Chapter 7

General discussion and future perspectives
Hepatic GSDs are ultra-rare, inherited disorders of carbohydrate metabolism, which usually present in early childhood\(^1\). Their multisystem involvement, requiring multidisciplinary professionals, raises huge organizational, logistic, and financial obstacles for affected families and healthcare providers. The potentially life-threatening nature of hepatic GSDs symptoms and high variability in hepatic GSDs patients’ phenotypes, treatment interventions and outcomes emphasize the need and urgency for improved monitoring options. The current diversity in management guidelines for hepatic GSDs causes unwanted variations in diagnosis and treatment, and necessitates standardisation of clinical care, aiming at the most favourable patient’s outcomes and healthy ageing.

Despite the increase in life expectancy over the past years, there is an unmet clinical need for improved management of hepatic GSDs. Standardisation of the patients’ management (including emergency situations), development of strategies to prevent and/or treat intestinal problems in GSDIb and muscle problems in GSDIII have been identified as top research priorities by patients, carers, and healthcare professionals\(^2\). Potential solutions for these priorities have been investigated in the present thesis.

Innovative management strategies and novel monitoring tools for hepatic GSDs are closely related challenges. The need for improved monitoring strategies can be considered as a direct consequence of the need for novel management strategies. Paragraph 7.1 focuses on the strategies to improve and (possibly) standardise management of patients with hepatic GSDs. In paragraph 7.2 an opportunity for minimally invasive monitoring and a possible novel biomarker for GSDI are discussed.

### 7.1 Developing novel management strategies

Current therapies for hepatic GSDs appear untargeted and generally do not target the primary metabolic defect but rather the related symptoms and signs. Frequent feedings and uncooked corn starch (UCCS) have been the cornerstone of the treatment since the 1970s\(^3\)–\(^5\). Some patients may require complementary continuous nocturnal gastric drip feeding (CNGDF) to avoid hypoglycaemia\(^6\). Additional and distinct dietary recommendations are provided for specific hepatic GSDs subtypes, such as avoidance of sucrose and lactose in GSDF\(^3\), and high-protein intake for GSDIII\(^4\). Such strict dietary regimens may heavily challenge patient’s quality of life and compliance. The development of dietary treatments has resulted in a dramatic reduction in hypoglycaemic events and changed the clinical focus of hepatic GSDs from mortality to morbidity. At the same time, several long-term complications have emerged which are not (entirely) prevented by currently available treatments. Among these, renal disease and liver adenomas in GSDIa\(^3\), neutropenia and inflammatory bowel disease (IBD) in GSDIb\(^7\), and (cardio)myopathy in GSDIIIa\(^4\) still heavily impact on patients’ prognosis and quality of life. In this respect, several novel and innovative treatments, such as gene (NCT03517085) and mRNA therapy\(^8\) are currently under investigation. Whether such treatments can provide an effective and permanent cure for patients with hepatic GSDs or realistically broaden the available therapeutic options is yet unclear.

In the “real world” amongst health care providers, controversies still exist on specific management topics, such as treatment of hyperlipidaemia, risks related to long-term G-CSF administration, and many recommendations are based on so-called best practice and expert opinions. Current guidelines mainly focus on the long-term management while little attention is paid to acute treatment\(^3\)–\(^7\).
Consequently, wide differences in patients’ management still exist among clinical centres impacting on patients’ outcomes and access to healthcare services.

7.1.1. Towards standardization of the management of patients with hepatic GSDs

One of the research questions for this thesis was: Can patients with hepatic GSDs benefit from dietary lipid manipulation? In recent years, various case studies have described reversal of cardiac hypertrophy and myopathy in GSDIII patients in response to ketogenic diets. Addressing this question will therefore contribute to development of novel treatment options to prevent and/or treat muscle problems in GSDIII patients.

In chapter 4 results on dietary lipid manipulations in patients with GSDIII are presented and discussed. A high fat diet represented the most common dietary lipid manipulation. Cardiomyopathy and myopathy were the main indications for switching to a high fat diet in GSDIII patients.

Firstly, a high fat diet appears safe in patients with GSDIII; also, no increase in patients’ BMI was observed. Secondly, significantly lower CK concentrations were observed after dietary lipid manipulation. Thirdly, reduced interventricular septum thickness was observed in paediatric but not adult GSDIII patients following dietary lipid manipulation. Lastly, most patients reported subjective improvements of exercise tolerance and/or muscle strength after dietary lipid manipulation. Overall, these findings suggest that a high fat diet can exert beneficial effects on the muscle phenotype in GSDIII patients. Available data support the inclusion of a high fat diet among the possible treatment options for GSDIII in future guidelines.

Interestingly, the benefit of the high fat diet on cardiomyopathy in GSDIII appears to be age dependent. Likely, an early switch to a high fat diet can reverse, or at least reduce cardiac glycogen accumulation. Following our literature search in December 2018, two additional reports were published that describe improvements in cardiac and skeletal muscle function after starting a ketogenic diet in adult and adolescent GSDIII patients, respectively.

Although the effect of a high fat diet on muscle outcomes seems promising in GSDIII patients, the underlying mechanism remains currently largely unresolved. In all reported dietary interventions, carbohydrates were replaced by lipids. Thus, the observed benefit may be driven by reduced carbohydrate intake. Alternatively, the properties of fat as an alternative energy substrate for muscle may contribute. In addition, a general improvement in dietary compliance could also play a role, regardless of the type of intervention. Therefore, it would be interesting to compare the efficacy of a high fat diet to that of improved metabolic control combined with appropriate protein intake on muscle signs/symptoms in GSDIII patients.

Notably, the long-term effect of a high-fat diet in patients with GSDIII should be monitored as these may increase the risk to develop steatohepatitis and osteoporosis. On the other hand, liver cirrhosis and osteopenia can naturally occur in patients with GSDIII, independent of a switch to a high fat diet. Follow-up studies are therefore warranted.
Chapter 5 presents a potential approach to optimise and uniform the initial, preventive management of emergency situations for patients with hepatic GSDs.

Although local or regional healthcare providers that lack specific metabolic training are often the first actors in metabolic decompensations, current disease-specific recommendations are not always easily accessible to non-metabolic specialists. Taking into account that such recommendations are largely based on expert opinions, standardisation of the initial emergency management for patients with hepatic GSDs is challenging.

After multiple revisions of the original “generic emergency protocol” which has been used at University Medical Centre Groningen (UMCG) since 2014, an international collaborating group consisting of healthcare providers and patient representatives from 32 centres and 15 countries worldwide released a shared emergency protocol for hepatic GSDs patients (and also fatty acid oxidation disorders (FAOD) patients) in 10 languages. This new protocol has several advantages. First, by providing shared and endorsed recommendations, it represents a major step towards standardised global management of emergency situations for hepatic GSDs patients. Second, it adds to current guidelines where practical instructions on prehospital phase management and communication are scarce. Third, it provides simple instructions which can be followed by both patients during the prehospital phase and local healthcare providers upon hospitalisation. Fourth, the personalised emergency letter can be easily generated and updated at any time via www.emergencyprotocol.net, only requiring the patient’s weight and diagnosis. This can be done either by the patient or the healthcare providers and in multiple languages.

Five-year single-centre experience suggests that the generic emergency protocol can safely prevent metabolic emergencies in patients with hepatic GSDs. The electronic emergency letters can be particularly helpful in case patients are far away from the metabolic centre of expertise. This is relevant for both prevention in the home setting and for in-hospital management. Taking into account its benefits on prevention of metabolic decompensations and guidance for local healthcare providers, we propose to include this protocol in future management recommendations.

Although the generic protocol provides simple instructions and can guide families and healthcare professionals, it does not to replace expert metabolic advice. The generic emergency protocol can guide decision making during the first hours of a metabolic emergency before reaching out to the metabolic specialist. Importantly, the proposed management strategies should not be executed extensively. Both the emergency solution and the glucose infusion rates are tailored to meet carbohydrate requirements under these circumstances, but the treatments do not provide sufficient calories in the long-term. Therefore, prolongation of the emergency treatments poses the risk of (protein) catabolism. This can be prevented by good communication between health care providers and families, for instance repeatedly during the intercurrent illness episode, in a shared care model including the metabolic centre of expertise, the local healthcare providers, the caregivers and the patients. In this respect, personal values, preferences, and individual circumstances (including psychosocial and cultural aspects) should at all times be considered to ensure optimal care.

Although a generic emergency protocol appears effective in hepatic GSDs and FAOD, it is as yet not in place for inherited metabolic disorders of the intoxication type (e.g., organic acidemias, urea cycle...
defects) or disorders associated with perturbed carbohydrate metabolism (e.g., idiopathic ketotic hypoglycaemia, congenital hyperinsulinism, and patients using ketogenic diets). Future studies may evaluate the cost-effectiveness of this emergency protocol.

7.1.2. Repurposing empagliflozin to treat inflammatory bowel disease (IBD) in GSDIb

Conventional treatments for IBD (i.e., corticosteroids, immunomodulators, biological agents, G-CSF) can be ineffective and/or associated with side effects (e.g., leucopenia, anemia, diarrhoea) in GSDIb patients. As patients sometimes even require abdominal surgery, improved prevention and treatment of intestinal problems is a compelling need in GSDIb. After elucidation of the pathogenic role of 1,5-anhydroglucitol accumulation in neutropenia/neutrophil dysfunction in GSDIb, two recent papers have shown that repurposing the antidiabetic drug empagliflozin exerts beneficial effect on neutropenia/neutrophil dysfunction in 5 patients with GSDIb.

Although non-invasive markers of IBD, i.e., Crohn disease activity index (CDAI), stool consistency and faecal calprotectin, were shown to be beneficially affected by empagliflozin, the chronic relapsing and remitting course of IBD warranted additional investigation to confirm efficacy of this treatment on IBD in GSDIb patients.

In chapter 6 the first evidence on the benefit of empagliflozin treatment on bowel (macro/microscopic) morphology in a GSDIb patient is presented. A significant decrease in disease length and activity as well as histological remission were documented 3 months and 5.5 months after empagliflozin treatment was started. Nonetheless clinical and biochemical improvements were observed, i.e., improved perineal pain and anal fissure as well as reduced stool frequency and increased haemoglobin levels within one week and the first month of treatment, respectively. Notably, as empagliflozin treatment in this patient was started during a IBD flare-up, these findings suggest its potential efficacy also during the acute phase. Still, the persistence of ileal stricture after the treatment suggests that empagliflozin may be effective in healing the inflammatory lesions/strictures but might not be able to reverse established fibrotic strictures. It can also be speculated that empagliflozin, by counteracting neutrophil dysfunction, and G-CSF, which mobilises neutrophils from the bone marrow, may exert a synergistic effect on neutropenia and bowel inflammation in GSDIb.

Bowel morphology can provide significant insight on the effect of empagliflozin in GSDIb patients. Results from the present case and literature data support an early empagliflozin administration in GSDIb patients with IBD before the onset of (irreversible) intestinal fibrosis. Interestingly, empagliflozin use has been proposed to prevent bleomycin-induced lung fibrosis and will likely reduce the healthcare costs for GSDIb (-59% medication-related costs in the present case).

Although empagliflozin appears to be a promising drug for IBD in GSDIb, several questions remain. Its effect on lymphocytes and/or macrophages likely explains its beneficial actions on bowel inflammation. In this respect, the proposed role for 1,5-anhydroglucitol (1,5AG) and 1,5-anhydroglucitol-6-phosphate (1,5AG6P) in modulating other peripheral blood mononuclear cells may be relevant for its effects on IBD in GSDIb patients. Interestingly, improved colonic inflammation through TNFα- and IL1β-independent mechanisms has been recently shown in IL-10−/− mice (experimental models of colitis) after 14 days treatment with empagliflozin. Follow-up
research elucidating the effects of empagliflozin on bowel inflammation (both in GSDIb and non-GSDIb patients) is needed.

7.2 Developing novel monitoring strategies

Several novel treatments options for hepatic GSDs are currently being explored (Table 1). Some studies aim for refinement of traditional treatments (e.g., optimisation of macronutrient composition) and novel/repurposed drugs, in addition to (potentially curative) treatments which can possibly restore enough working enzyme.

Longitudinal monitoring of patients with hepatic GSDs receiving such novel treatments may include a combination of (1) assessment of traditional biochemical biomarkers, (2) assessment of enzyme activities ex vivo, (3) execution of (invasive, clinical) fasting challenges in vivo, (4) continuous glucose monitoring (CGM), and (5) application of stable isotope methods to longitudinally quantify endogenous glucose production (EGP) rates in vivo31.

<table>
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<th>Drug</th>
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Table 1. Ongoing clinical trials assessing novel medical treatment options for hepatic GSDs. Data retrieved from Clinicaltrials.gov, last access on October 3rd, 2021. LNP: lipid nanoparticle. *This is an observational study of patients enrolled in the trial NCT03517085. No drug is administered during this study.

Although various biochemical markers of metabolic control are included in current guidelines3,7 and clinical trial protocols, they do not always appear sufficiently reliable to dissect the phenotypic heterogeneity and to assess the (expected) efficacy of novel treatment on the affected tissues32. Enzyme testing may involve invasive procedures (e.g., liver biopsy for G6Pase)3, may not always retrieve conclusive results (e.g., phosphorylase kinase)33 and the results may be dependent on the sample type (e.g., whole cell or endoplasmic reticulum fractions for G6Pase). Additionally, for most
hepatic GSDs no clear correlation between residual enzyme activity and clinical phenotypes is established 

A controlled fasting challenge can dynamically assess the metabolic changes that occur upon fasting and postprandially, but poses a significant organizational burden, e.g., hospital admission, a designated team and a fully equipped laboratory are required, and potential safety issues, as the test is continued until patients develop signs/symptoms of hypoglycaemia.

CGM represents a potential tool for minimally invasive monitoring of patients with hepatic GSDs. It constitutes a highly attractive approach to longitudinally monitor glucose trends both in the hospital and in the home-setting. Previous research has confirmed the efficacy of CGM to monitor the efficacy of novel/optimized dietary and/or medical treatments in patients with hepatic GSDs. Reference values for the CGM-related outcome measures in GSDIa patients, however, are as yet lacking.

Chapters 2 and 3 address the generation of reference values for CGM-derived parameters in GSDIa patients, therefore implementing the CGM use into clinical research, and the identification of a novel biomarker for GSDIa.

### 7.2.1 Towards minimally invasive monitoring of patients with GSDIa

The research question: *Can CGM reference values be defined for adult GSDIa patients?* was addressed in chapter 2. This study allowed to generate reference values for CGM-derived outcomes in adult GSDIa patients. Unlike diabetes mellitus (DM), in which CGM is a recognised tool for patients’ monitoring and to support decision making on dietary and/or medical adjustments, the lack of CGM reference values for hepatic GSDs currently limits the use of this technology for follow up and monitoring during regular healthcare or clinical trials.

Prospective CGM data on 10 GSDIa patients and 10 age-, gender- and BMI-matched healthy volunteers were collected. Reference values for major CGM-derived outcome parameters, (i.e., descriptive parameters, glycaemic variability, time below range, time in range, time above range) were generated.

This study also revealed that GSDIa patients display higher time below range (TBR) and time above range (TAR), lower time in range (TIR) and larger glycaemic variability (GV) compared to healthy controls. Furthermore, 9/10 GSDIa patients did not demonstrate level 2 hypoglycaemia (i.e., glucose values <3.0 mmol/L) overnight.

This work demonstrates that individual GSDIa patients’ CGM outcomes can be compared to reference values obtained from a matched GSDIa reference population, as well as from matched healthy volunteers. Separately analysis of CGM data collected during day and night-time may allow for optimal interpretation of the CGM results. Obviously, other factors that may influence glucose homeostasis, such as dietary management and exercise, should be considered when interpreting the glucose patterns. The correlation between CGM results and dietary intake or physical activity was not considered in the current study. Follow-up studies investigating the major determinants of CGM-derived parameters are warranted.

Collecting CGM data from GSDIa patients poses major challenges. First, no general agreement on CGM outcome parameters in GSDIa exists. In this study we referred to parameters commonly used
for DM\textsuperscript{42}. Second, GSDIa patients display large variability with regard to their clinical phenotype, dietary scheme and physical activity\textsuperscript{32}. It is not clear whether the sample size in the present study adequately covers such variability. Third, several types of CGM devices have been previously used in patients with hepatic GSDs presenting with different functionalities, advantages, and limitations (Table 2). Notably, none of them has been formally licensed for use in patients with hepatic GSDs. Additionally, data management applications currently vary depending on the type of CGM device installed and interconnectivity between CGM softwares and digital health records is lacking. Fourth, it is currently unknown how many measurements are minimally required to generate reliable CGM profiles in GSDIa patients. In DM patients 14-day data collection is recommended to adequately predict the GV over a 3-month period\textsuperscript{46}. Within the current study, this was unfortunately not feasible. Based on the above-mentioned considerations, this work provides insights that are of great importance towards the (routine) use of CGM in clinical research and care for GSDIa patients.

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<tr>
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Table 2. Previous studies using CGM in hepatic GSDs patients.
7.2.2 Cortisol: a novel biomarker for GSDI

Although endocrine abnormalities have been extensively reported in GSDI\textsuperscript{47-51}, adrenal cortex function had not been assessed systematically. Chapter 3 presents our study of baseline and ACTH-stimulated adrenal cortex hormone responses in 17 GSDI patients (10 GSDIa, 7 GSDIb) and 34 age- and gender-matched healthy volunteers.

This study reveals that imbalanced serum cortisol levels are a feature of GSDI. Specifically, GSDIa patients exhibit increased baseline and ACTH-stimulated cortisol levels while GSDIb patients show reduced baseline cortisol levels. We hypothesise that cortisol imbalance in GSD I may result from deregulation of adrenal cortex or hepatic 11\beta-hydroxysteroid dehydrogenase type 1 (11\betaHSD1) activity. 11\betaHSD1 is an ER-bound enzyme that catalyses the conversion of inactive cortisone in active cortisol. Its activity is determined by G6P levels within the ER\textsuperscript{52}. Thus, 11\betaHSD1 activity potentially links endocrine regulation and metabolic derangement in GSDI. Notably, cortisol imbalance may also increase the risk for metabolic syndrome development in GSDIa patients\textsuperscript{53}.

A direct correlation between baseline cortisol serum levels and both cholesterol and TG serum levels is also found in GSDI patients. Since cellular glucocorticoid synthesis involves the shuttling of (lipid) precursors between mitochondria and the ER\textsuperscript{54}, high cortisol levels might represent a mechanism to divert lipid excess within the mitochondria in GSDIa. Interestingly, increased G6P levels in ER\textsuperscript{55} and mitochondrial dysfunction\textsuperscript{56} have been proposed as the cause and the effect of hypercholesterolemia in GSDIa, respectively.

Notably, GSDIb patients exhibited lower basal cortisol levels while they generally display remarkably less severe hyperlipidaemia as compared to GSDIa patients\textsuperscript{50,53}. A reduction of 11\betaHSD1 activity in GSDIb immune cells may represent one of the factors contributing to impaired immune cell function and chronic inflammation\textsuperscript{57} as 11\betaHSD1 deficiency is associated with delayed resolution of inflammation\textsuperscript{58} while glucocorticoids, which are amongst the major modulators of regulatory T cells\textsuperscript{59}, can protect from the development of autoimmunity\textsuperscript{60}.

Overall, we demonstrate for the first time that GSDI patients display imbalanced cortisol homeostasis. This result is particularly relevant as it extends the current disease phenotype. Also, cortisol might serve as an additional biomarker for patients’ monitoring. Although we hypothesise a role for tissue 11\betaHSD1 activity in mediating imbalanced cortisol homeostasis in GSDI, the underlying mechanisms remain largely unresolved. Besides being regulated by 11\betaHSD1 activity, serum cortisol levels are also subject to regulation by the hypothalamic-pituitary-adrenal axis as well as by circulating glucose concentrations. The unaltered adrenal cortex hormone levels suggest absence of hypothalamic-pituitary-adrenal axis dysfunction in GSDI patients. Baseline glucose levels were comparable between patients and healthy volunteers and the ACTH stimulation test was designed not to exceed patients’ fasting tolerances. Although glucose concentrations were not routinely monitored during the ACTH stimulation test, available data from 4 patients indicate relatively stable glycaemia during the test suggesting that changes in glucose concentrations likely did not affect the measured cortisol levels in the present study.
7.3 Future perspectives

Despite the progress made over the past decades, there still exists a compelling need to improve clinical outcomes and to uniformly deliver state-of-the-art healthcare to patients with hepatic GSDs\(^2\). In addition, novel promising treatments for hepatic GSDs are becoming available, requiring more reliable, safer, and easier monitoring tools. Surrogate endpoints need to be defined in order to identify early treatment responses. Moreover, methodologies to integrate standardised and structured data for so-called real-world databases are urgently warranted. The research presented in this thesis aimed to provide possible solutions to these needs. Future research challenges can hence be summarised in three categories: novel treatment strategies, novel monitoring tools and (re)organization of healthcare.

Developing novel treatment strategies is a compelling need for patients with hepatic GSDs\(^2\). Although switching to a high fat diet appears to be promising for patients with GSDIII many uncertainties remain on the long-term effect of dietary modifications as well as on the optimal dietary regimen. Recordings of dietary intake are often complicated by poor documentation and compliance. Also, discrepancies between described and consumed diets often exist. These factors make it challenging to identify correlations between dietary patterns and long-term complications. In this respect telemedicine platforms allowing for home-site monitoring of dietary habits could provide valuable tools\(^61\). In addition, evidence should be collected to define the recommended daily amount of lipids and to determine whether specific lipids (e.g., medium chain triglycerides) may provide additional benefits. Furthermore, assessment of the potential synergistic effects of combined therapeutic approaches (e.g., high-fat diet together with exercise training\(^62\) or acute nutritional ketosis\(^63\)) is worthwhile. Finally, the efficacy of dietary lipid modifications in other hepatic GSDs subtypes remains to be assessed.

Our work furthermore expands the evidence on the benefits of empagliflozin treatment for GSDIb patients. Shortly after release of our paper, a short report was published which confirmed improvement of IBD symptoms in response to empagliflozin treatment\(^64\). Yet, current experience and evidence is limited, while three clinical trials are currently ongoing (Table 1). In addition, an international collaborative retrospective study on empagliflozin treatment in GSDIb patients is currently integrating all published and unpublished cases. One major issue is that as empagliflozin is currently an off-label drug for GSDIb each healthcare professional takes the responsibility of independently treat his/her patients after obtaining a written informed consent. This can result in supply/reimbursement issues depending on the local healthcare policies. Expansion of current evidence on the efficacy of empagliflozin is expected to ameliorate these challenges by including this drug as a licensed treatment option for GSDIb. Besides these regulatory issues, aspects that need further investigation include the optimal daily dosing, and the potential of baseline 1,5AG concentrations to predict treatment responses in GSDIb patients. Additionally, the (dis)advantages of other SGLT2-inhibitors (i.e., dapagliflozin, canagliflozin), and the (side) effects of long-term empagliflozin treatment remain to be established.

The novel promising therapies that are currently being investigated aim to target GSDIa disease pathophysiology rather than its symptoms and/or signs. Among these, gene-based therapies are of particular interest. Gene therapy (GT) with adeno associated (AAV) vectors was shown to restore G6Pase activity and ameliorated disease sequelae in murine and canine models for GSDIa\(^65-66\).
Although challenged by the large size of the human gene, hepatic correction and rescued muscle function was also observed after dual-vector AGL administration in GSDIII mice\textsuperscript{67–68}. Reduced glycogen content and improvement liver and muscle function was also observed in the murine model for GSDIV after AAV9-GBE infusion\textsuperscript{69}. GT appears to be less effective in GSDIb as the loss of vector genomes during cell division only allows for transient reversal of neutropenia\textsuperscript{70}. Alternative approaches are therefore also explored. For example, mRNA therapy delivered to the target tissue via lipid nanoparticles improved fasting glucose concentrations and prevented the occurrence of liver neoplasms in the murine model of GSDI\textsuperscript{8}. Following these promising preclinical results, several clinical trials were initiated to assess the safety and efficacy of novel therapies in hepatic GSDs patients (Table 1).

Since current tools do not always appear sufficiently reliable and/or safe/simple to assess treatment efficacy, development of novel monitoring tools is essential. In this thesis two tools that could potentially expand current monitoring of hepatic GSD patients have been presented. Previously collected evidence supporting the (routine) use of CGM in clinical research and care for GSDI\textsuperscript{a} patients was extended by the study described in chapter 2. Although several studies on hepatic GSDs made use of CGM (Table 2) a number of unsolved questions prevent widespread and optimal CGM use in hepatic GSDs patients. First, consensus should be reached on the definition of “low-glucose” and “high-glucose” thresholds. Second, the relationship between CGM-derived outcome parameters and traditional biomedical outcomes as well as the prognostic role of these parameters should be investigated. Third, a thorough integration of CGM data and information on the diet and physical activity should be attained. Fourth, harmonising the CGM data management systems and developing infrastructures to integrate CGM data into EHR is a compelling need. Fifth, reference values for CGM parameters should also be generated for the hepatic GSDs subtypes other than type Ia.

Extension of the GSDI phenotype with perturbed cortisol homeostasis (chapter 3) may have intriguing implications. Our findings are particularly remarkable considering that hormonal perturbations in GSDI patients potentially complicate monitoring of clinical trials on novel therapies which involve corticosteroid treatment to prevent potential treatment side-effects (Table 1). As next research step it is critical to investigate (1) the relationship between chronic hypercortisolism and growth problems in GSDI\textsuperscript{a}, and (2) cortisol homeostasis in hypoglycaemic GSDI patients.

As previously mentioned, the application of stable isotope methods to longitudinally quantify EGP rates in humans\textsuperscript{71} could provide a means for minimally invasive monitoring of patients with hepatic GSDs. Changes in EGP may reflect specific enzyme defects in hepatic GSDs. Therefore, at least in theory, stable isotope-based EGP assessment could enable monitoring efficacy of novel treatments. Yet, the need for intravenous (or via nasogastric tube) tracer administration and repeated venous blood sampling\textsuperscript{72–74} currently limits the application of this method and its use in the home-setting. Future studies exploring alternative administration routes and sampling modalities are therefore warranted. The ongoing ENGLUPRO GSDI\textsuperscript{a} study (NCT04311307) is aiming to assess glucose homeostasis in GSDI\textsuperscript{a} patients using an orally administered stable isotope and dried blood spot sampling.
The use of emerging high-throughput analytical technologies such as metabolomics, proteomics and lipidomics greatly enhances the potential for identification of novel disease biomarkers. Integration of clinical, nutritional, biochemical, CGM, imaging, and omics data will subsequently contribute to the establishment of personalized disease profiles for hepatic GSDs patients. The availability of novel biomarkers may also open new perspectives for population newborn screening for hepatic GSDs. In this respect, identifying sensitive and specific biomarkers for specific disorders to be assessed on dried blood spots is crucial.

Delivering standardized high-quality healthcare to patients worldwide is amongst the top research priorities for hepatic GSDs. To achieve this aim, (re)organization of healthcare over the next years is essential. The development of a generic emergency protocol constitutes a major step towards this aim. Formal agreement between all contributors is required prior to protocol inclusion in consensus guidelines. Expansion of knowledge and experience will drive protocol revisions. Since ethical and organizational aspects prohibited direct comparison of “generic” and “personalised” emergency protocols, additional data on worldwide protocol utilization are warranted to confirm its efficacy. Prevention and reversal of catabolic states are critically important in hepatic GSDs as well as other disorders in which carbohydrate metabolism is perturbed, such as idiopathic ketogenic hypoglycaemia, congenital hyperinsulinism, and patients using ketogenic diets and patients with inherited metabolic disorders of the intoxication type, e.g., organic acidemias, urea cycle defects. It is therefore worthwhile to investigate whether the approach herein presented may also benefit the management of such disorders.

Major challenges to ensure optimal healthcare and perform high-quality research for patients with hepatic GSDs remain. Research and clinical expertise on hepatic GSDs are generally fragmented and confined to personal interest of a limited number of experts, and interaction between stakeholders, i.e., healthcare professionals, fundamental/translational scientists, patients, industry, regulatory agencies, is not sufficiently guaranteed. In the everyday reality, directing research agendas towards the most urgent needs and getting access to state-of-the-art healthcare and therapeutic options, is extremely challenging for patients with hepatic GSDs. Traditionally health care systems are focused on local delivery of care, while hepatic GSDs patients usually do not live close to expert health care providers. Large clinical and dietary heterogeneity in GSD patients furthermore challenges the interpretation of traditional outcome parameters. Moreover, due to the rapid fluctuations in glucose homeostasis, there is high degree of self-management while monitoring and management guidelines for GSD patients still differ between parts of the world, causing unwanted variations in diagnosis, treatment, and outcomes. Finally, information on guidelines and care pathways does not always reach every patient. There is a strong compelling need to develop inclusive collaborative networks to efficiently provide knowledge to individual GSD patients at any time or place. Ideally, such networks would integrate and expand existing patient registries and telemedicine/knowledge dissemination platforms.

Integrating healthcare and research, homeside monitoring and establishment of standard outcome measures are key for effective characterisation of rare diseases. It is increasingly recognised that patients and families need to be involved when prioritizing (patient-reported) outcome measures. Notably, the generic emergency protocol presented in chapter 5 included patients’ input, underlining...
General discussion and future perspectives

that active participation of patients at early stages of biomarkers/management strategies/drug development processes is paramount. By organising healthcare according to the needs and preferences of the individual patient, value-based healthcare (VBHC) intends to achieve better outcomes for patients and hence, improve quality of patient care, at reduced cost. In the VBHC approach patients’ relevant medical outcomes define their view, whereas Integrated Practice Units (IPU) define the organizational view. An IPU can be defined as “organized around the patient and providing the full cycle of care for a medical condition, including patient education, engagement, and follow-up and encompass inpatient, outpatient and rehabilitative care as well as supporting services”\textsuperscript{79}. In this respect, development of collaborative networks organised according to a VBHC approach, including health care providers, scientists, patients and their families has the potential to radically impose positive changes on the future of research and healthcare.

7.4 Concluding remarks

Until the 1970s, hepatic GSDs were mostly fatal diseases. Subsequently frequent feeding, continuous nocturnal gastric drip-feeding and UCCS contributed to maintain normoglycaemia, hence increasing patients’ life expectancies\textsuperscript{3-7}. The availability of these treatment options and establishment of biomarkers and guidelines have improved patients’ prognosis and outcome, changing the clinical focus of hepatic GSDs from mortality to morbidity over the past decades. Nowadays additional efforts are needed to improve quality of life and healthy ageing for hepatic GSDs patients. This thesis combined studies on novel modalities for monitoring and management. Our studies have opened doors for future research directing precision medicine for individual GSD patients. Multistakeholder meetings in which of variety of professionals (including scientists, healthcare professionals, data analysts and software developers), patients, industry and regulators interact should be facilitated to prioritise strategies for research and care\textsuperscript{80}. Patient value will be maximized when patients and their families actively participate during all phases of the process.
REFERENCES


Chapter 7


