the wide variation between days and between times of day. It is preferable to repeat these estimations at home preprandial and in the night over 48 h. The preprandial blood glucose concentrations should be above 3.5–4.0 mmol/l and adjusted to the actual urinary lactate excretion. Lactate/creatinine ratio in urine should be estimated in 12 h portions collected at home and delivered to the laboratory in the frozen state [12, 16, 25]. Serum uric acid concentration, serum cholesterol and triglyceride concentrations, and venous blood gases should be estimated during each outpatient visit. A good marker for the degree of IBD activity in GSD Ib is faecal alpha-1-antitrypsin [43].

Some evidence exists that long-term optimal metabolic control with normoglycaemia and (almost) no secondary metabolic disturbances (especially normal blood lactate concentration) reduces the risk of development of these long-term complications [10]. On the other hand, moderate hyperlactacidaemia protects against cerebral symptoms, even when the blood glucose concentration is very low, as lactate serves as an alternate fuel for the brain [13].

Recommendations for dietary treatment

The aim of dietary treatment is to achieve optimal metabolic control by mimicking the demanded endogenous glucose production, in healthy persons a result of glycogenolysis and gluconeogenesis, as closely as possible during the day and night, hereby avoiding hypoglycaemia and suppressing secondary metabolic decompensation as much as possible [12, 14]. No consensus exists about the extent of avoiding lactate production from galactose, fructose and saccharose.

Provision of exogenous glucose to GSD I patients has altered over the years [1, 6, 7, 11, 12, 15, 26, 36, 37, 45, 46]. Methods are frequent feedings, meals and snacks preferably with precooked cornstarch (PCCS), continuous nocturnal gastric drip feeding (CNGDF) and administration of uncooked cornstarch (UCSS). The application of these methods among different age groups of GSD I patients is shown in Table 3 and is very demanding, not only for both patients and parents, but also for dieticians and physicians.

Glucose requirements decrease with age (Table 3) and are calculated from the theoretical glucose production rate. Only the required amount of glucose should be given since larger quantities of exogenous glucose will cause undesired swings in blood glucose. This makes patients more sensitive to rebound hypoglycaemia and will induce peripheral body fat storage.

In infants it is not necessary to replace breast milk for a milk-based formula as long as the biomedical targets are reached. If breast milk is given, one should accept a higher urinary lactate excretion.

CNGDF can be introduced in very young infants. Both a glucose/glucose polymer solution or a sucrose-free, lactose-free/low formula enriched with maltodextrin may be used. There are no studies comparing both methods. CNGDF should be started within 1 h after the last meal, otherwise a small oral or bolus feed should be given. Within 15 min after the discontinuation of the CNGDF, a feed should be given. CNGDF can be given using a nasogastric tube or by gastrostomy. Gastrostomy is contraindicated in type Ib patients because of the problems that can arise in the case of development of IBD and the risk of local infections. A reliable feeding pump which accurately controls flow rate and has alarms in case of a fault in the system should be used. Parents need thorough teaching with meticulous explanation of both technical and medical details and should be completely confident with the feeding pump system.

Glucose is slowly released from UCCS and absorbed. During the day it prolongs the fasting period, overnight it may be used in children if CNGDF is not an option. Furthermore it may replace CNGDF in adults. No significant differences in growth and biochemical parameters between the use of CNGDF and UCCS overnight have been found [9, 47]. Theoretically, pancreatic amylase activity is insufficiently mature in children less than 1 year of age and therefore UCCS should not be started in these patients [17]. However it may be effective and useful in younger children. Starting dose is 0.25 g/kg body weight and the dose should be increased slowly to prevent side-effects such as bowel distension, flatulence and loose stools. The side-effects are usually transient. Precaution is needed in GSD Ib patients since UCCS may exaggerate IBD. UCCS can be mixed in water in a starch/water ratio of 1:2. No glucose should be added to avoid insulin release. Especially if UCCS is used overnight, an UCCS tolerance test should be performed to investigate the possible duration of the fasting period.

The total dietary plan should provide 60%–65% of the total energy intake from carbohydrates, 10%–15% from protein, and the reminder from fat (preferably vegetable oils with high linoleic acid content). Lactose, fructose and sucrose should be restricted except for fruits, vegetables and (small amounts of) milk products.

Recommendations for pharmacological treatment

Xanthine oxidase inhibitor (allopurinol)

Uric acid is a potent radical scavenger and it may be a protective factor in the development of atherosclerosis. Therefore, it is recommendable to accept serum uric acid concentrations in the higher ranges of normal. To prevent for gout and urate nephropathy, allopurinol should be started if serum uric acid concentration exceeds the upper level of normal for age and laboratory despite optimal dietary treatment. Starting dose is 10 mg/kg per day, three times orally (maximum 900 mg/day).

Bicarbonate/citrate

If, despite optimal dietary treatment, venous blood base excess is below –5 mmol/l or venous blood bicarbonate is below 20 mmol/l, it is recommended to correct lactacidaemia. Until now, (sodium) bicarbonate was advised: starting dose 1–2 mmol (85–170 mg)/kg per day orally in four doses. Apart from correcting lactacidaemia, bicarbonate also induces alkalinisation of the urine, hereby diminishing the risk for the development of urolithiasis and nephrocalcinosis [12]. Recently it was found that hypocitraturia that worsens with age occurs in patients with GSD Ia [44]. Therefore alkalinisation with citrate may be even more beneficial in preventing or ameliorating urolithiasis and nephrocalcinosis. Starting dose: potassium citrate 10 mEq orally every 8 h (adults), 5–10 mEq every 12 h (children). Check for potassium concentration (DA Weinstein, oral communication).

Angiotensin converting enzyme inhibitor/additional blood pressure lowering drugs

If persistent microalbuminuria is present a (long-acting) angiotensin converting enzyme (ACE) inhibitor should be started to slow-down or prevent further detoriation of renal function, in analogy to diabetic nephropathy. Starting dose depends on choice of ACE inhibitor. Additional blood pressure lowering drugs should be started if despite ACE inhibition blood pressure remains above P95 for age.

Supplementation of vitamins and minerals

The dietary plan should be carefully designed and followed to provide enough essential nutrients as recommended by the WHO. Otherwise supplementation should be started. Special attention is needed regarding calcium (limited milk intake) and vitamin D. Furthermore, increased carbohydrate metabolism needs sufficient vitamin B1.

Iron

After excluding other causes (vitamin B12, folic acid deficiency), in the case of (micro- or normochronic) anaemia, oral iron can be given. Starting dose 3 mg Fe^{2+}/kg per day. After 2–3 months, the effects should be evaluated. Iron given parenterally is more effective, especially in older patients.

Miscellaneous

To reduce the risk of cholelithiasis and pancreatitis, triglyceride-lowering drugs (nicotinic acid, fibrates) in GSD I seem only indicated if serum triglyceride levels

remain above 10.0 mmol/l despite optimising dietary treatment.

Life-long hypercholesterolaemia in young adult GSD Ia patients is not associated with the development of premature atherosclerosis [20, 39]. Therefore, cholesterol-lowering drugs seem not to be indicated in younger GSD I patients. In adult patients, however, progressive renal insufficiency may deteriorate hyperlipidaemia. This 'renal' contribution to the hyperlipidaemia may play a more important role in the development of atherosclerosis. Therefore, if in these adults, despite optimising dietary treatment and reducing microalbuminuria/proteinuria (ACE inhibitors), cholesterol remains strongly elevated (> 8–10 mmol/l), statins (hydroxymethylglutaryl-coenzyme-A-reductase inhibitors) may be indicated, although no evidence exists.

Fish-oil seems not be indicated since its positive effect on serum triglyceride and cholesterol does not last and it even may lead to increased lipoprotein oxidation hereby increasing atherogenecity [3].

At this moment it is our opinion that there is no place for growth hormone therapy in GSD I since it may enhance growth during therapy but does not exert a positive influence on final height. Also oestrogens and testosterone to enhance pubertal development seem not be indicated since they have a negative influence on final height.

For oral anticonceptives, see [27].

Metabolic decompensation/intercurrent infections/emergency treatment/preparation for elective surgery

Parents and patients need to recognise different stages in metabolic decompensation: from the impending metabolic situation with paleness, sweating and abnormal behaviour (irritability), to more serious metabolic decompensation with decreased consciousness and hyperventilation, to severe metabolic crisis with coma, convulsions and ultimately death. Impending metabolic decompensation can be elicited by trivial events such as short delay of a meal, or an intercurrent illness. Parents and patients should respond by giving/taking a glucose drink (low osmolarity), and after recovery, slowly released carbohydrates. If unsuccessful, repetitive small amounts of a glucose solution should be administered by gastrostomy, by nasogastric tube, or orally to overcome the time to intravenous therapy. An emergency protocol in case intravenous therapy is needed is summarised in Table 4. Since not all (emergency) doctors are familiar with GSD I, it is advisable for patients to always have an emergency protocol with them.

During infections, the frequent supply of exogenous glucose must be maintained. However anorexia, vomiting and diarrhoea do endanger this. Furthermore, glucose metabolism is increased in the case of fever. Replacement of meals and snacks by glucose polymer drinks is often needed. Nasogastric drip feeding 24 h a day may be necessary. If this is not tolerated, a hospital admission is needed for intravenous therapy.

Prior to elective surgery, bleeding time (platelet aggregation) should be normalised by continuous gastric drip feeding during 24 h for 1 week or by intravenous glucose infusion over 24–48 h [12]. Close peri-operative monitoring of blood glucose and lactate concentration is essential.

Management of complications (directly) related to metabolic disturbances and complications that may develop with ageing and follow-up guidelines

By adjusting metabolic control in GSD I patients as optimal as possible, the occurrence of symptoms/complications directly related to metabolic disturbances will diminish: growth improves, liver size decreases, the risk of gout, urolithiasis, xanthomas and pancreatitis decreases, platelet function normalises, and, as long as cerebral symptoms (coma, convulsions) of acute metabolic decompensation can be prevented, cerebral function is preserved [6, 12, 32]. Optimal metabolic control implies, however, that patients are more prone to

Table 4. Emergency protocol in case of acute metabolic decompensation in GSD I

Emergency procedure for acute metabolic decompensation in patients with GSD I

1. Intravenous glucose solution should be given immediately, initially as bolus injection (in 10 min), followed by 125%–150% of normal glucose requirement (depending on body temperature) for 12 h followed by 100%–125% of normal glucose requirement thereafter

Age	Bolus	Normal glucose requirement
0–12 months	500 mg glucose/kg (5 ml 10% glucose/kg)	7–9 mg/kg per min
1–6 years	400 mg glucose/kg (4 ml 10% glucose/kg)	6–8 mg/kg per min
6–12 years	350 mg glucose/kg (3.5 ml 10% glucose/kg)	5–6 mg/kg per min
Adolescents	300 mg glucose/kg (3 ml 10% glucose/kg)	5 mg/kg per min
Adults	250 mg glucose/kg (2.5 ml 10% glucose/kg)	3–4 mg/kg per min

2. Metabolic acidosis should be corrected with intravenous bicarbonate solution

[a]GSD I (von Gierke disease) is an inborn error of carbohydrate metabolism. Due to deficient glycogenolysis and gluconeogenesis, patients develop hypoglycaemia and hyperlactacidaemia after a short period of fasting, for instance in case of high fever in combination with vomiting and diarrhoea or at surgical procedures

develop these cerebral symptoms since they become more glucose-dependent and the ability to use lactate as a fuel for the brain reduces.

With ageing several complications may develop (Table 1).

Liver adenoma, single or multiple, may develop in the second or third decade. One should realise that on ultrasound focal fatty sparing may be thought to be adenomas, especially if observed before 10 years of age [21, 23]. Adenomas may remain constant during many years of intensive dietary treatment. Also a reduction in size and or number of adenomas has been observed following optimal metabolic control. Liver adenomas may cause mechanical complaints and acute haemorrhage. Furthermore, they may transform into carcinomas. To screen for adenomas and to follow them in size and number, ultrasonography should be performed regularly (Table 5). Increase in size of nodules or change to poorly defined margins necessitates further investigations such as CT scans or MRI [12]. In addition, serum α-fetoprotein and carcino-embryonal antigen can be used to screen for malignant transformation. However, both CT and MRI are not highly predictive of malignant transformation [19], and of both tumour markers, false negative results in the case of malignant transformation of adenoma(s) in GSD I have been reported [4]. The management of liver adenomas is either expectant or surgical [26]. In severe cases of adenomas, enucleation or a partial liver resection are therapeutic options. By recurring adenomas or on suspicion of malignant transformation,, orthotopic liver transplantation is a therapeutic options if metastases are not present. It corrects also glucose homeostasis [18], but it does not prevent the development of renal failure [28]. Immunosuppression may even worsen renal function.

Progressive renal disease in GSD I starts with a 'silent' period of hyperfiltration already in the first years of life [2]. Microalbuminuria (urinary albumin excretion of 30–300 mg/24 h or 20–200 μg/min) may develop at the end of the first or in the second decade of life and is an early detectable manifestation of the progression of renal disease [5, 33,34]. Estimation of urinary albumin excretion should be done regularly (Table 5). Microalbuminuria observed before 5 years of age must be

Table 5. Follow-up guidelines for patients with GSD I. For additional guidelines for GSD Ib patients see [43]. (*AFP* alpha fetoprotein, *CEA* carcino-embryonal antigen)

History[a]
Frequency: age 0–3 years every 2 month; 3–20 years every 3 months; adults every 6 months
(A)symptomatic hypoglycaemia; hospitalisation (causes); physical complaints; frequency of infections, epistaxis, bruises, diarrhoea; medicines; social life
Dietary history
Frequency: age 0–3 years every 2 month; 3–20 years every 3 months; adults every 6 months
Coping and compliance; analysis (carbohydrates, protein, fat, calcium, vitamins) adjustment based on history, physical examination, biochemical results and dietary analysis
Physical examination[a]
Frequency: age 0–3 years every 2 month; 3–20 years every 3 months; adults every 6 months
Height, weight, liver size, spleen size, blood pressure, skin, joints
48 h blood glucose curve: estimated at home; preprandial and during the night
Frequency: 0–20 years every 1–2 months; adults every 2–3 months
Urinary lactate excretion (lactate/creatinine ratio): 4–8 frozen 12 h samples collected at home
Frequency: age 0–3 years every 2 month; 3–20 years every 3 months; adults every 6 months
Routine investigations[a]
Frequency: age 0–3 years every 2 month; 3–20 years every 3 months; adults every 6 months
Total blood cell count with differential; serum uric acid, cholesterol, triglycerides, venous blood gas analysis, (platelet aggregation/bleeding time)
Investigations for detection or follow-up of complications
Serum creatinine, urea, sodium, potassium, calcium, phosphate[a] every 6 months
Serum ASAT, ALAT, AP, γGT, protein, albumin[a]: every 6 months
If renal or hepatic complications are present: on demand
Urine sediment[a]: every 6 months
Urine microalbumin, protein, creatinine, calcium, citrate[a]: 0–5 years: every year; > 5 years: every 6 months
If microalbuminuria/proteinuria is present or if using ACE-inhibitors: every 3 months
Creatinine clearance (GFR measurement): > 5 years: every year
Ultrasonography abdomen[a]: 0–10 years: every year; > 10 years: every 6 months
Liver: size, parenchym, adenomas, other focal anomalies
Kidneys: size, calcifications, stones
Spleen: size
Ovaries: cysts
If liver adenoma(s) are present: ultrasonography and serum αFP, CEA every 3 months
CT/MRI: on demand
Ultrasonography heart and ECG: > 10 years: every year
Bone densitometry: > 5 years: every 1–2 years
Faecal-1-antitrypsin: on demand
If anaemia is present: iron status, vitamin B12 and folic acid status
If (acute) abdominal pain is present: blood amylase, ERCPG, ultrasonography liver, pancreas, ovaries
At diagnosis, the marked investigation and DNA analysis *G6Pase* gene or *G6PT* gene (enzyme-activities in fresh liver tissue)

differentiated from urinary excretion of small proteins caused by proximal tubular dysfunction. Some evidence exists that optimal metabolic control will reduce the incidence and diminish the progression of renal disease [38, 48]. In analogy to diabetic nephropathy, an ACE inhibitor should be started if persistent microalbuminuria exists over a period of 3 months. A moderate dietary restriction of protein is recommended. Blood pressure should be below P95 for age and gender and, if necessary, additional blood pressure lowering drugs should be started. Haemodialysis, continuous ambulatory peritoneal dialysis and renal transplantation are all therapeutic options for end-stage renal disease in GSD I.

In contrast to renal proximal tubular dysfunction that is related to poor metabolic control [8], renal distal tubular dysfunction with hypercalciuria and hypocitraturia [35,44] is also observed in more optimally controlled patients. It contributes to the development of urolithiasis. Alkalinisation of the urine may be protective. Citrate supplementation seems to be most beneficial in preventing or ameliorating urolithiasis and nephrocalcinosis [44]. Regular ultrasonography of the kidneys is recommended (Table 5).

Osteopenia in GSD I seems to be a result of both decreased bone matrix formation and decreased mineralisation [24, 30]. Decreased bone mass formation is already observed in prepuberal patients. Limited peak bone mass formation increases the risk of pathological fractures later in life. Important for normal bone formation is suppressing secondary metabolic and hormonal disturbances, especially chronic lactacidaemia. Calcium intake and vitamin D intake should be within the ranges recommended by the WHO. Monitoring bone density by quantitative CT or dual-energy X-ray absorptiometry is recommended.

Anaemia in GSD I is observed at all ages. However, especially adolescent and adult patients have complaints [32]. If there are complaints, and after excluding other causes (vitamin B12 or folic acid deficiency), a trial with iron should be started (orally, and if unsuccessful, parenterally).

Polycystic ovaries (PCOs) have been observed in adolescent and adult female patients [22]. The pathophysiology is still unresolved. The effects on reproductive function are also still unclear. In some patients, complaints of enlarged cysts have been reported, which in the case of vascular disturbances, cause acute abdominal pain. Abdominal pain caused by vascular disturbances related to PCOs should be differentiated from pancreatitis (serum and urine amylase, CT, endoscopic retrograde cholangiopancreatography) and haemorrhage into an adenoma (decrease in blood haemoglobin, CT/MRI). In severe cases, surgical resection of the PCOs may be indicated.

Although GSD I is associated with chronic hyperlipidaemia, atherosclerosis in the ageing GSD I patient is remarkably rare [20, 39]. A vascular complication that may cause more morbidity and mortality in the ageing patient is pulmonary hypertension followed by progressive heart failure. Its pathophysiology is still unclear. It may develop in the second decade or later. No specific therapeutic options are available. Monitoring by ECG and cardiac ultrasonography is recommended after the first decade.

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