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Glycogen storage disease type I

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**Glycogen Storage Disease type I:
introduction and outline thesis**

Chapter 1



The Glycogen Storage Diseases

Glycogen is a giant molecule in which glucose is stored. It was discovered, isolated and characterised both chemically and physiologically in the mid 19th century by Claude Bernard⁶. Glycogen is a polysaccharide with a molecular weight varying from a few million to well over several hundred million. It has a spherical form and consists of D-glucose residues which are joined in straight chains by α 1-4 linkages. The straight chains are branched at intervals of 4 to 10 residues with α 1-6 linkages (Figure 1.1)⁶⁵.

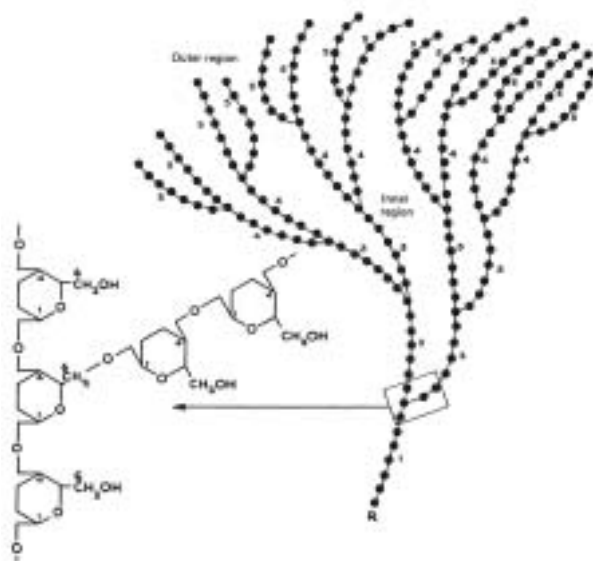


Figure 1.1 The glycogen molecule with enlargement of the structure at a branch point (adapted from Harper's Review of Biochemistry)

Although almost all cells of the human body are capable of storing at least some glycogen, especially muscle and liver cells store large amounts. Muscle cells can store up to 1 to 3 per cent of their weight as glycogen, whereas liver cells can store up to 5 to 8 percent glycogen. The role of glycogen in muscle is to provide substrates for the generation of ATP for muscle contraction, whereas glucose derived from glycogen in liver is mainly used to maintain normal blood glucose concentration during fasting¹⁶.

Glycogen storage diseases (GSDs) are inherited disorders that affect glycogen metabolism. Synthesis and degradation of glycogen are catalysed by enzymes that are (in)activated by hormones (Figure 1.2)²⁸. Nowadays, defects in virtually all proteins involved in this synthesis or degradation of glycogen and its regulation have been found to cause some type of GSD¹⁶.

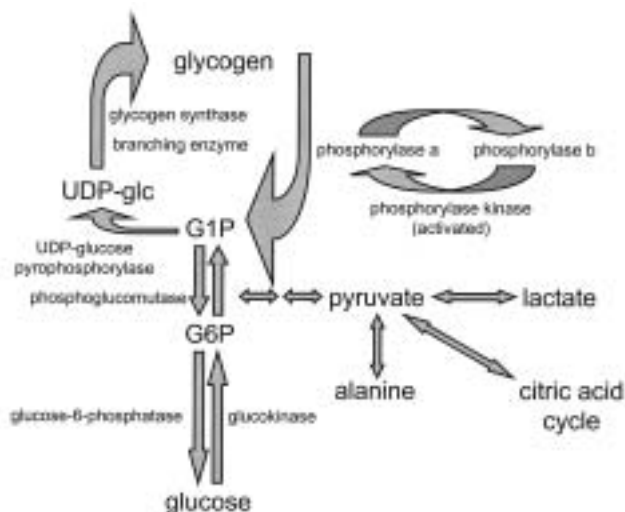


Figure 1.2 Liver glycogen metabolism and its enzymes

GSDs that affect glycogen degradation in liver cause hepatomegaly as a consequence of glycogen storage and (features of) hypoglycaemia. GSDs that affect glycogen degradation in muscle cause muscle cramps, exercise intolerance, susceptibility to fatigue, progressive weakness and other features of (cardio)myopathy. An overview of GSDs affecting the liver is given in Table 1.1.

Historical background Glycogen Storage Disease type I

The first clinical description of a patient with GSD was given by van Creveld, a Dutch pediatrician. At a meeting of the Dutch Society for Pediatrics in 1928, he gave a lecture titled 'Over een bijzondere stoornis in de koolhydraatstofwisseling in den kinderleeftijd' ('an unusual disturbance of carbohydrate metabolism in childhood')^{22,75}. In retrospect this patient had GSD III. The first report of a patient with GSD I is attributed to von Gierke, a German pathologist. 'Hepatonephromegalia glykogenia' was the title of his description of an autopsy, performed at the cemetery, of a girl with enlargement of the liver and kidneys due to deposition of massive amounts of glycogen³⁰. Biochemical tests on liver material of this patient performed by Schoenheimer, a German chemist, revealed that the glycogen was exclusively composed of glucose residues and could be degraded by minced normal liver⁶¹. Von Gierke and Schoenheimer concluded that in their patient a glycogen-degrading substance was missing. In 1952, Cori and Cori²¹ demonstrated that absence of glucose-6-phosphatase (G6Pase) activity was the enzymatic defect

Table 1.1 Classification of Glycogen Storage Diseases affecting the liver (adapted from³⁶ and²⁸)

Type	Synonym	Subtypes	defective enzyme / transporter	tissue	chromosome	(main) symptoms
I	von Gierke	Ia I-non-a	glucose-6-phosphatase glucose-6-phosphate translocase (Ib) phosphate translocase (Ic)	L, K L, K, NG L, K, NG	17q21 11q23 11q23, ?	HM, GR, HG, LA, HL as Ia, + or - NP, I, IBD as Ia, + or - NP, I, IBD
III	Cori / Forbes	IIIa IIIb IIIc	debranching enzyme (transferase + glucosidase) debranching enzyme (transferase + glucosidase) debranching enzyme (transferase)	L, M L L, M	1p21 1p21 1p21	HM, GR, HG, HT, (C)MP HM, GR, HG as IIIa
IV	Andersen		branching enzyme	L, (M)	3p12	HM, C, (HT, (C)MP)
VI	Hers		phosphorylase	L	14q21-22	HM, GR, (HG), HL
IX		IXa - XLG I IXa - XLG II IXa IXb	phosphorylase-b-kinase phosphorylase-b-kinase phosphorylase-b-kinase phosphorylase-b-kinase	L, E, LC L L L, M	Xp22 Xp22 ? 16q12-13?	HM, GR, (HG), HL HM, GR, (HG), HL HM, GR, (HG), HL HM, GR, (HG), HT, MP
XI	Fanconi-Bickel		GLUT 2	L, K, I	3q26	HM, GR, HG, RPTD, OP
0			glycogen synthase	L	12p12	GR, HG

GSDs are caused by enzyme defects of glycogen degradation. Classification is usually still done by type number, which reflects the historical sequence of elucidation of the underlying defect. GSD-0 is grouped under the GSDs as it shares many clinical and metabolic abnormalities with other (liver-related) GSDs.

The GSDs affecting merely (heart) muscle (GSD II, m. Pompe, acid α -glucosidase; GSD V, m. McArdle, myophosphorylase deficiency; GSD VII, m. Tarui, phosphofructokinase deficiency; GSD IXc, myophosphorylase-b-kinase deficiency; phosphoglucomutase deficiency; phosphoglycerate-kinase deficiency; phosphoglycerate-mutase deficiency; lactate-dehydrogenase deficiency) are not included in this table.

Abbreviations: GSD glycogen storage disease; XLG x-linked glycogenosis; GLUT glucose transporter; L liver; K kidney; NG neutrophil granulocyte; M muscle; E erythrocyte; LC leucocyte; I intestine; HM hepatomegaly; GR growth retardation; HG hypoglycaemia; LA lactic acidosis; HL hyperlipidaemia; NP neutropenia; I recurrent infections; IBD inflammatory bowel disease; HT hypotonia; (C)MP (cardio)myopathy; RPTD renal proximal tubular dysfunction; OP osteopenia

responsible for the disease. This made GSD I the first ever metabolic disorder in which an enzyme defect was identified.

In the late 50's, patients were described having the same clinical and biochemical abnormalities as 'classic' GSD I but having normal G6Pase activity in frozen liver tissue⁵¹. In 1968, Senior and Loridan⁶³ proposed the term GSD Ib for this specific subtype. In the late 70's, it was demonstrated that these patients had deficient G6Pase activity in fresh (unfrozen) liver tissue⁵³.

The glucose-6-phosphatase enzyme system and genetics

Among the enzymes involved in glycogen synthesis and breakdown, G6Pase is unique since its active hydrolysing site is situated inside the lumen of the endoplasmic reticulum (ER), whereas the other enzymes involved in glycogen metabolism are in the cytoplasm⁵⁶. This means that the substrate, glucose-6-phosphate (G6P), and the products, glucose and phosphate, must cross the ER membrane. In 1975, Arion³ postulated a model for the function of the G6Pase system. In this transport-model, the G6Pase system consists of a catalytic subunit, G6Pase, situated on the luminal surface of the ER, and at least one membrane transporter (Figure 1.3)^{4,80}. Despite the fact that a lot of progress has been made, the controversy about the exact working mechanism of the G6Pase system still remains: the number of proteins, stoichiometry of each of these proteins, exact topology and whether these proteins form a complex are still unanswered questions¹⁶.

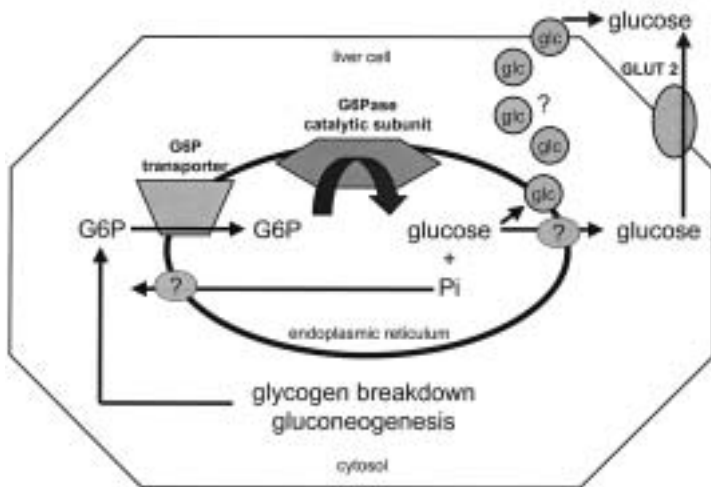


Figure 1.3 The glucose-6-phosphatase complex

Until recently, four different types of GSD I were distinguished based on kinetic enzyme studies in hepatic microsomal preparations⁵⁴. Deficient G6Pase activity in intact and disrupted microsomes indicate a defect in the catalytic unit, the actual G6Pase, and is called GSD Ia. Deficient G6Pase activity in intact microsomes and (sub)normal G6Pase activity in disrupted microsomes indicate a defect of the transporter proteins. Using different substrates a further differentiation was made between GSD Ib, GSD Ic and GSD Id. GSD Ib is caused by defects of the G6P transporter, which transports G6P from the cytoplasm to the inside of the ER^{53,40}. GSD Ic is caused by defects of the putative phosphate/pyrophosphate transporter, which transports phosphate from inside ER back to the cytoplasm⁵⁵. The suggestion was made that there might also be a GSD Id, attributed to defects of glucose transporter (GLUT) 7, a protein which transports glucose from inside ER to the cytoplasm. However, this observation has been withdrawn⁸, and so far, no patient with GSD Id has been really described⁷⁵.

In 1993 the gene encoding the catalytic unit of the G6Pase complex was identified. It is located in band q21 of chromosome 17. It consists of 5 exons and has a genomic length of 12.5 kb. It encodes a protein of 357 amino acids with a calculated molecular mass of 35-40 kD^{45,46,64}. More recently also the gene encoding the G6P transporter has been identified. It is located in band q23 of chromosome 11. It consists of 9 exons^{2,29}. Patients diagnosed by enzyme studies as GSD Ib, Ic and the putative Id, all had mutations in this G6P translocase gene^{70,71}. Furthermore, in GSD Ib and GSD Ic identical mutations were found. This is consistent with the clinical findings as GSD I can be divided in two clinical phenotypes: GSD Ia patients have 'classical' findings as listed below, whilst those with 'GSD I non-a' (GSD Ib and Ic) may have recurrent bacterial infections and inflammatory bowel disease (IBD) associated with neutropenia and neutrophil dysfunction in addition^{73,74}. However, recently a GSD Ic patient without mutations in the G6P transporter gene was described suggesting the existence of a distinct GSD Ic locus⁵⁰. Furthermore, some GSD Ia patients who are homozygous for the G188R mutation, a missense mutation which most likely also disturbs a correct splicing of the G6Pase mRNA¹⁷, have neutropenia and neutrophil dysfunction⁸¹. In this thesis the term GSD Ib includes patients in whom GSD Ic had been diagnosed formerly.

Metabolic derangements in Glycogen Storage Disease type I

Hypoglycaemia, hyperlactacidaemia, hyperlipidaemia and hyperuricaemia are the most characteristic metabolic derangements of GSD I²⁸.

Hypoglycaemia occurs during fasting as soon as exogenous sources of

glucose are exhausted, since deficiency of G6Pase activity in the liver blocks the final step in both the glycogenolytic and gluconeogenic pathway. Although both pathways of endogenous glucose production are blocked, evidence exists that GSD I patients are capable of some endogenous glucose production^{19,37}. The mechanism behind this endogenous glucose production is still unclear.

Hyperlactacidaemia is a consequence of excess of G6P which can not be hydrolysed to glucose. G6P is further metabolised following the glycolytic pathway, generating ultimately pyruvate and lactate¹⁶. Lactate may serve as alternate fuel for the brain when the blood glucose concentration drops, hereby protecting patients against cerebral symptoms²⁵. However, hyperlactacidaemia may be associated with the development of long-term complications. Metabolic substrates as galactose, fructose and glycerol need the G6P-pathway in the liver to be metabolised to glucose. Therefore, in GSD I, ingestion of sucrose and lactose results in hyperlactacidaemia with only little rise in blood glucose²⁴.

Hyperlipidaemia is thought to be a result of both increased synthesis of lipids from excess acetyl-CoA and decreased serum lipid clearance^{35,48,49,62}. Excess of pyruvate and lactate is converted into acetyl-coenzyme A (CoA), which is further converted to malonyl-CoA, an intermediate of fatty acid synthesis. Furthermore, malonyl-CoA inhibits mitochondrial β -oxidation which results in reduced ketone production^{23,28}. Elevated serum triglycerides predominate; cholesterol and phospholipids are less elevated.

Hyperuricaemia is a result of both increased hepatic production and decreased renal clearance of uric acid¹⁶. Increased production is caused by increased degradation of adenine nucleotides to uric acid, associated with decreased intrahepatic phosphate concentration and ATP depletion³³. Decreased renal clearance is caused by competitive inhibition of the excretion of uric acid by lactate¹⁸.

Clinical findings and long-term complications in Glycogen Storage Disease type I

Untreated patients display short stature, a rounded 'doll face', protruding abdomen (marked hepatomegaly), truncal obesity, and wasted muscles (Figure 1.4).

Hypoglycaemia may occur frequently, especially in childhood. Trivial events (short delay of a meal or a lower carbohydrate intake as consequence of an intercurrent illness) may elicit hypoglycaemia²⁸. Symptoms of hypoglycaemia (paleness, sweating, abnormal behaviour, decreased consciousness, coma, convulsions) are usually accompanied by hyperventilation, a symptom of

Figure 1.4 Italian boy with glycogen storage disease type Ia



lactic acidosis. Long-term cerebral function seems to be normal if hypoglycaemic damage is prevented. Other symptoms directly related to metabolic derangements are skin xanthomas, which are positively correlated with the degree of hyperlipidaemia, and gout, which is associated with hyperuricaemia but rarely develops before puberty¹⁶. Patients bruise easily, and epistaxis is common as a result of impaired platelet function²⁰. Furthermore, they may suffer from episodes of chronic diarrhoea^{52,77}, the mechanism still being unresolved. Patients with GSD Ib may have neutropenia and neutrophil dysfunction that predispose to frequent infections and IBD⁷⁴.

Marked hepatomegaly in GSD I is caused by storage of glycogen and fat. Except for glucose homeostasis, liver functions are normal and cirrhosis does not develop²⁸. In the second decade of life, patients may develop liver adenomas^{39,44}, which have the potential to transform into carcinomas⁷.

In most patients, the kidneys are moderately enlarged. 'Silent' glomerular hyperfiltration may be observed already in prepubertal patients^{5,59}. Microalbuminuria and subsequently proteinuria may develop, proceeding to hypertension and eventually end-stage renal disease^{12,14,42}. Also renal proximal

and distal tubular functions may be impaired, especially in metabolically poorly controlled patients^{13,60}.

Other complications that may develop are anaemia, osteopenia, ovarian cysts, pancreatitis and pulmonary hypertension²⁸.

The prevalence, severity and pathogenesis of most of the complications are still unknown, as is their association with metabolic control. Also the management of most of the complications is an open question.

Dietary treatment in Glycogen Storage Disease type I

The aim of treatment is to prevent hypoglycaemia in order to suppress secondary metabolic derangements as much as possible²⁸. Maintaining normoglycaemia will reduce the morbidity (and mortality) associated with the disease¹⁶. Initially, treatment consisted of frequent carbohydrate-enriched meals during day and night. In 1974 continuous nocturnal gastric drip feeding (CNGDF) via a nasogastric tube was introduced^{9,32} allowing the patient and parents to sleep during the night. In 1983 uncooked (corn) starch (UCCS), from which glucose is much more slowly released than from cooked starch, was introduced^{10,11}. Both CNGDF and UCCS have been proven to be able to maintain normoglycemia during night with equally favourable (short-term) results^{15,27,34,66,82,83,84}. UCCS during daytime is used to prolong the fasting period. As the diet is restricted, dietary supplements of multivitamins and calcium may be required¹⁶.

The collaborative European Study on Glycogen Storage Disease type I

GSD I has an estimated frequency among newborns of one in 100.000¹⁶. Thus, no single metabolic centre has experience with large series of patients. To share experience and knowledge, the collaborative European study on GSD I (ESGSD I) was initiated in 1996. Objectives of this study-group were to evaluate the management, clinical course and long-term outcome in both paediatric and adult patients with GSD I, to study the (long-term) complications, to develop therapeutic strategies and to develop guidelines for (long-term) management and follow-up. A management team consisting of GPA Smit (chairman) and J Fernandes (Groningen, The Netherlands), Ph Labrune (Clamart, France), JV Leonard (London, United Kingdom) and K Ullrich (Hamburg, Germany) was formed to supervise the ESGSD I. Twenty-five colleagues from 16 metabolic centres from 12 countries participated: D Skladal (Innsbruck, Austria); E Sokal (Brussels, Belgium); J Zeman (Prague, Czech Republic); Ph Labrune (Clamart, France); P Bührdel (Leipzig), K Ullrich (Münster/Hamburg), G Däublin, U Wendel (Düsseldorf, Germany); P Lee, JV Leonard (London), G Mieli-Vergani (London, Great Britain); L Szönyi

(Budapest, Hungary); P Gandullia, R Gatti, M di Rocco (Genoa), D Melis, G Andria (Naples, Italy); S Moses (Beersheva, Israel); J Taybert, E Pronicka (Warsaw, Poland); JP Rake, GPA Smit, G Visser (Groningen, The Netherlands); H Özen, N Kocak (Ankara, Turkey). The department of Metabolic Diseases of the 'Beatrix Kinderkliniek', University Hospital Groningen, The Netherlands served as the co-ordinating centre and hosted the central database. The ESGSD I was executed by Jan Peter Rake and Gepke Visser.

Parts of the thesis 'Glycogen Storage Disease type Ib: clinical and biochemical aspects and implications for treatment' by Gepke Visser⁷⁵ and parts of this thesis are based on data obtained in the ESGSD I. The thesis of Gepke Visser describes the incidence, severity and course of neutropenia, neutrophil dysfunction, infections and IBD in GSD Ib⁷⁴ and the benefits and hazards of G-CSF treatment in these patients⁷⁶. In vitro studies to gain more insight in neutrophil dysfunction in GSD Ib are also included^{72,79}. Furthermore, it describes in vivo studies performed to investigate intestinal (dys)function in both GSD Ia and GSD Ib patients⁷⁷. Finally, it provides guidelines for follow-up and treatment of the specific GSD Ib complications⁷⁸. These consensus guidelines are also incorporated in chapter 7 of this thesis.

Outline of this thesis

GSD I represents a rare disease. In literature there is a relative paucity of data on outcome of this disease, and all these reports^{15,26,57,67,68,84}, except one⁶⁹, focus on small groups of patients under 18 years. The first aim of the ESGSD I was to increase knowledge of diagnosis, management, (natural) clinical course, and (long-term) outcome in GSD I. Therefore, data on these aspects obtained from the ESGSD I were elaborated. Results are described in **chapter 2.1** '*Glycogen Storage Disease type I: diagnosis, management, clinical course, and outcome. Results of the European study on Glycogen Storage Disease type I (ESGSD I)*'. Outcome of (adult) GSD I patients born before 1975 were studied in more detail. Results are described in **chapter 2.2** '*Glycogen Storage Disease type I: long-term outcome of patients born before 1975. Results of the European study on Glycogen Storage Disease type I (ESGSD I)*'.

In 1993 the gene encoding the G6Pase catalytic unit was identified^{45,64}. We started to perform DNA-based diagnosis in GSD Ia using a modification of a method described previously by others^{45,47}. Mutations were identified by direct sequencing of PCR-amplified fragments showing an aberrant single strand conformation polymorphism (SSCP) migration pattern. Firstly, it was studied if this procedure is a reliable and save method allowing DNA-based

diagnosis in GSD Ia instead of enzyme assays in liver tissue obtained by biopsy and prenatal DNA-based diagnosis. Furthermore, a genotype-phenotype correlation was studied since it may be helpful in adjusting dietary and pharmacological strategies. A final study question was whether among our (North-Western) European GSD I population other (novel) mutations exist compared to mutations described in literature among other GSD I populations. Identified novel mutations are described in **chapter 3.1** '*Glycogen Storage Disease type Ia: four novel mutations (175delGG, R170X, G266V and V338F) identified*' and **chapter 3.2** '*Identification of a novel mutation (867delA) in the glucose-6-phosphatase gene in two siblings with Glycogen Storage Disease type Ia with different phenotypes*'. The other above mentioned study-questions are answered in **chapter 3.3** '*Glycogen Storage Disease type Ia: recent experience with mutation analysis, a summary of mutations reported in literature, and a newly developed diagnostic flowchart*'.

Although abnormal bone formation and bone mineralisation in GSD I was already demonstrated more than 30 years ago⁵⁸ and the occurrence of pathological fractures is a known complication in the ageing patients nowadays⁶⁹, so far, only one study concerning bone mineralisation in GSD I has been published⁴³. It showed reduced bone mineral content in the studied prepubertal patients. We investigated bone mineralisation in GSD I using dual energy X-ray absorptiometry. Results are described in **chapter 4** '*Bone mineral density in children, adolescents and adults with Glycogen Storage Disease type Ia: a cross-sectional and longitudinal study*'.

Data about the development of (premature) atherosclerosis in (young) adult GSD I patients are very scarce^{41,69}. However, in familial hypercholesterolaemia or familial combined hyperlipidaemia, a comparable degree of hyperlipidaemia is associated with cardiovascular morbidity and mortality at early age^{31,38}. We performed non-invasive vascular measurements to study if GSD Ia is associated with premature atherosclerosis. Condensed results are described in **chapter 5.1** '*Is Glycogen Storage Disease type Ia associated with atherosclerosis?*' and more extended results are presented in **chapter 5.2** '*Are dyslipidaemia and microalbuminuria in adolescents with Glycogen Storage Disease type Ia associated with cardiovascular disease?*'.

Hyperlipidaemia is a very well known metabolic derangement in GSD I. However, the exact pathogenesis is still not fully clarified. It is thought to be a result of both increased synthesis of lipids from excess of acetyl-CoA and lactate, and decreased serum lipid clearance^{1,35,48,49,62}. In vivo stable-isotopes studies were performed to investigate lipid synthesis in more detail.

Furthermore in vitro studies were performed to unravel the protective factor(s) against the development of premature atherosclerosis in GSD Ia. Results are described in **chapter 5.3** *'Increased lipogenesis and resistance of lipoproteins to oxidative modification in two patients with Glycogen Storage Disease type Ia'*.

Life-expectancy in 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. Furthermore, there is a large variation in long-term management and follow-up. One of the main objectives of the ESGSD I was to develop guidelines for long-term management and follow-up. These guidelines are based on the data of the ESGSD I, discussions with the members of the ESGSD I and participants of a international symposium 'Glycogen Storage Disease type I and II: recent developments, management and outcome' (Fulda, Germany; 22-25th November 2000) and on data from literature. The guidelines are described and discussed in **chapter 6.1** *'Guidelines for management of Glycogen Storage Disease type I - European Study on Glycogen Storage Disease type I (ESGSD I)'* and **chapter 6.2** *'Consensus guidelines for management of Glycogen Storage Disease type Ib - European Study on Glycogen Storage Disease type I (ESGSD I)'*.

Finally, in **chapter 7** (English) **and chapter 8** (Dutch), a summary and conclusions along with a discussion and future perspectives are presented.

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