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Glycogen storage disease type I

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**Summary, conclusions, general
discussion and future perspectives**



Chapter 7

Summary and conclusions

Glycogen storage diseases (GSDs) are inherited disorders that affect glycogen metabolism. Glycogen storage disease type I is 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. As a result of inadequate glucose production patients have severe fasting hypoglycaemia with secondary biochemical abnormalities such as hyperlactacidaemia, hyperuricaemia and hyperlipidaemia. Untreated patients show 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.

In the most likely model, the G6Pase complex consists of a catalytic subunit, G6Pase, situated on the luminal side of the endoplasmic reticulum (ER) and one or more membrane transporters. Deficient activity of the catalytic unit of G6Pase underlies GSD Ia. The gene encoding this unit (G6PC) has been localised to band q21 of chromosome 17. Disorders caused by 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 either GSD Ib, Ic or the putative Id, all had mutations in the G6P translocase gene (G6PT) identified in band q23 of chromosome 11. This is consistent with clinical findings, as GSD I can clinically be divided in only two distinguished phenotypes: GSD Ia patients who 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.

The aim of (dietary) treatment is to prevent hypoglycaemia hereby suppressing secondary metabolic derangements as much as possible. Maintaining normoglycaemia will reduce morbidity (and mortality) associated with the disease. Methods of dietary treatment are frequent carbohydrate-enriched feedings/meals (FMs), continuous nocturnal gastric drip feeding (CNGDF), and the use of uncooked (corn)starch (UCCS).

As a result of this intensive dietary treatment, life-expectancy in GSD I has improved considerably. However, with ageing numerous complications may develop such as liver adenomas, which have the potential to transform into carcinomas, progressive renal disease, anaemia, osteopenia, ovarian cysts, pancreatitis and vascular abnormalities.

GSD I has an estimated prevalence among newborns of one in 100.000. No single metabolic centre has therefore experience with large series of patients. Also in literature there is paucity of data on management and

outcome in GSD I. The reports available focus on relatively small groups of especially paediatric patients^{20,35,106,135,136,138,162,164}.

To share experience and to combine knowledge, the collaborative European Study on GSD I (ESGSD I) was initiated in 1996; 26 colleagues from 16 metabolic centres from 12 countries participated. Objectives were to increase knowledge about the management, clinical course and long-term outcome in paediatric and adult patients with GSD I, to study in more detail the (long-term) complications, to develop new therapeutic strategies, and to develop guidelines for long-term management and follow-up.

Long-term management and outcome of patients with Glycogen Storage Disease type I, and implications for treatment and follow-up (chapters 2.1, 2.2, 6.1, 6.2)

The first aim of the ESGSD I was to increase knowledge about clinical course, management, and outcome of patients with GSD I.

In *chapter 2.1* data on these aspects obtained in the ESGSD I are presented¹¹⁷. 231 GSD Ia and 57 GSD Ib patients were included. Median age of data collection was 10.4 years (range 0.4 - 45.4) for Ia and 7.1 years (0.4 - 30.6) for Ib patients. From 1981 until 1996, ca. 50 GSD Ia and 14 GSD Ib patients born in each period of 5 years were included, with smaller numbers born before 1981. Patients born before 1981 were underreported most likely because they had died (undiagnosed) in earlier years. 80% of the GSD Ia and 90% of the GSD Ib patients showed symptoms before the age of 1 year, with a median age of 6 months and 4 months respectively.

Among the ESGSD I cohort, a wide variation in methods of dietary treatment was reported: at latest follow-up, during daytime, more than 90% used FMs, and 70% had UCCS in addition; overnight 41% used CNGDF and 45% UCCS. In most patients, FMs were started immediately after the diagnosis GSD I was suspected. UCCS during daytime was introduced with increasing concentration in most patients after the age of 1 year. Overnight, the majority of the paediatric patients from Northwestern European countries used CNGDF, and the majority of the paediatric patients from Southern- and Eastern European countries UCCS. Restriction of lactose and fructose was reported in two-third of the patients. In almost 10% of the patients it was reported that dietary compliance was low.

The ESGSD I showed that current intensive dietary treatment has led to a decrease in mortality as a consequence of (acute) metabolic derangement. However, after starting intensive dietary treatment, episodes of coma were still recorded in one-third of the patients, and episodes of acute metabolic derangement necessitating admission in two-third. The majority of episodes

of acute metabolic derangement appeared at the time of infections and gastrointestinal complaints. Episodes of acute metabolic derangement were reported more frequently in GSD Ib patients compared to GSD Ia patients.

The ESGSD I demonstrated normal long-term cerebral function as long as episodes of hypoglycaemic comas were prevented: 16% of the patients who had not experienced hypoglycaemic coma, had retarded or borderline mental development. This is comparable with the normal population. Of the patients who had experienced one or more episodes of hypoglycaemic coma, 32% had retarded or borderline mental development.

Most of the GSD I patients were leading fairly normal lives and were educated or had professions comparable to the normal population. At least 10% of the adult patients were suffering from depressive illness needing treatment.

Among the ESGSD I cohort, stunted height was observed frequently, even in paediatric patients who started stringent dietary treatment at early age. Height was between -2.0 and -2.5 standard deviation score (SDS) in 9% of the GSD Ia and 15% of the GSD Ib patients, and < -2.5 SDS in 27% and 38% respectively. Patients with delayed pubertal development or bone maturation had more stunted (adult) height. Body mass index (BMI) was above p90 in 23% of the patients.

Secondary metabolic abnormalities as hyperlipidaemia and hyperuricaemia were observed frequently despite intensive dietary treatment. Mild hypercholesterolaemia was observed in 41% of the GSD Ia and in 9% of the GSD Ib patients and severe hypercholesterolaemia in 12% and 5% respectively; mild hypertriglyceridaemia was observed in 19% of the GSD Ia and 36% of the GSD Ib patients and severe hypertriglyceridaemia in 73% and 43% respectively. Hyperuricaemia was observed in 29% of the patients using xanthine oxidase (XO)-inhibitors and in 33% of those who did not. Related complications as skin xanthomas, pancreatitis, urate related nephrolithiasis, gouty arthritis and tophi occurred less frequently in more recent years, as an effect of partial correction of the secondary metabolic abnormalities, as a result of stringent dietary treatment.

The ESGSD I showed that of the complications developing with ageing, progressive renal disease and complications related with liver adenomas are the two major causes of (future) morbidity and mortality. Among the entire ESGSD I cohort, 13% had proteinuria, and another 31% microalbuminuria. Of the GSD I patients above the age of 25 years, 50% had proteinuria and all others microalbuminuria. Hypertension, a subsequent consequence of the progression of renal disease, was observed in 7%. Six patients had elevated serum creatinine concentrations, in two of them this was the

consequence of urolithiasis and not of glomerular disease. Of the other four, three required renal replacement therapy (RRT) of whom two underwent kidney transplantation (KT). Among the entire ESGSD I cohort, 16% had one or more liver adenomas. Of the GSD I patients above the age of 25 years, more than two-third had liver adenomas. Six patients developed serious complications as complaints of compression and haemorrhage into the tumour(s). Three of them underwent surgical resection, two liver transplantation (LT). Among the ESGSD I cohort, no malignant transformation was observed. Other significant complications reported were anaemia (ca. one-third of the GSD Ia patients and two-third of the GSD Ib patients), osteopenia, diarrhoea, pulmonary hypertension, and ovarian cysts.

In *chapter 2.2* data of the adult GSD I patients included in the ESGSD I were elaborated to study long-term outcome in more detail¹²⁰. 60 GSD I patients born before 1975 were identified among the ESGSD I cohort. Included were 47 patients with a follow-up of at least 20 years (43 GSD Ia patients: median age 25.6 years, range 20.0 - 45.4; 4 GSD Ib patients: median age 25.0 years, range 23.8 - 30.6).

Most of the adult 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 subjects. Adult height was < -2.0 SDS in 46% of the GSD Ia and 3 out of 4 GSD Ib patients. A history of hypoglycaemic 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 other patients except one GSD Ia patient), and hypertension (31% of the GSD Ia patients; 1 GSD Ib patient). Three adult GSD Ia patients underwent partial liver resection (PLR), and one GSD Ia patient LT. Four GSD Ia patients and one GSD Ib patients needed RRT, of whom two underwent KT.

Among the adult GSD I patients, a large variation in history of dietary treatment was registered. At latest follow-up, three-quarter of the patients

used FMs during daytime and more than 50% UCCS in addition. Overnight, one-fourth used CNGDF and almost 50% UCCS. Almost one-fourth of the adult GSD I patients had no dietary treatment at all.

In adult patients who started stringent dietary treatment before the age of 5 years and continued this lifelong, a lower prevalence of liver adenomas was demonstrated, along with a trend to a lower prevalence of delayed pubertal development, gouty arthritis, hypertension, and stunted adult height compared to those who started dietary treatment after the age of 10 years or had no dietary treatment at all. However, stringent dietary treatment started at early age was also associated with increased prevalence of hypoglycaemic comas.

Data obtained in the ESGSD I on neutropenia, neutrophil dysfunction, infections, IBD, and the use of granulocyte colony-stimulating factor (GCSF) in GSD Ib are presented in detail in the thesis of Gepke Visser^{148,149,150}. In a nutshell, neutropenia was found in 95% of the GSD Ib patients; in 64% it was documented before the age of 1 year, however in 18% it was not first noted before the age of 6 years. In 90% neutropenia was intermittent, without a clear cycle course. Neutrophil function was abnormal in all investigated GSD Ib patients: a wide variety of disturbances in neutrophil functions was observed. Almost 75% of the GSD Ib patients had symptoms of IBD, including peri-oral infections, peri-anal infections and protracted diarrhoea. All patients with IBD had neutropenia. GCSF was started in one-third of the GSD Ib patients. In these patients the number and severity of infections decreased and the severity of IBD improved subjectively. Furthermore, neutrophil counts increased and simultaneously leucocyte counts and platelet counts decreased. The most serious complication of GCSF treatment was marked splenomegaly.

One of the main objectives of the ESGSD I was to develop guidelines for the (long-term) management and follow-up of patients with GSD I. In *chapter 6.1* these guidelines are presented¹¹⁸. These guidelines were based on data obtained in the ESGSD I and on data from literature, and were discussed with the participants of the ESGSD I and with the participants of the international SHS-symposium 'Glycogen Storage Disease type I and II: Recent Developments, Management and Outcome' (Fulda, Germany 2000). Guidelines were developed 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. In *chapter 6.2* additional guidelines for the management of the specific complications in GSD Ib related to neutropenia and neutrophil dysfunction as recurrent infections and IBD are presented¹⁵¹.

Conclusions long-term management and outcome of patients with Glycogen Storage Disease type I, and implications for treatment and follow-up

- The ESGSD I has added to the understanding of the management, clinical course, and outcome of GSD Ia and GSD Ib.
- Progressive renal disease and complications related to liver adenomas are two major causes of morbidity and mortality in adult GSD I patients.
- Among patients with GSD I, a wide variation in methods of dietary and pharmacological treatment exists.
- In GSD I, current intensive dietary treatment has led to a decrease in mortality as a consequence of acute metabolic derangement. However, such episodes of acute metabolic derangement are still a major cause of morbidity.
- In GSD I, life-long continuation of stringent dietary treatment started in early childhood decreases 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 progressive renal disease. Stringent dietary treatment may increase however the risk to develop episodes of acute metabolic derangement.
- Long-term cerebral function in GSD I is normal as long as episodes of recurrent hypoglycaemic comas are prevented.
- Despite intensive dietary treatment, stunted height is still one of the clinical abnormalities in GSD I. GSD Ib patients have more stunted height compared to GSD Ia patients.
- More than 50% of the GSD I patients have delayed bone maturation and more than 50% delayed pubertal development. Patients with normal bone maturation and normal pubertal development have less stunted height.
- Hyperlipidaemia is more pronounced in GSD Ia patients compared to GSD Ib patients.
- In GSD I, absence of cardiovascular morbidity and mortality despite life-long hyperlipidaemia is observed. This makes GSD I an interesting model to elucidate possible protective mechanisms against the development of atherosclerosis.

- In GSD I, the presence of liver adenomas is associated with lower hemoglobin concentrations and a trend to higher prevalence of anaemia.
- Lifelong intensive dietary treatment, in combination with serious medical problems and an uncertain future, is a major burden for both patients and parents.
- Among GSD I, type Ib is more frequent than formerly stated: more than 20% of all paediatric GSD I patients have type Ib.
- GSD Ib patients are more prone to episodes of acute metabolic derangement.
- Almost all patients with GSD Ib have intermittent neutropenia; however, in one-sixth of these patients neutropenia is not observed before the age of six years.
- Neutropenia and neutrophil dysfunction and IBD in GSD Ib are causally related.
- In GSD Ib, IBD is underdiagnosed.
- In view of the uncertainty of the positive effects and (long-term) side effects of GCSF, prospective controlled trials are warranted to clarify the indication(s) for the use of GCSF in GSD Ib.
- For the first time, extensive guidelines for the management of GSD Ia and GSD Ib patients are formulated.

*DNA-based diagnosis in Glycogen Storage Disease type Ia
(chapters 3.1, 3.2 and 3.3)*

The gene (G6PC) encoding the G6Pase catalytic unit was identified in 1993^{83,131} and the gene (G6PT) encoding the G6P translocase protein in 1997^{4,46}. In our centre, mutation analysis of the G6PC and G6PT genes was initiated in 1996 and 1999 respectively.

In *chapter 3.1*, analysis of the G6PC gene of 16 GSD Ia patients is described¹¹³. DNA was extracted from peripheral blood from leucocytes. The coding regions and intron/exon borders were amplified by PCR into six fragments. These PCR amplified fragments were subjected to single strand conformational polymorphism (SSCP). Fragments showing an aberrant SSCP migration pattern were subjected to direct sequencing by an automated sequencer. On both alleles of the G6PC gene of all 16 GSD Ia patients mutations were identified. Four novel mutations were found: 175delGG, R170X, G266V, V338F. 175delGG creates a frame shift, resulting in a stopcodon at position 59 leading to truncated protein, which is expected to be unstable at cellular level. Also the nonsense mutation R170X leads to a

truncated protein. Both G266V and V338F are missense mutations. Although no transient expression analyses were performed, different arguments give reason to expect that both mutations are true mutations and not sequence variations with minor effects on the activity of the gene product: in 216 alleles of healthy subjects these substitutions were not found, the segregation of both mutations through the families was as expected, and in mouse liver G6Pase, both positions and its direct surroundings are conserved, indicating its importance for functional activity. In the 13 GSD Ia patients from Northwestern Europe, Q347X was identified most frequently (5/26), eleven additional mutations accounted for the remaining 21 mutant alleles. In both patients from Italian descent and in the patient from Moroccan descent, R83C was homozygously present.

In *chapter 3.2* analysis of the G6PC gene of two Dutch siblings with GSD Ia is described¹¹⁵. Both brother and sister were heterozygous for 175delGG/867delA. The frameshift mutation 867delA had not been identified before. It results in a stopcodon at position 300. Although no transient expression analyses were performed, this mutation leads to a truncated protein with, most likely, completely abolished G6Pase activity. Both siblings shared the same G6PC gene mutations, and both had comparable life-long stringent dietary treatment. However, phenotype regarding residual G6Pase activity in liver tissue (10% vs. no residual activity), adult height (+ 2.0 SDS vs. - 0.4 SDS) and hepatomegaly (2 cm vs. 9 cm. below costal margin) differs. Differences in residual G6Pase activity may be caused by differences in quality of liver tissue, by hepatic zonation of G6Pase activity or by the different methods used to measure G6Pase activity. The in vitro observed variability however, could also reflect real difference in residual G6Pase activity. Also glycogen breakdown or glucose production by alternative pathways may play a role. Furthermore, other (unknown) modifying genes may be involved.

In *chapter 3.3* an overview is given of the DNA-analyses we performed in 30 families with GSD Ia¹¹⁶. In 21 families the diagnosis GSD Ia was already established by enzyme analyses, in 9 families mutation analysis was performed to establish the diagnosis. In all 30 patients mutations were identified on both alleles of the G6PC gene. Two DNA-based prenatal diagnosis were performed successfully. Carrier detection was performed in two partners of GSD Ia patients; no aberrant SSCP patterns were detected. Among the 30 families (except for 3 families, all from Northwestern Europe) we investigated, R83C (16/60), 158delC (12/60), Q347X (7/60), R170X (6/60) and Δ F327 (4/60) were found most frequently. Nine other mutations accounted for the

other 15 mutant alleles. In literature, among 300 families, 56 different mutations in the G6PC gene were described: 11 frameshift, 3 splice site, 7 nonsense, 34 missense, and 1 codon deletion mutation. Except for R83C (32.5%), Q347X (14.3%) and the splice site mutation 727G→T (11.3%) no other mutation accounted for more than 5%. However, in patients of some specifically defined ethnic and/or geographical origin, one or two predominantly occurring mutations were found: Jewish patients (R83C, 93%), Chinese patients from the United States of America (USA) (R83H, 70%), Hispanic patients (459insTA, 50% and R83C, 28%), Japanese patients (727G→T, 88%), patients from South-Europe (R83C, 48% and Q347X, 21%) and Turkish patients (R83C, 60%). Evidence for a clear genotype-phenotype correlation could be established neither from our data nor from literature. A newly developed flowchart for the diagnosis of GSD Ia and Ib was constructed: usually the diagnosis GSD Ia or GSD Ib can be based on clinical and biochemical abnormalities combined with mutation analysis, instead of enzyme assays in (fresh) liver tissue obtained by biopsy.

Conclusions DNA-based diagnosis in Glycogen Storage Disease type Ia

- Increased knowledge of the genetic basis of GSD Ia and Ib allows DNA-based diagnosis in leucocytes and prenatal DNA-based diagnosis in chorionic villus samples instead of enzyme assays in liver tissue obtained by (fetal) biopsy.
- If, based on clinical and biochemical abnormalities, the suspicion on GSD I arises, it is malpractice to perform enzyme studies in liver tissue or function tests prior to DNA-analysis of the G6PC and/or G6PT gene.
- Using SSCP prior to automated sequencing of exons revealing an aberrant SSCP pattern is a reliable and save procedure to identify mutations in the G6PC gene.
- The high detection rate of mutations in the G6PC and G6PT genes allows carrier detection in partners of a known G6PC or G6PT mutation carrier.
- Among ou GSD Ia population, five novel mutation were identified: 175delGG, R170X, G266V, 867delA, and V338F.
- Allelic heterogeneity exist among Caucasian GSD Ia patients from Northwestern Europe and the USA, whereas allelic homogeneity exists in GSD Ia patients from some specifically defined ethnic and/or geographical origin.
- In GSD I, no genotype-phenotype correlation could be detected from our data, nor when combined with data from the literature.

Osteopenia in Glycogen Storage Disease type Ia (chapter 4)

Although the occurrence of symptoms related to osteopenia is a known complication in ageing GSD I patients, only very limited information is available about bone mineral density (BMD) in GSD I.

We studied lumbar spine BMD in pre-pubertal, adolescent and adult patients with GSD Ia using dual energy X-ray absorptiometry (DXA). Cross-sectional and longitudinal results are presented in *chapter 4*¹⁹.

Z-scores were calculated for lumbar spine areal BMD (BMD_{areal} in g/cm^2), areal BMD corrected for delayed bone maturation ($BMD_{\text{bone age}}$ in g/cm^2) and volumetric BMD (BMD_{vol} in g/cm^3) which is independent for (stunted) height. Prepubertal GSD Ia patients ($n=8$) had normal BMD (median Z-scores BMD_{areal} -0.6, $BMD_{\text{bone age}}$ -0.5 and BMD_{vol} -0.5), whereas adolescent patients ($n=12$) and adult patients ($n=9$) had significantly reduced BMD (BMD_{areal} -2.3, $BMD_{\text{bone age}}$ -1.6, BMD_{vol} -2.0 and BMD_{areal} -1.9, BMD_{vol} -1.5 respectively). Our longitudinal study, showing a stable BMD_{areal} but a trend to a decrease in BMD_{vol} in prepubertal patients during follow-up, did not clarify if the difference in BMD between prepubertal and adolescent/adult patients reflected a diminished accretion of BMD during childhood or reflected historical differences in treatment. Follow-up studies are warranted to clarify this. In adolescent and adult GSD Ia patients, BMD_{areal} and BMD_{vol} were reduced but stable during follow-up. Especially patients with delayed bone maturation were at risk for reduced BMD. No correlation between parameters of (short-term) metabolic control and BMD could be detected. Daily calcium-intake was within recommended allowances ranges. Abnormal biochemical results included hypomagnesaemia (29%), hypercalciuria (34%) and reduced tubular resorption of phosphate (21%). Blood concentrations of parathyroid hormone, osteocalcitonin, vitamin D, and alkaline phosphatase were generally within normal ranges. Theoretically, a number of metabolic and endocrine disturbances influencing both bone matrix formation and bone mineralisation might explain reduced lumbar spine BMD in GSD Ia. Bone matrix formation could be influenced negatively by reduced non-enzymatic glycosylation, insulinopenia, altered growth hormone levels, altered insulin like growth factor levels, endogenous glucocorticoid excess and hyperlactacidaemia. Bone mineralisation in GSD Ia might be influenced negatively by low calcium intake (lactose restriction), decreased intestinal calcium absorption, chronic lactacidaemia, and renal tubular dysfunction related to the disease itself or related to chronic acidaemia. Furthermore, decreased muscle function and decreased physical activity may play a role in decreased bone mass formation.

Although the underlying pathophysiology of reduced BMD in GSD Ia remains still unsolved, metabolic control should be optimised to correct as

much as possible metabolic and endocrine abnormalities that may negatively influence bone matrix formation and bone mineral accretion in GSD Ia.

Conclusions osteopenia in Glycogen Storage Disease type Ia

- Prepubertal GSD Ia patients have normal lumbar spine BMD, whereas adolescent and adult GSD Ia patients have significantly reduced lumbar spine BMD.
- The difference in BMD between prepubertal and adolescent/adult GSD Ia patients may reflect the natural course of bone mineralisation in GSD Ia with diminished mineral accretion during childhood. However, it may also reflect improvement of metabolic control during more recent years.
- A number of endocrine and metabolic sequelae of GSD Ia may influence normal bone matrix formation and normal bone mineralisation. The precise pathophysiology of reduced BMD in GSD Ia remains unsolved.
- In GSD Ia, dietary treatment, including calcium – and vitamin D intake, should be optimised to prevent hypoglycaemia and secondary endocrine and metabolic abnormalities that may have a negative influence on both normal bone matrix formation and mineralisation.

Hyperlipidemia and Atherosclerosis in Glycogen Storage Disease type I (chapters 5.1, 5.2 and 5.3)

Despite intensive dietary treatment, hyperlipidaemia is still one of the biochemical abnormalities in GSD Ia. Furthermore, microalbuminuria is observed in almost all patients starting in the 2nd decade of life as a consequence of progressive renal disease. Both hyperlipidaemia and microalbuminuria are known atherosclerotic risk factors. Although more and more GSD Ia patients reach adult age, information about accelerated atherosclerosis is scarce.

The results of a study to investigate whether GSD Ia is associated with premature atherosclerosis are described in *chapter 5.1 and 5.2*^{142,143}. Nine adult GSD Ia and nine matched healthy controls were studied. Lipid profiles were significantly unfavourable in the patient group: cholesterol and triglycerides concentrations and cholesterol/high density lipoprotein (HDL)-cholesterol ratio were strongly elevated. However, no differences compared to the control group could be found using non-invasive vascular measurement techniques suitable for detecting premature atherosclerosis as blood pressure, ankle-brachial indices, aortic distensibility, and intima media thickness segments. The relative myocardial wall thickness was higher, and the early

to arterial filling ratio lower in the patient group suggesting concentric remodelling of the left ventricle. The importance of this finding as well as the pathogenic mechanisms behind this remodelling are still unclear.

Although GSD Ia is characterised by severe hypertriglyceridaemia and hypercholesterolaemia, the exact mechanism of hyperlipidaemia in GSD Ia is still not elucidated. Both decreased plasma lipid clearance and increased lipid production may play a role.

We studied lipogenesis and the susceptibility of low-density lipoproteins (LDL) to oxidative modification in two patients with GSD Ia. Results are described in *chapter 5.3*⁷. Plasma triglyceride concentrations (18.2 and 11.9 mmol/l respectively) and cholesterol concentrations (15.0 and 10.8 mmol/l) were strongly elevated. These increased concentrations were almost solely caused by increases in the very-low-density lipoproteins (VLDL) fraction. A more than 40-fold increase in newly synthesised VLDL-palmitate was found, along with a 7-fold increase in absolute cholesterol synthesis. Furthermore, a decreased acetyl-coA pool enrichment (during [1-¹³C]acetate infusion) was observed. Fatty acid composition of LDL particles and, to a lesser extent, of VLDL particles showed increased saturated fatty acid (SFA) contents and decreased polyunsaturated fatty acid (PUFA) contents. Susceptibility of both LDL and VLDL to oxidative modification was markedly lowered in GSD Ia patients, as indicated by an increased lag time and a decreased propagation time. Furthermore, lower propagation rates of LDL with higher SFA and lower PUFA contents was found. No role for the antioxidants α - and γ -tocopherols, β -carotene, ubiquinol and uric acid could be demonstrated.

Conclusions hyperlipidemia and atherosclerosis in Glycogen Storage Disease type I

- GSD Ia is not associated with premature atherosclerosis, despite the existence of longstanding dyslipidaemia and microalbuminuria
- In GSD Ia, a strongly elevated VLDL-palmitate synthesis (40-fold) and cholesterologenesis (7-fold) is observed, associated with increased lipoprotein SFA content
- The decreased acetyl-CoA pool enrichment reflects a higher glycolytic flux towards the acetyl-CoA pool, contributing to the higher fatty acid synthesis
- The relative high lipoprotein SFA content may well play a role in the protection of plasma lipoproteins against oxidative modification in GSD Ia
- Fish oil should not be used in GSD Ia as it leads to increased lipoprotein oxidizability by increasing the lipoprotein PUFA content

Addendum

No specific studies concerning progressive renal disease and hepatic tumours in GSD I are described in this thesis. Since both complications cause great concern in ageing GSD I patients, and since both complications will be discussed in paragraph 7.3 *general discussion and future perspectives*, a concise literature review regarding these two complications is given in this addendum.

Progressive renal disease in Glycogen Storage Disease type I

Although the original pathological description of GSD I in 1929 by von Gierke was titled 'hepatonephromegalia glycogenika'⁴⁷ not much attention was drawn to the renal complications in GSD I until 15 years ago. This changed after a report on end-stage renal disease leading to death in three adult GSD I patients¹⁷.

In GSD I, proximal and distal renal tubular functions as well as glomerular renal functions are at risk^{19,79,122}. Proximal renal tubular dysfunction is observed in poorly metabolically controlled GSD I patients; amelioration is observed after starting intensive dietary treatment¹⁸. Distal renal tubular dysfunction is observed in optimally controlled patients as well, and may lead to hypercalciuria and hypocitraturia^{64,123,156}, risk factors for the development of urolithiasis and nephrocalcinosis. Another contributing factor to the development of urolithiasis and nephrocalcinosis is hyperuricaemia. Normal to near normal uric acid concentrations as a result of stringent dietary treatment and the use of XO-inhibitors, along with (potassium) citrate administration¹⁵⁶, has led to a reduced risk for the development of urolithiasis and nephrocalcinosis in GSD I¹¹⁷.

The first manifestation of glomerular renal disease in GSD I is hyperfiltration¹⁷. In paediatric and young adult patients, increased glomerular filtration rate (GFR)^{10,121}, indicating hyperfiltration, and increased effective renal plasma flow (ERPF)⁵⁴, indicating hyperperfusion, can be demonstrated. We revealed a non-linearity in the course of GFR and ERPF: an increase till the age of 10 to 15 years, after which a decrease is observed [unpublished data]. In the 2nd decade of life, microalbuminuria develops, which may progress to proteinuria^{10,163,117}. Subsequently, hypertension and progressive renal insufficiency may develop leading to end-stage renal disease in the 3rd-5th decade of life. Striking is the similarity in natural course of renal disease in GSD I and nephropathy in insulin dependent diabetes mellitus (IDDM)⁹⁷. Both RRT (hemodialysis or continuous ambulatory peritoneal dialysis) and KT are therapeutic options for end-stage renal disease in GSD I^{19,75}. KT does not improve glucose metabolism^{19,30}.

Little is known about the mechanism underlying the development of this progressive renal disease in GSD I. Deficiency of G6Pase within the proximal renal tubulus cells may cause tubular dysfunction with glomerular hyperfiltration as a secondary phenomenon⁷⁹. Hyperlactacidaemia may also induce hyperfiltration and hyperperfusion^{140,163}. Glomerular hyperfiltration itself is important in the development of glomerular sclerosis⁴⁵. Hyperlipidaemia may accelerate this process. Histological examinations of renal biopsies of GSD I patients with proteinuria showed focal segmental glomerulosclerosis as the predominant finding along with glomerular basement alterations, glomerular hypertrophy, intestinal fibrosis, tubular atrophy, glycogen deposits in proximal tubular cells and some arteriosclerosis¹⁴⁶.

Some evidence exists that intensive dietary treatment instituted in early childhood, hereby preventing biochemical and endocrine abnormalities, may prevent, delay, or at least slow down progressive renal disease in GSD I. So far, most GSD I patients who developed end-stage renal disease had not received effective dietary treatment from an early age¹⁷. Furthermore, urinary albumin excretion was higher and more common in patients with less optimal metabolic control compared to those with optimal metabolic control¹⁶³. Moreover, patients with microalbuminuria started intensive dietary treatment at an older age, and had more stunted height and higher blood lactate concentrations compared to patients without microalbuminuria¹⁵⁷.

In renal disease with proteinuria (diabetic nephropathy), angiotensin converting enzyme (ACE)-inhibitors are used as reno-preservative drugs^{45,111}. ACE-inhibitors have been proven to reduce microalbuminuria and proteinuria by lowering systemic blood pressure, reducing intra-glomerular pressure by post-glomerular vasodilatation, and counteracting the proliferative effects of angiotensin II, a potent renal growth promoting factor which causes glomerular hypertrophy and glomerulosclerosis in the remaining nephrons after initial nephron loss⁴⁴. The degree of proteinuria has been shown to correlate with the rate of renal deterioration. Therefore, intervention with ACE-inhibitors to reduce urinary protein excretion may prevent for or at least slow down the progression of renal disease. Except for some case-reports^{9,102,109} no studies are available yet to support the use of ACE-inhibitors in GSD I. Nevertheless, ACE-inhibitors are recommended, and used, in GSD I patients with microalbuminuria or proteinuria^{37,117,118}.

Hepatic tumours in Glycogen Storage Disease type I

A number of different focal abnormalities of the liver have been described in GSD I: adenoma, carcinoma, focal fatty infiltration, focal fatty sparing,

and focal nodular hyperplasia⁸². Adenomas, which may have the potential to progress into hepatocellular carcinomas, are of most importance⁷⁴. The overall prevalence of adenomas among the ESGSD I cohort was 16%¹¹⁷. However, more than 70% of the patients older than 25 years had adenomas. Previous reports show a prevalence from 22% to 75% depending on the study population with a lowest prevalence observed in the youngest population studied and a highest prevalence observed in the oldest GSD I population studied (18-43 years)⁸¹. Adenomas can be solitary and multiple, develop in general in the mid - to end 2nd decade of life and progression in size and number is common¹¹⁷. However, also regression after initiating dietary treatment has been described¹⁰⁵.

Liver adenomas may be complicated by complaints of compression, haemorrhage into the tumour, malignant transformation and an association with severe anaemia has been postulated. At least 10 cases of hepatocellular carcinoma in GSD I have been described^{12,99}, most likely all cases of transformation of adenomas into carcinomas and not of malignancy occurring de novo⁸². Among the ESGSD I cohort, no patients with hepatocellular carcinoma were reported¹¹⁷. Recently it was demonstrated that liver adenomas produce inappropriately high levels of hepcidin mRNA. Hpcidin, a peptide hormone, has been implicated in controlling the release of iron from intestinal cells and macrophages and an association with chronic, iron-unresponsive anaemia in GSD I has been made¹⁵⁸. Severe anaemia is indeed observed more often in GSD I patients with adenomas compared to those without^{120,157}.

Although a number of theories have been postulated, the pathogenesis of liver adenomas is still unclear^{12,82}. Altered glucagon/insulin levels, but also inappropriate levels of other growth factors have been suggested to play a role. Moreover, glycogen storage itself has been recognised as a pre-neoplastic condition. Furthermore, in GSD I, increased concentrations of malonyl-CoA inhibits mitochondrial β -oxidation by inhibiting carnitine palmitoyl-transferase I, thereby facilitating oxidation of fatty acids in peroxisomes favouring the generation of hydrogen peroxide. Oxidative stress leads to alterations in gene expression and mutagenesis¹⁰⁰. It may also activate proto-oncogenes as fos, myc, p53 and ras, which may play a role in the development of liver tumours¹².

Although the pathophysiology is not clear, some evidence exist that optimal metabolic control started at early age may prevent for, or at least postpone the development of liver adenomas. Patients with liver adenomas started intensive dietary treatment at older age, had more stunted height and higher blood lactate concentrations compared to patients without adenomas¹⁵⁷. Furthermore, in a cohort of 13 GSD Ia patients, who started stringent dietary

treatment in early childhood and who were since then in excellent metabolic control, no liver adenomas could be detected in their 2nd and early 3rd decade of life²⁶.

To screen for lesions and to follow them to monitor size and number, ultrasonography should be performed on a regular basis^{77,82}. Increase in size of nodules or change to poorly defined margins, necessitates further investigations such as CT scans and MRI³⁷. Furthermore, serum α -fetoprotein and carcino-embryonal antigen may be used to screen for malignant transformation. However, both CT and MRI are not highly predictive of malignant transformation⁸¹ and of α -fetoprotein both false positive and false negative results have been reported^{24,89}.

The management of liver adenomas in GSD I is either expectant or surgical⁸². In severe cases of a solitary large adenoma, enucleation or PLR are therapeutic options. However, the recurrence of tumours in the remaining liver parts is well known⁹¹. LT should be considered in patients with unresectable and dietary unresponsive multiple adenomas if associated with serious complaints of compression or haemorrhage and may be also in case of severe hepcidin induced anaemia. Furthermore, LT should be considered in case of the development of carcinoma, as long as metastases are not present³¹. LT corrects also glucose homeostasis⁶⁹, but it does not prevent the development of renal failure⁹¹. In fact, immunosuppressive medicines may even worsen renal function.

General discussion and future perspectives

It is evident that during the 73 years since Von Gierke's first clinical pathological description of GSD I, major progress has been made in the understanding of the clinical, biochemical and genetic features of this disease, offering diagnostic and therapeutic options^{21,95}. The ESGSD I has made an important contribution to this progress by studying for the first time clinical course, treatment, and outcome among a large group of paediatric and adult patients with GSD I^{117,120,148,150}. As a result of intensive dietary treatment including meals around the clock, the administration of UCCS during daytime and overnight, and CNGDF, morbidity and mortality as a consequence of metabolic derangement has decreased, prevalence of complications directly related to metabolic and endocrine abnormalities has decreased, and quality of life and prognosis have improved. However, with ageing, GSD I patients develop complications of different organ systems. Some of these long-term complications are directly related to metabolic and endocrine abnormalities, and are therefore affected by dietary treatment. Other complications are not or only partially related, and are therefore not or only partial affected by

dietary treatment.

Some significant remarks concerning the ESGSD I should be made. Data on clinical course, treatment, and outcome are all retrospective. This implicates that patients may have been lost to follow-up, important clinical data may have been lost, formerly unknown complications may not have been recognised in earlier days, and that (dietary) treatment has been changed dramatically over the years. Particularly the long-term outcome data are determined by patients with GSD I that are survivors from a period when dietary and pharmacological treatment was less than optimal. It is hoped that those who receive more optimal treatment from an early stage will have less complications in the future. On the other hand, these survivors may have a 'mild' GSD I (although genotypes of these adult patients do not differ from genotypes of younger patients) and that a group of patients who previously would not have survived, will now reach adulthood and present with new complications.

The ESGSD I has led for the first time to extended recommendations for long-term treatment and follow-up of patients with GSD Ia and GSD Ib^{118,151}. However, only very little evidence for both treatment modalities and follow-up in GSD I exists and most of the guidelines are therefore by definition 'best-practice'. From the data of the ESGSD I it was not possible to identify clear differences in outcome between different dietary regimes as a result of many confounding factors, which we were not able to disentangle because of the retrospective character of the study. An important confounding factor is dietary compliance, which was not documented carefully in the ESGSD I. In literature, studies comparing long-term outcome between different dietary regimes as well as (placebo-controlled) pharmacological studies are also lacking. This implicates that about some hallmarks, but especially about practical interpretation, of dietary and pharmacological treatment and follow-up, controversy still exists.

To meet these open questions in the future, the ESGSD I has been continued as the international study on glycogen storage disease type I (ISGSD I). The continuation of this collaboration makes it possible to have continuous follow-up of a large group of patients, to study in detail differences in outcome between patients with different dietary regimes, to verify and adjust the recommendations as formulated from the ESGSD I, and to develop new therapeutic strategies. Furthermore the pathophysiology, the management and the possibility of prevention of the (long-term) complications should be studied in more detail. Especially the exact causative nature of most of these complications are still open questions. Ultimately, we hope to

come with evidence-based consensus guidelines for the management of GSD I. All participants from the ESGSD I have agreed to continue their collaboration. Furthermore, two more metabolic centres from Europe (Lyon, France and Huddinge, Sweden) and two metabolic centres from the USA (Durham and Boston) requested to participate. The effect of this extension will not only be an increase of the number of patients enrolling the study, but also an increase in knowledge since both centres from the USA are leading centres on clinical and research aspects regarding GSD I. Next to this, also the impact of the results of the study will increase: succeeding (consensus) guidelines on the management of patients with GSD I will have even a more international effect.

A network of excellence has been created to serve as a communication tool between the ISGSD I participants and the co-ordination centre in Groningen, but also to communicate with other medical professionals, patient support groups, and patients and parents themselves. This network has been constructed by Topshare® (Wageningen, The Netherlands). Encoded data from case record files will be interchanged between co-ordination centre and the participating centres by this network as well as preliminary results, reports and other information within the ISGSD I. These data are not available for other site visitors than the ISGSD I participants. Separate accesses have been constructed for medical professionals containing first (ongoing) results of the ISGSD I and for patients, parents and general public containing information about GSD I with respect to pathophysiology and guidelines regarding (prenatal) diagnosis, dietary and pharmacological treatment, and management and follow-up of short-term and long-term complications.

The main objectives of the ISGSD I are: (1) to study short-term and long-term outcome of paediatric and adult patients with GSD I both retrospectively and prospectively in more detail; (2) to verify and to adjust the recommendations concerning treatment and follow-up in GSD I; (3) to evaluate differences in outcome between different dietary regimes prospectively; (4) to establish a genotype-phenotype correlation in GSD Ia and GSD Ib; (5) to serve as a central database to store, process and deliver patient data and patients material; and (6) to come to evidence-based consensus guidelines for the management of GSD I.

The first objective is to study short-term and long-term outcome of paediatric and adult patients with GSD I related to methods and accuracy of (dietary) treatment and to the extent of metabolic control. The ESGSD I has learnt us about the treatment and course of the disease and its short-term and long-term complications^{117,120,148,150}. However, as pointed out before, in the ESGSD I, long-term outcome is determined by patients with GSD I that

are survivors from a period when dietary and pharmacological treatment was less than optimal. Although these survivors may have a mild GSD I and patients that survive nowadays may present even a more complicated course, most probably GSD I patients who receive optimal treatment from early childhood on, will have less complications in the future. Some evidence exists already that patients who start intensive dietary treatment in early childhood have a favourable clinical course. By maintaining blood glucose concentration in the high normal range and avoiding lactate production from early age on, normal growth and prevention or at least postponement of the development of long-term complications as liver adenomas and renal disease have been observed²⁶. The other way round, having long-term complications as liver adenomas and renal disease has been associated with less optimal metabolic control, whereas patients without these complications started intensive dietary treatment in early childhood¹⁵⁷. Another important question that will be addressed by a long-term follow-up of a large cohort of patients is if novel, formerly unknown complications related to GSD I will develop in the ageing patients.

A second objective of the ISGSD I is to verify and to adjust the recommendations concerning treatment and follow-up in GSD I as proposed from the ESGSD I^{118,151}. The following study-questions will be addressed: Is it possible for the individual patient to meet the proposed biomedical targets as agreed in the ESGSD I? Do the proposed biomedical targets improve the short-term and long-term outcome of the disease? And finally, do patients who met the proposed medical targets have a better (short-term) outcome and less (long-term) complications in terms of morbidity and mortality compared with patients who did not?

A third objective is to study differences in outcome between different dietary regimes. 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 day and night, hereby avoiding hypoglycaemia and suppressing secondary metabolic derangements as much as possible^{37,118}. The fundamentals of providing exogenous glucose to GSD I patients are well known and broadly used: frequent meals, the administration of UCCS, and CNGDF^{3,16,20,52,133,134,161,162}. However, about the practical interpretation still controversy exists: the frequency of meals during the day, the frequency of UCCS administration during the day and the timing in relation with the other meals, CNGDF versus UCCS overnight, the composition of CNGDF (glucose solution or a combination of carbohydrates, protein, fat and vitamins), and the rate of exogenous glucose provision during day and night (100-200%

and 100%-150% of normal hepatic glucose production rate respectively). Also about the necessity and the degree of galactose, fructose, and saccharose restriction opinions differ. These sugars need the G6P-pathway in the liver to be metabolised to glucose. In GSD I, ingestion of these sugars results in hyperlactacidaemia³³. Moderate hyperlactacidaemia may protect against cerebral symptoms, even when blood glucose concentration is very low, as lactate serves as an alternate fuel for the brain³⁴. Furthermore, milk products, fruit and vegetables are important sources for vitamins and minerals. On the other hand, stringent maintenance of normolactacidaemia by complete avoidance of lactose and fructose ingestion may lead to a favourable outcome²⁶.

A fourth objective is to study a genotype-phenotype correlation in GSD Ia and GSD Ib. Since substantial heterogeneity in phenotype in both GSD Ia and GSD Ib is observed, a genotype-phenotype correlation would be very helpful to adjust dietary, pharmacological, and follow-up strategies based on genotype¹¹⁸. We were not able to establish a genotype-phenotype correlation for GSD Ia from our own data nor from data from literature¹¹⁶, nor were Matern and colleagues⁹² for GSD Ia and GSD Ib. A difficulty in establishing a clear genotype-phenotype correlation is that both GSD Ia and GSD Ib are genetically heterogenous disorders and there are no true common mutations; a lot of patients are compound heterozygous for different mutations. However, recently, accurate expression analyses have been performed for most mutations in the G6PC and G6PT genes^{21a,132} which may facilitate establishing a genotype-phenotype correlation. Another difficulty in establishing such a correlation is that phenotype of GSD I patients is in great extent a result of (dietary) treatment. Moreover, even siblings sharing identical G6PC genotypes and sharing nearly identical treatment may have variable phenotypes^{107,115}.

A fifth objective is to serve as a central database to store, process and deliver patient data and patients material necessary to answer some of the specific study-questions tackled by (groups of) participating centres and addressed below.

A sixth objective is to come to evidence-based consensus guidelines for the management of GSD I. The ESGSD I has led for the first time to extended recommendations for long-term treatment and follow-up^{118,151}. As pointed out above, only little evidence on both treatment and follow-up exists however, and most of these guidelines are therefore so called 'best-practice'. We assume that the ISGSD I will yield (some of) this evidence, and that the guidelines presented in 2008 will be more evidence-based.

In the following paragraphs, most of the unsolved clinical and biochemical questions in GSD Ia and GSD Ib will be discussed, along with plans for future studies. Efforts to tackle these questions may not only be of benefit for GSD I patients (therapy, follow-up), but may also be of benefit in the understanding of the (patho)physiology of other, more common, disorders. Inborn errors of metabolism are unique experiments of nature and have proven to be valuable models to study the biological roles of metabolites and metabolic pathways. The pathophysiological association in GSD Ia and GSD Ib between the defect and the occurrence of the different (long-term) complications is largely unknown. Resolving the biological role of the defect on the pathogenesis of these specific complications may therefore be of benefit for both GSD I patients and patients with other disorders. The ISGSD I offers the possibility to tackle some of the unsolved questions in studies amongst larger groups of GSD I patients. Recently generated G6Pase-deficient mice⁸⁴ and naturally G6Pase-deficient Maltese puppies¹³ are available to study these questions in more detail. Moreover, specific pharmacological inhibitors (chlorogenic acid derivatives) of G6Pase activity and G6P translocase activity^{58,60} can be used in *in vitro* and *in vivo* studies to create (acute) GSD Ia and GSD Ib models.

structure and function of the glucose-6-phosphatase complex, genetics, gene therapy

The topology of both G6Pase and G6P translocase are known: human G6Pase has a transmembrane helical structure with the N-terminus and four loops localised on the luminal side of the ER^{59,103} and human G6P translocase has a transmembrane helical structure with five loops localized on the luminal side of the ER¹⁰⁴. The exact structure of the G6Pase complex, however, has still to be elucidated. Both G6Pase and G6P translocase are tightly associated with the ER membrane, and are highly hydrophobic, making purification difficult. As the active hydrolysing site of the G6Pase complex is situated inside the lumen of the ER, the substrate G6P has to be transported into the ER and the products phosphate and glucose back to the cytosol. Two models have been proposed: a multicomponent translocase catalytic model^{5,6,154}, consisting of a catalytic G6Pase unit and specific membrane transporter proteins for G6P, phosphate and glucose, and a conformation-substrate transport model¹²⁸ in which catalytic and transport activities are performed by one or two tightly coupled proteins. A debate over the feasibility of various aspects of the two proposed models of the G6Pase complex persists, and the functional/structural relationships of the individual components of the system remains a hot topic of interest⁴¹.

Increased knowledge about the genetic basis of GSD I creates the possibility to generate knock-out animal models and to develop new

therapeutic strategies^{4,46,83,90,92,113,115,116,131}. GSD Ia knock-out mice have been generated by targeted disruption of G6PC^{84,21a}. Homozygous mice show all the characteristics of GSD I patients except for hyperlactacidaemia and, without appropriate treatment, they die shortly after birth as a consequence of hypoglycaemia. An increasing number of inborn errors of metabolism are being treated with enzyme replacement therapy: Gaucher disease, Pompe disease, Fabry disease, and most recently mucopolysaccharidosis type I¹⁵⁵. Enzyme replacement therapy in GSD Ia is not an option: the protein G6Pase can not be expressed in a soluble form and must be embedded correctly in the membrane of the ER and coupled with other proteins to be functional^{21a}. Somatic gene therapy, targeting DNA encoding G6Pase to the liver and the kidney is therefore an attractive possibility²². By infusing an adenovirus vector containing the G6PC gene into G6Pase-deficient mice, restoration of hepatic G6Pase activity to 19% of control values was demonstrated. This led to normalisation of glucose, lipid and uric acid profiles, decrease of liver and kidney glycogen content, improved physical growth and 100% survival rate¹⁶⁶. G6Pase expression was restored to about 50% of normal activity resulting in normalisation of fasting blood glucose in Maltese puppies with GSD I after applying adeno-associated virus vectors encoding G6Pase¹¹. A combined adenovirus and adeno-associated virus vector mediated gene transfer led to sustained G6Pase expression in both liver and kidneys and correction of the GSD Ia phenotype in G6Pase-deficient mice for at least 12 months¹³⁷.

glucose - and fat metabolism in GSD I, atherosclerosis

Although the broad outlines of the biochemical pathways in GSD I are well known, some puzzling questions concerning carbohydrate and fat metabolism and their relation in GSD I are unanswered.

In GSD I, theoretically no hepatic glucose production is possible. However, a variable but significant endogenous hepatic glucose production is demonstrable, particularly if exogenous glucose provision is low^{23,141}. The mechanism behind this endogenous glucose production in GSD I is still not elucidated. Three possible mechanisms have been postulated: residual G6Pase activity or activity of non-specific phosphatases may result in hydrolysis of G6P to glucose; increased glycogen turnover may result in hepatic glucose production from the hydrolytic activity of amylo-1,6-glucosidase; and autophagy combined with lysosomal acid α -glucosidase activity may lead to glucose production. Studies favouring and studies objecting these hypotheses exist^{21,65,124}. We hope to clarify this by determination of hepatic glucose fluxes in both GSD I patients and animals models. Tracer dilution techniques and mass isotopomer distribution analysis (MIDA) in plasma glucose and urinary

paracetamol-glucuronide will be used to determine rates of glucose production, glycogen synthesis and breakdown, and gluconeogenesis^{28,29}.

Apart from abnormalities in carbohydrate metabolism, GSD I is associated with distinct hyperlipidaemia. Both plasma triglyceride and cholesterol concentrations are increased³², and only partially respond to intensive dietary treatment^{36,53,86}. Increased concentrations of cholesterol and triglycerids are found in VLDL and LDL fractions, whereas HDL cholesterol and apolipoprotein A-1 concentrations are decreased^{1,85,86}. Besides an increased number of VLDL and LDL particles, indicated by increased apolipoprotein B concentration, these particles are also increased in size due to accumulation of triglycerides^{1,85}. The exact mechanism underlying the development of hyperlipidaemia in GSD I has not yet been elucidated, but evidence exists that it is a result of both increased synthesis and decreased serum clearance⁸. Recently, we demonstrated strongly increased hepatic lipogenesis and cholesterolgenesis associated with an increased flux through the acetyl-CoA pool⁷. This enhanced glycolytic flux increases lipid synthesis. Also elevated hepatic G6P levels may play a role via activation of transcription of lipogenic genes⁹⁶. If elevated hepatic G6P levels play a role in activation of lipogenic genes, it might be that compartmentalisation of G6P explains the difference in the degree of hyperlipidaemia between GSD Ia and GSD Ib patients⁸ as was demonstrated in the ESGSD I¹¹⁷. In GSD Ia, G6P concentrations are theoretically increased in both cytoplasm and in the lumen of the ER, whereas in GSD Ib, G6P concentration is likely increased in cytoplasm, but decreased in the lumen of the ER. In addition to increased synthesis, decreased plasma clearance of lipids seems to play also a role in the hyperlipidaemia in GSD I¹²⁷. Lipolysis of circulating lipoproteins has been found to be impaired in GSD Ia: a decreased lipoprotein lipase activity is demonstrated in patients with GSD I^{40,86}, along with decreased uptake of LDL particles by fibroblast of GSD I patients⁸⁷. The effects of the balance between lipid storage and lipolysis in adipose tissue on the hyperlipidaemia in GSD I is still a puzzle. By studying lipid production and lipid clearance simultaneously in both patients and animal models using - amongst other techniques - tracer dilution techniques and MIDA, we hope to elucidate the mechanisms underlying this hyperlipidaemia in GSD Ia and GSD Ib.

Despite severe hyperlipidaemia, cardiovascular morbidity and mortality in GSD I is observed infrequently^{138,120,143} and if observed, it may be related to secondary metabolic changes caused by progressive renal disease¹¹⁷. Using non-invasive vascular measurement techniques, we¹⁴² and others⁷⁶ were not able to demonstrate sub-clinical premature atherosclerosis in young adult GSD Ia patients despite lifelong severe hyperlipidaemia¹⁴². A comparable

degree of hyperlipidaemia in familial hypercholesterolemia or familial combined hyperlipidemia, is a strong risk factor for cardiovascular morbidity and mortality at an early age^{51,66}. Protective factors in GSD I may be diminished platelet aggregation^{25,62} or increased levels of apolipoprotein E¹³⁹. Recently, we demonstrated a decreased susceptibility of LDL to oxidation⁷, possibly related to the altered lipoprotein fatty acid profile in GSD Ia with a relative high SFA content. Moreover, in GSD Ia, the total radical trapping ability is increased indicating increased antioxidative defense in plasma which may protect against lipid peroxidation¹⁵⁹. The complete protecting mechanism however, has not been elucidated yet. Understanding this mechanism in detail may have major implications for GSD I patients (abandon treatment with fish oil; keep uric acid levels in the high normal range) but also in terms of therapeutic possibilities for patients with hyperlipidaemic disorders complicated by premature atherosclerosis.

progressive renal disease

Progressive renal disease is one of the most serious complications which may develop in the ageing GSD I patient^{117,120,138}. A concise literature review is given in the *Addendum*. Questions that should be addressed in the near future are what is the pathophysiology of renal disease in GSD I, and is it possible to prevent or slow down (further) deterioration of renal function.

The pathophysiology of renal disease in GSD I is still unclear. Striking is the similarity in pattern and progression of renal dysfunction in GSD I and IDDM. GSD I may therefore be an interesting model to unravel the pathophysiology of diabetic nephropathy and conversely patients with GSD I have much to gain from the innovative and vastly greater body of research carried out in diabetes⁹⁷. Evidence exists that glomerular hyperfiltration itself is important in the development of glomerular sclerosis⁴⁴, and that the hyperlipidaemia may accelerate this process⁶⁸. The initial trigger for hyperfiltration, however, has not been elucidated: deficiency of G6Pase within the proximal renal tubulus cells may cause tubular dysfunction with glomerular hyperfiltration as a secondary phenomenon⁷⁹; (lact)acidaemia itself causes hyperfiltration^{140,163}; an increased flux through the pentose phosphate pathway yields triose phosphate molecules, which are precursors of diacylglycerol which plays a role in the intrarenal renin-angiotensin system via the protein kinase C pathway⁹⁷; and elevated G6P levels in renal tubular cells may activate the transcription of genes encoding proteins involved in proliferation (e.g. transforming growth factor beta).

Optimal dietary treatment instituted in early childhood may prevent, delay, or at least slow down progressive renal disease in GSD I^{120,157,163}.

However, despite intensive dietary treatment, drug intervention may be necessary. In diabetic nephropathy, ACE inhibitors are used as renopreservative drugs^{45,111}. Intervention with ACE inhibitors in order to reduce urinary protein excretion in GSD I may prevent or at least slow down the progression of renal disease. Some case-reports^{9,102,109} have demonstrated a decrease in urinary protein excretion after starting ACE inhibitors in proteinuric and albuminuric patients. Own observations showed that the individual short- and long-term response to ACE-inhibitors in GSD I vary largely regarding the extent and duration of reduction of urinary protein excretion (unpublished data). Although, ACE-inhibitors are already widely used and recommended in GSD I patients with microalbuminuria or proteinuria^{37,117,118}, no studies are available yet to underline the evidence for this use. It will be worthwhile to execute a study to investigate the short-term and long-term effects of ACE-inhibitors (or Angiotensin II receptor blockers⁸⁸) on the preservation of renal function in GSD I patients, taking the extent of urinary protein excretion (hyperfiltration without microalbuminuria, microalbuminuria or proteinuria), metabolic control, ACE genotype, protein intake (low protein diet versus normal protein diet)⁴³ and sodium balance⁷¹ in account.

liver adenomas and related complications

Another serious complication in the ageing GSD I patient is the development of liver adenomas^{12,74,82,117}. A concise literature review is given in the *Addendum*. Questions that should be addressed in the near future are what is the pathophysiology of liver adenomas in GSD I and what is an optimal follow-up and management of this complication.

Although different hypotheses about the aetiology of liver adenomas have been postulated (see *Addendum*)⁸², the exact causative nature is still an open question. More and more evidence arises that optimal metabolic control may prevent for or at least postpone the development of these adenomas^{26,120,157}. Using micro arrays techniques (DNA chips, protein chips) we hope to gain insight in patterns of up- and down regulation of genes and proteins involved in the cause of their development.

Follow-up of liver adenomas, and especially early detection of malignant transformation, remains an ongoing diagnostic enigma^{77,78}. Ultrasonography is a reliable technique to screen for lesions and to follow them to monitor size and number. Early detection of malignant transformation, however, is more difficult. Ultrasonography, CT and MRI are not highly predictive of malignant transformation⁸¹ and for α -fetoprotein both false positive and false negative results have been reported^{24,89}. At present, it is even said that simple clinical evaluation provides the best clue with increase in liver size and the

onset of abdominal pain being sinister, but not necessarily specific, indications of malignant transformation⁸². A challenging goal is to find highly sensitive and specific serum markers and imaging techniques (positron emission tomography (PET) imaging, HIDA scintigraphy) to detect early malignant transformation of liver adenomas in GSD I.

The management of liver adenomas in GSD I is either expectant or surgical⁸². LT should be considered in patients with unresectable and dietary unresponsive multiple adenomas if associated with serious complications or in case of the development of carcinoma, as long as metastases are not present³¹. LT provides enzyme replacement therapy hereby correcting glucose homeostasis⁶⁹. LT does not prevent the development of renal failure⁹¹. If LT is indicated, combined liver and kidney transplantation may be a choice when end-stage renal disease is present⁷⁵. It is our opinion that LT is contraindicated in dietary unresponsive poorly metabolic controlled patients, since not being able to comply dietary treatment strictly may indicate poor compliance to necessary immunosuppressive treatment and follow-up after LT¹¹⁸. Recently, hepatocyte transplantation was performed in a poorly metabolically controlled adult GSD Ia patient with debatable results: a partial improvement of the metabolic status (fasting tolerance of 7 hours, some improvement of hypertriglyceridaemia, however, no effects on lactic acidosis, hypercholesterolaemia, and hyperuricaemia) was demonstrated up to 9 months after transplantation⁹⁸. In conclusion, LT is a therapeutic option for some patients with GSD I. It has its own hazards, but survival rates after transplantation are acceptable. In our centre, the actuarial one- and five-year patient survival rates after LT for metabolic diseases are 96% and 84%, respectively¹⁰⁸. However, especially timing of this procedure in GSD I remains difficult. Guidelines regarding indication for LT and its timing should be developed.

anaemia

Anaemia is observed rather frequently in patients with GSD I^{136,117,138}. In most patients it is micro-normocytic, and especially in adult patients iron-refractory. The pathophysiology seems to be multi-factorial: anaemia has been associated with decreased intestinal iron absorption due to primary intestinal dysfunction or secondary to ingestion of UCCS^{2,152}, chronic blood loss (into liver adenomas in GSD Ia and GSD Ib patients, and intestinal in GSD Ib patients with IBD)^{148,152} and as part of a hypersplenism syndrome in GSD Ib patients treated with GCSF¹⁵⁰. Recently, it was demonstrated that liver adenomas produce inappropriate concentrations of hepcidin¹⁵⁸. Hepcidin, a peptide hormone, has been implicated in controlling the release of iron

from intestinal cells and macrophages and an association with chronic, iron-unresponsive anaemia has been made. The ESGSD I confirmed this association showing lower hemoglobin concentrations and a higher prevalence of anaemia in patients with liver adenomas compared to those without¹²⁰. This relation between liver adenomas, hepcidin overproduction and anaemia needs to be studied in more detail. It may not only have implications for patients with GSD I, but may also learn us more about the pathophysiology of anaemia in chronic disease¹²⁵.

osteopenia

Normal bone formation in childhood and young adulthood has become more and more important as more GSD I patients will reach 5th and 6th decades of life.

We demonstrated normal BMD of the lumbar spine in pre-pubertal GSD Ia patients, along with reduced BMD in adolescent and adult GSD Ia patients compared to healthy controls using DXA^{114,119}. Earlier studies showed moderately low bone mineral content (BMC) in pre-pubertal and adolescent GSD I patients using single photon absorptiometry⁸⁰ or peripheral quantitative computed tomography¹²⁹, and severely decreased BMD in adult GSD Ia patients using DXA⁵⁰. Follow-up studies of BMD in GSD Ia and GSD Ib patients are necessary to elucidate if the difference in BMD between pre-pubertal and adolescents/adults patients reflects the natural course of BMD in GSD Ia, with a diminished accretion of BMD during childhood, or that it is based on improvement of dietary and pharmacological treatment during more recent years¹¹⁹.

A variety of metabolic and endocrine abnormalities in GSD I may contribute to abnormal bone matrix formation and/or altered mineralisation¹¹⁹. By determination of serum markers of bone formation and bone degradation we hope to elucidate in the near future part of the pathophysiology of decreased bone mass formation in GSD I. Some evidence exists that meticulous dietary treatment started at early age, hereby preventing as much as possible metabolic and endocrine abnormalities - including hyperlactacidaemia (lactose and fructose restriction) - may influence bone mass formation positively^{129,165}. Consequently, the provision of adequate amounts of supplemental calcium and vitamin D should be ensured.

According to the Utah paradigm, control of bone strength and mass depends strongly on muscle strength⁴². Recently it was demonstrated that besides moderately low BMC, also muscle force was moderately low in most patients with GSD I¹²⁹. This implicates that in most GSD I patients, bone mass is decreased compared to healthy subjects, but adequately adapted to

the mechanical requirements imposed by their own muscle contractions. In other words, in GSD I the adaptation mechanism of bones to respond with an increase in cortical thickness and cross-sectional area in response to biomechanical loads, especially muscular strength, may well be understimulated as a result of decreased muscle force and decreased physical activity. It would be very interesting to study the beneficial effects of stimulating physical activity on muscle force and bone mass in GSD I.

The question has risen whether biphosphonates, known to decrease bone turn-over, may be of value in GSD I patients with severely decreased bone mass. Biphosphonates have been used extensively in adults¹⁴⁴; reports of (long-term) use in (young) children however are scarce. Especially about the long-term side-effects less is known. It is therefore, our opinion that in paediatric and young adult GSD I patients improving metabolic control with complete avoiding of lactate production, along with optimal calcium and vitamine D intake, is preferable to pharmacological intervention. If no amelioration is observed, or in case of severe complaints as pathologic fractures or bone pain, pharmacological intervention with biphosphonates may be an option in adult patients. However, controlled clinical studies are warranted to study the beneficial effects and to register side-effects.

intestinal (dys)function

Patients with GSD Ia as well as patients with GSD Ib may suffer from intermittent diarrhoea³⁹. Among the ESGSD I cohort, diarrhoea was reported in 35% of the GSD Ia patients and in 55% of the GSD Ib patients¹¹⁷. In GSD Ib, loss of mucosal barrier function due to inflammation seems to be the main cause^{148,152}. In GSD Ia, no common cause could be demonstrated¹⁵². Several hypotheses have been postulated but not been confirmed so far: disturbed intestinal glucose absorption leading to osmotic diarrhoea⁹⁴, intestinal glycogen storage³⁸, and persorption of cornstarch leading to inflammation⁴⁹. G6Pase activity has been demonstrated in liver cells, renal tubulus cells, and intestinal cells¹⁴. Its role in intestinal cells is not fully understood. There is evidence, however, that the microsomal G6Pase complex is involved in transcellular glucose transport. In addition to a GLUT 2 pathway, a second microsomal membrane traffic-based transport pathway of which the G6Pase complex forms a part, seems to play a major role in transcellular monosaccharide transport of the human intestine¹²⁶.

Using tracer dilution techniques and MIDA, kinetic studies will be performed in GSD Ia patients, GSD Ib patients, and healthy volunteers, to investigate intestinal absorption of different carbohydrates. Also mice studies using different pharmacological inhibitors of the systems involved in transcellular

intestinal glucose transport will be initiated to elucidate the role of the G6Pase complex in the intestinal cells.

in vivo studies concerning slowly released carbohydrates

The role of slowly released carbohydrates has been a breakthrough in the dietary treatment of patients with GSD I^{16,20,134}. UCCS is used most generally. Although the positive effect on blood glucose concentration of continual breakdown of polysaccharides providing a constant supply of glucose from the intestine, is undoubted, the use of UCCS has its disadvantages. For patients the taste and structure of UCCS and the abdominal complaints (flatulence, puffed feeling, abdominal pain, diarrhoea) may be a burden for optimal compliance. Furthermore it is relatively contraindicated in very young children because of immature amylase activity⁵⁷ and in patients with GSD Ib as it may cause deterioration of pre-existent inflammation. UCCS may also be associated with chronic diarrhoea in GSD Ia and with IB as observed in adult GSD Ia patient on long-term treatment with UCCS¹²⁰. We speculate that increased colonic starch allows the flora to generate increased butyrate. Absorbed butyrate causes upregulation of prostaglandin E series production causing water and electrolyte loss and a colitis when this process is extreme⁶⁷. At this moment studies are being planned to investigate this in more detail. Furthermore, the development of alternatives for UCCS is in progress. In the near future clinical studies to prove effectiveness, palability and tolerance of these UCCS alternatives will be performed.

pulmonary hypertension

Pulmonary hypertension is a rare complication in ageing GSD I patients^{55,70,101} which may develop throughout life and in most patients leads to a fatal outcome in a few weeks or months after diagnosis. The pathogenesis is unclear, but may be due to vasoconstrictive amines such as serotonin, a pulmonary vasoconstrictor and growth factor for vascular smooth muscle cells, stored in platelets⁶³. To determine the prevalence and severity of this complication, pre-symptomatic studies are warranted in paediatric and adult GSD I patients. Furthermore, early detection at a time when dynamic and reversible pathogenic mechanisms are present allows early treatment hereby increasing the likelihood of a successful outcome⁶³.

psychomotor development and cerebral function

The ESGSD I has demonstrated normal long-term cerebral function in GSD I as long as hypoglycaemic comas are prevented¹¹⁷. However, no IQ-studies have been performed in GSD I. A recent study showed asymptomatic

epileptic activity in one-fifth, altered BAEP, VEP and SEP results in one-third, and MRI abnormalities in more than 50% of a small group of GSD I patients with 'normal' psychomotor development⁹³. To investigate the consequences of hypoglycaemic hyperlactaemic episodes on cerebral development and functions in more detail, neurological examinations, IQ-studies, and neuro-electrophysiological studies will be planned in paediatric and adult patients with GSD I.

quality of life

As a result of intensive dietary treatment, life expectancy in GSD I has improved considerably. However, a significant number of (young) adult GSD I patients suffer from depressive illness needing therapy^{117,138}. Life-long intensive dietary treatment 24 hours a day in combination with serious medical problems and an uncertain future seems to be a burden for both parents and patients⁵⁶. Quality-of-life assessments will be initiated among parents and patients to investigate whether and which way prevention of psychological deterioration is necessary.

neutropenia and neutrophil dysfunction, inflammatory bowel disease and GCSF in GSD Ib

The ESGSD I showed intermittent neutropenia and abnormal neutrophil functions in almost all patients with GSD Ib¹⁴⁸. Almost all patients had recurrent bacterial infections and some had life-threatening infectious diseases. Furthermore, symptoms (highly suggestive) of IBD were reported in three-fourth of the GSD Ib patients. IBD and neutropenia were strongly associated. GCSF was started in one-third of the GSD Ib patients: the number and severity of infections decreased and de severity of IBD improved subjectively. Neutrophil counts increased and simultaneously leucocyte counts and platelet counts decreased. The most serious complication of GCSF treatment was marked splenomegaly¹⁵⁰. In view of the uncertainty of the positive effects of GCSF, along with the possible serious side-effects as hypersplenism and the development of leukaemia¹¹², prospective trials are warranted to clarify the value of the use of GCSF and its indications in GSD Ib. These prospective studies will be embedded in the ISGSD I.

The exact pathogenesis of neutropenia and neutrophil dysfunction in GSD Ib is still unknown. In the resting state, neutrophils are metabolically inactive, the transition to an active state is associated with a marked increase in metabolic activity termed the respiratory burst¹⁴⁹. An abnormal respiratory burst is observed in neutrophils of patients with GSD Ib, along with a variety of disturbed neutrophil functions^{48,148}. Neutropenia in GSD I seems to be a

secondary phenomena to neutrophil dysfunction¹⁴⁸. The role of G6PT in leucocyte pathobiology is presently unknown. Neutrophils do not contain mitochondria, and are dependent for their energy supply and the production of NADH on the mobilisation of intracellular glycogen or on extracellular glucose. Neutrophils of patients with GSD Ib are unable to increase intracellular G6P concentrations on addition to glucose, thereby limiting the ability to generate reduced NADH from the hexose-monophosphate shunt¹⁴⁷. As a result of the inability to increase intracellular G6P concentration, all metabolic functions could be deficient. Furthermore, the import of G6P into the ER is critical to effective Ca²⁺ sequestration and signalling^{15,160}. Abnormal Ca²⁺ sequestration can result in defective margination of neutrophils. We showed however, that acute inhibition of G6PT does not negatively affect the respiratory burst as is seen in chronic G6PT dysfunctional GSD Ib neutrophils, indicating that neutrophil dysfunction in GSD Ib may be caused by another factor¹⁵³. Furthermore, more recently it was demonstrated that GSD Ib neutrophils behave dysfunctional because they are apoptotic, which is associated with progressive loss of all functions⁷³. This may be associated with the incapability of optimal function of antioxidant systems as a result of the inability to produce NADH. Antioxidant systems are necessary for neutrophil survival during oxidative stress. Further studies however are warranted to elucidate the underlying mechanism of neutrophil dysfunction in GSD Ib.

Another interesting puzzle remains the association of neutropenia and neutrophil dysfunction and the development of IBD in GSD Ib. The IBD in GSD Ib resembles Crohn's disease (CD) and may involve the entire gastrointestinal tract^{148,27}. Beside GSD Ib, also other diseases with neutropenia or neutrophil dysfunction (cyclic neutropenia, congenital neutropenia, chronic granulomatous disease) may present with a CD phenotype¹³⁰. In the absence of a single etiologic factor, CD can be regarded as a manifestation of poorly regulated immune and inflammatory processes within the gut wall^{61,72}. Further investigations are needed to elucidate the association between neutropenia and neutrophil dysfunction and IBD in GSD Ib. This may also have relevance to the understanding of the pathogenesis of idiopathic CD and its treatment.

In conclusion, the ESGSD I and its related studies have added to a better understanding of the clinical course, treatment, outcome and pathophysiology of GSD I and its complications. This increased insight has offered the possibility to develop extended recommendations for long-term treatment and follow-up. However, about some hallmarks and the practical interpretation of dietary treatment controversy still exists. Furthermore, a lot of questions about the

pathophysiology and management of the (long-term) complications are not solved yet. Continuation of the ESGSD I as the ISGSD I offers the possibility to tackle these questions. In 2008, we hope to present some of the answers along with improved consensus guidelines for the management of GSD I, and we will come up, for certainty, with new unsolved questions.

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