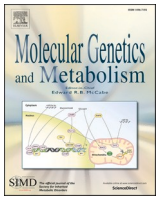
Molecular Genetics and Metabolism 145 (2025) 109129

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Research Paper

State of the art management practices for liver glycogen storage disorders: Results from an international survey among metabolic centres

Sarah C. Grünert [a,*], Terry G.J. Derks [b,c,1], Alessandro Rossi [d,1], GSD Collaboration group

[a] Department of General Pediatrics, Adolescent Medicine and Neonatology, Medical Centre - University of Freiburg, Faculty of Medicine, Freiburg, Germany
[b] Section of Metabolic Diseases, Beatrix Children's Hospital, University Medical Center of Groningen, University of Groningen, Groningen, the Netherlands
[c] UMCG Center of Expertise for Carbohydrate, Fatty Acid Oxidation and Ketone Bodies Disorders, University Medical Center Groningen, Groningen, the Netherlands
[d] Department of Translational Medicine, Section of Pediatrics, University of Naples "Federico II", Naples, Italy

ARTICLE INFO

Keywords:
Liver glycogen storage diseases
Diagnostics
Monitoring
Treatment
Management

ABSTRACT

Background: Liver glycogen storage disorders (GSDs) are rare inherited disorders of carbohydrate metabolism that are clinically characterized by hepatomegaly and fasting intolerance. This group of disorders comprises GSD Ia and Ib as well as the so-called ketotic GSDs including GSD III, VI, IX, XI and 0a. Although clinical practice guidelines exist for most GSD subtypes, diagnostics, treatment and monitoring differ significantly among metabolic centres. The aim of this study was to gain insight into current clinical practice for liver GSDs.
Methods: An international web-based survey was performed among health care professionals involved in the care of individuals with liver GSDs.
Results: Sixty-seven respondents from 28 different countries caring for approximately 2650 liver GSD patients completed the survey. While the diagnostic approach was generally consistent, significant differences among metabolic centres are still observed with respect to monitoring parameters and treatment approaches. Reasons for these differences are local availability of management tools and treatment options, the rarity of the different GSD subtypes, the experiences of health care professionals, and the existence of extreme phenotypes.
Conclusion: The development of a standard set of outcomes for patients with liver GSDs is warranted as a reference for both daily care and the evaluation of safety and efficacy of future therapies. For various parameters that serve as valuable outcome measures, tools and target values should be better defined.

1. Introduction

Liver glycogen storage disorders (GSDs) are a group of inherited metabolic disorders caused by enzyme or transporter defects that lead to an impaired synthesis or degradation of glycogen in the liver [1–3]. Liver GSDs addressed in this article comprise GSD Ia and Ib as well as the so-called ketotic GSDs including GSD III, VI, IX, XI (Fanconi-Bickel syndrome, FBS) and 0a. Most liver GSDs are clinically characterized by hepatomegaly (except in GSD 0a) and a reduced fasting tolerance resulting in recurrent hypoglycemia. Additional extrahepatic features characterize specific GSD subtypes, such as neutropenia/neutrophil dysfunction and inflammatory bowel disease (IBD) in GSD Ib (and rarely also in GSD Ia), skeletal and cardiac muscle involvement in GSD IIIa, and renal tubular disease in FBS.

Clinical practice guidelines based on expert opinions have been developed for GSD I, GSD III, GSD VI, and hepatic GSD IX [4–9]. These guidelines contain both diagnostic and therapeutic considerations. Nevertheless, clinical practice remains heterogenous and often depends on the local availability of monitoring tools/parameters or treatment options. To gain insight into current clinical practice, we performed a web-based questionnaire among metabolic centres involved in the clinical care of patients with liver GSDs.

Abbreviations: GSD, glycogen storage disorders; IBD, inflammatory bowel disease; HCP, health care professional; MetabERN, European Metabolic Reference Network for Hereditary Metabolic Disorders; ACE, angiotensin converting enzyme; AR, angiotensin receptor.

* Corresponding author at: Department of General Pediatrics, Adolescent Medicine and Neonatology, Medical Center - University of Freiburg, Breisacher Straße 62, 79106 Freiburg, Germany.
E-mail address: sarah.gruenert@uniklinik-freiburg.de (S.C. Grünert).

[1] Equal contribution.

https://doi.org/10.1016/j.ymgme.2025.109129
Received 8 February 2025; Received in revised form 23 April 2025; Accepted 25 April 2025
Available online 6 May 2025

2. Methods

A web-based questionnaire for health care professionals (HCPs) involved in the care of individuals with liver GSDs was developed by three of the authors (SCG, AR and TGJD) using SurveyMonkey®.

The questionnaire consisted of 60 questions in the following categories: 1) demographic data of the respondents' contact details and information on clinical experience in the treatment of GSD patients (e.g. number of patients, subtypes of liver GSDs), 2) methods used for confirmatory diagnostics, and 3) current practices for treatment and monitoring. The questionnaire is available as supplementary material (Additional File 1).

The survey was distributed through e-mail to HCPs taking care of individuals with liver GSD who: (a) were invited participants of the workshop on the management of liver GSDs during the European Metabolic Group Meeting in Leuven on June 20, 2024; (b) collaborate within the European Reference Network for Hereditary Metabolic Disorders (MetabERN); (c) collaborate within the GSDValue project, aiming to develop a standard outcome set for liver GSDs; (d) have participated in the International Priority Setting Partnership for liver GSDs [10]; or (e) work in locations where relevant clinical trials in liver GSDs are conducted. HCPs were asked to complete only one survey per metabolic centre.

The survey was distributed in April 2024 and closed on June 1, 2024. For this non-interventional questionnaire study, no ethics approval was necessary.

2.1. Statistics and data analysis

All data are presented using descriptive statistics. Results are expressed as percentages and medians (ranges). Not all HCPs answered all questions of the survey, therefore the total number of respondents varies between questions.

3. Results

3.1. Information on HCPs

Sixty-seven respondents from 28 countries across Europe, North America, Africa, Asia, and Australia answered the survey. Of these, 63 (95 %) were physicians, 10 were researchers, two each were dieticians or caregivers of a person with liver GSD, and one each was a nurse practitioner or a nutrition scientist (multiple responses were possible).

Most of the HCPs take care of both children and adults (60 %), while 34 % only care for pediatric patients and 6 % only follow adult patients with liver GSDs. The estimated total number of liver GSD patients followed by all respondents is about 2650. More than 80 % of centres take care of individuals with GSD types Ia, Ib, III and IX. Patients with less common GSD subtypes such as GSD type VI are seen by 57 % of respondents, while less than 45 % of respondents report to follow patients with GSD types IV, FBS and 0 (32 %, 35 % and 42 % for GSD IV, FBS and 0, respectively). These data are shown in Fig. 1.

3.2. Confirmatory diagnostics

For confirmatory diagnostics, most respondents prefer genetic techniques such as gene panel analysis (75 %), targeted genetic studies (Sanger sequencing, 36 %) or whole exome sequencing (27 %). Whole genome sequencing is rarely performed as primary confirmation diagnostic method (8 %). Enzymatic studies in blood cells, liver tissue or cultured fibroblasts only play a minor role (< 10 %) and are mainly performed if genetic studies are inconclusive.

3.3. Clinical and laboratory monitoring

Beyond infancy, patients are clinically monitored every 6 months (62 %), every 3 months (31 %) or every 12 months (9 %). However, follow-up intervals may vary depending on the age, the GSD subtype, the phenotype and clinical condition or patients' needs. Some patients are followed in a shared care model (metabolic expert together with the family/general practitioner or a local paediatrician, internal medicine specialist or metabolic specialist).

Continuous glucose monitoring (CGM) has become widely available for the monitoring of GSD patients within the last decade. Of 65 respondents, 30 (46 %) recommend CGM for all their liver GSD patients. Sixteen (25 %) only recommend CGM for GSD I patients and 5 (8 %) only for patients with ketotic GSDs. The recommendation may depend on the metabolic stability of the patient, patients' age, risk factors, the patients' preference, insurance coverage, activity levels, daily life, work, and others. CGM is also used to monitor and evaluate dietary interventions. Forty-five percent of respondents recommend to use CGM continuously, 34 % intermittently, 29 % only for unstable patients, and 35 % only for certain indications such as dietary adaptations (multiple answers were possible). Three respondents do not routinely use CGM for their patients,

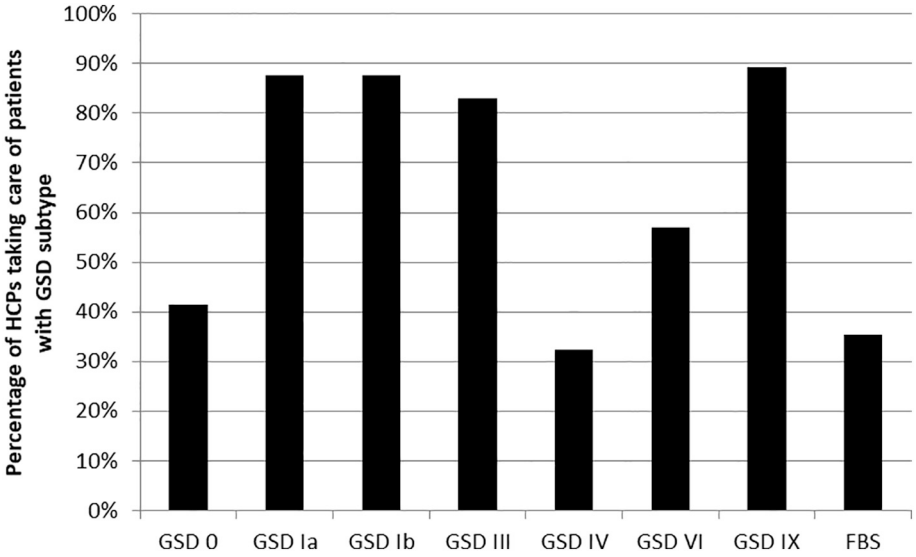


Fig. 1. Different GSD subtypes treated by international metabolic centres. While most HCPs have experience in the treatment of GSD Ia, Ib, III, VI and IX, less than 50 % follow patients with IV, FBS, 0 and FBS.

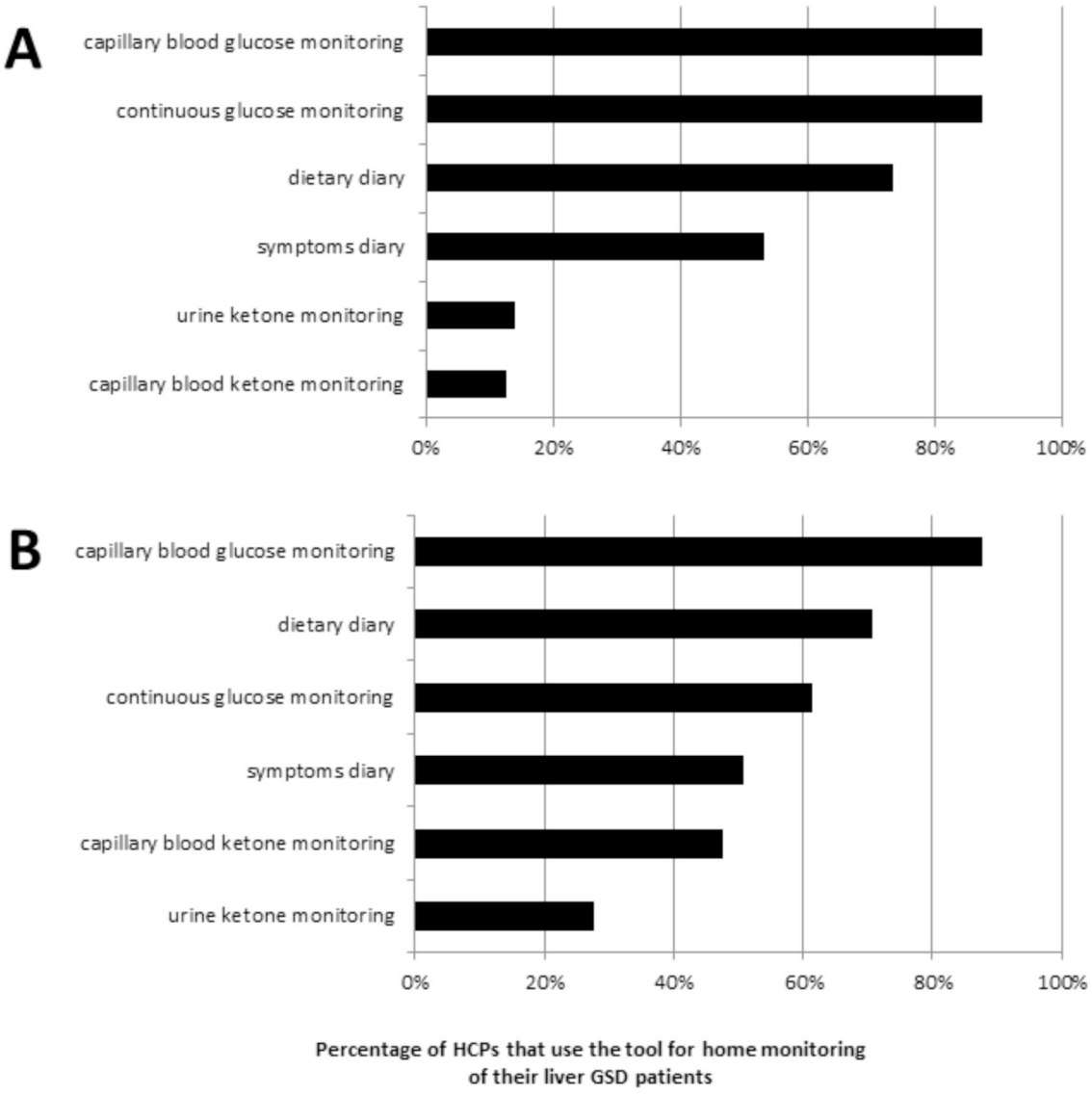


Fig. 2. Components of home monitoring for GSD I (A) and ketotic GSDs (B) recommended by individual HCP survey responders. The three most important components of home monitoring comprise capillary glucose monitoring, CGM and a dietary diary for all GSD subtypes.

mainly because it is not available in their centres.

Recommended parameters for home monitoring in GSD I and ketotic GSDs are shown in Fig. 2A and B, respectively. Among these, capillary glucose monitoring, CGM and a dietary diary are recognized by HCPs as the three most important components of home monitoring for all GSD subtypes. Capillary blood glucose monitoring by finger sticks is considered the most important parameter of home monitoring for all GSD subtypes.

For GSD I, recommended limits for the glucose target values ranged from 2.8 to 4.4 mmol/L with a median of 3.7 mmol/L (67 mg/dL) for the lower limit and from 5.5 to 10.0 mmol/L with a median of 6.7 mmol/L (121 mg/dL) for the upper limit. The proposed targets for ketotic GSDs were not different (median lower limit 3.6 mmol/L and median upper limit 6.9 mmol/L, respectively). While 63 % of respondents report to use the same glucose targets for all their patients with the same GSD subtype, 37 % think that glucose targets should be adjusted dependent on the patients' metabolic stability (91 %), number of clinically significant hypoglycemic episodes (76 %), patients' age (73 %), liver size (15 %) and other factors such as patients' needs (multiple answers were possible).

HCPs were asked to rank different clinical and laboratory monitoring parameters with respect to their importance for the evaluation of metabolic stability in GSD I patients and patients with ketotic GSDs. The results are displayed in Fig. 3. Capillary and continuous glucose monitoring are considered the most important measures for both GSD I and ketotic GSDs.

To evaluate the protein status of ketotic GSD patients, the following parameters are used: albumin concentration in serum or plasma (71 %), total protein in serum or plasma (66 %), prealbumin or transthyretin concentration in serum or plasma (54 %), creatine kinase concentration in serum or plasma (25 %) and morning capillary ketone (β-hydroxybutyrate) levels in blood (25 %). Few respondents also report to regularly measure plasma amino acids and blood urea. In one centre, the body composition is assessed on a routine basis.

For the assessment of liver complications such as adenoma or hepatocellular carcinoma, the majority of respondents uses plasma alpha fetoprotein (AFP) concentrations (77 % and 59 % in GSD I and ketotic GSD patients, respectively), while des-gamma-carboxy prothrombin (DCP,PIVKA-II) levels are used by less than 8 % of HCPs for all liver GSD types. Routine screening for pancreatitis in patients with GSD I is performed by 37 % of respondents, while the remainder only performs lipase or amylase measurements in patients with a high triglyceride

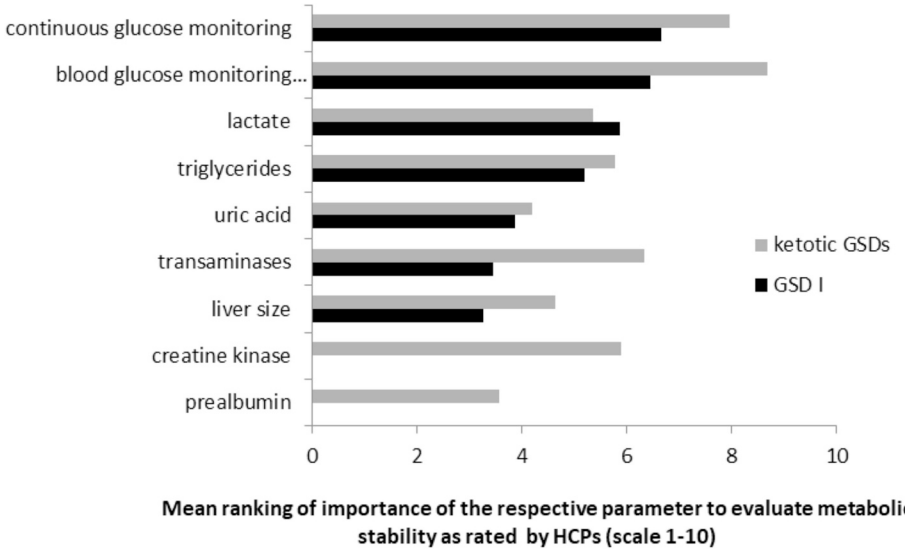


Fig. 3. Ranking of different clinical and laboratory monitoring parameters with respect to their importance for the evaluation of metabolic stability in GSD I patients and patients with ketotic GSDs based on individual HCP survey responses.

concentration and/or clinical symptoms suggestive of pancreatitis.

Regular spot urinalysis to screen for proteinuria in GSD I patients is performed by 84 % of HCPs, whereas 24-h urinalysis is only performed by 39 %. Lactate monitoring in urine is not part of routine care in most centres (74 % of respondents). In the remainder, lactate monitoring is either performed in random samples (18 %), 24 h urine samples (4.8 %) or in samples reflecting times between meals (4.8 %).

Regular liver ultrasound investigations are recommended by most HCPs (94 % for GSD I patients and 91 % for ketotic GSD patients). Additionally, transient elastography investigations are recommended for GSD I patients by 52 % of respondents and for ketotic GSD patients by 66 % of HCPs. Liver magnetic resonance imaging (MRI) is recommended for patients with abnormalities in ultrasound by 85 % of HCPs, and patients with elevated AFP or DCP (PIVKA-II) concentrations by 58 % of HCPs. Nine percent recommend routine MRI of the liver for all patients and another 9 % only for all adult patients. Regular kidney ultrasound investigations in GSD I patients are performed by 86 % of HCPs.

3.4. *Dietary interventions and supplements*

Despite the administration of galactose with human milk, one third of respondents (33 %) considers full breast-feeding of a baby with GSD I possible, while another 53 % think that partial breast-feeding is possible in individuals with GSD I.

Uncooked corn starch is used for GSD Ia, GSD Ib and ketotic GSDs by 95 %, 89 % and 91 % of HCPs, respectively. Respondents consider starting corn starch treatment from a mean age of 10 months (range 0–24 months) (Fig. 4a). Glycosade®, a commercially available extended-release waxy maize cornstarch, is used for GSD Ia, GSD Ib and ketotic GSDs by 82 %, 74 % and 68 % of respondents, respectively. Starting Glycosade® treatment is recommended by respondents from a mean age of 23 months (range 4–60 months) (Fig. 4b).

For ketotic GSD patients, a protein-rich diet is recommended by almost all HCPs (98 %), usually in combination with the reduction of simple sugars (76 %). A reduction of the overall carbohydrate intake (30 %), a fat-rich diet (22 %), a carbohydrate-rich diet (19 %), and the supplementation of medium-chain triglycerides (10 %) are only recommended by a minority of HCPs. Protein supplements are used by 70 %

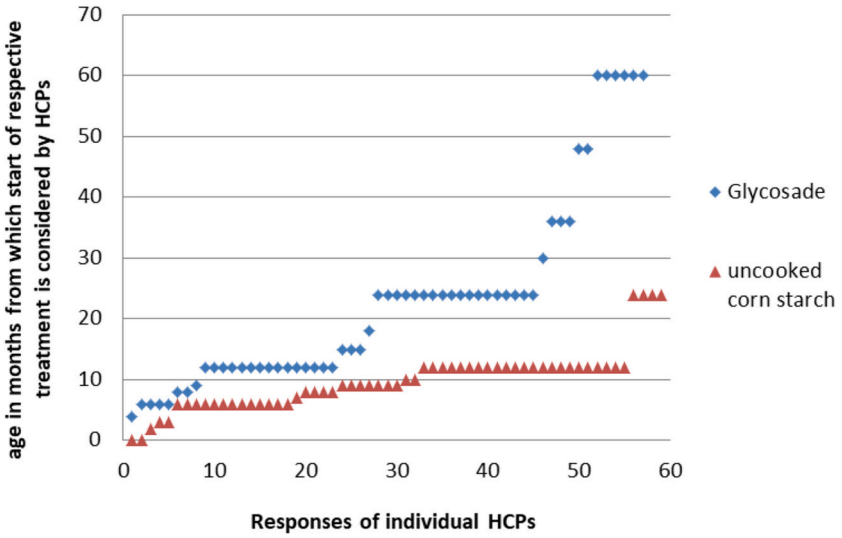


Fig. 4. Age at which start of uncooked corn starch and Glycosade® treatment is considered by individual HCPs.

of respondents to meet the high protein demands of patients with ketotic GSDs.

Fibre supplements are routinely used in all GSD patients by only 5 % of HCPs. However, 48 % of respondents report to use fibre supplements in some of their GSD patients.

More than half of the respondents (54 %) routinely supplement vitamins in all their GSD I patients, whereas others only recommend vitamin supplementation in patients with vitamin deficiencies (43 %) or patients with a severely restricted diet (19 %). For patients with ketotic GSDs, only 26 % of HCPs recommend vitamin supplements for all patients, 55 % in patients with vitamin deficiencies and 35 % for patients with a severely restricted diet.

3.5. Medications

3.5.1. GSD I

Eighty-one percent of respondents recommend xanthine oxidase inhibitor treatment in patients with elevated blood uric acid levels, while 13 % consider starting treatment only after the first gout attack. Citrate supplementation is used in all GSD I patients by 10 % of HCPs, while 44 % only start treatment in patients with nephrolithiasis and 39 % in patients with kidney stones on ultrasound. Twenty-seven percent of respondents do not use citrate supplementation at all in their patients.

Seventy-five percent of HCPs recommend angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor (AR) blocker treatment in patients with GSD I displaying microalbuminuria or proteinuria, while only 3 % start treatment in all GSD I patients, irrespective of the presence of proteinuria. Seventeen percent report to not use ACE inhibitors or AT blockers in their GSD I patients.

Forty percent of HCPs recommend vitamin D supplementation for all their GSD I patients, while 58 % only supplement in patients with vitamin D deficiency.

Nowadays, neutropenia and neutrophil dysfunction in patients with GSD Ib can be causally treated with SGLT2 inhibitors, however, until that therapy was identified in 2020, treatment with granulocyte colony stimulating factor (G-CSF) had been the standard of care for neutropenic GSD Ib patients. Currently, 44 % of HCPs already treat all their GSD Ib patients with empagliflozin. One third (33 %) recommends the use of empagliflozin in neutropenic patients, and 30 % in patients with neutropenic symptoms such as mucosal lesions, diarrhea or skin infections. Eight percent consider empagliflozin in patients in whom G-CSF treatment is not sufficient, and 5 % do not use empagliflozin at all. Seventy-two percent of HCPs consider empagliflozin treatment in their patients before the onset of neutropenic complications. The respondents consider starting treatment at a mean age of 10 months (range 0–100 months). Only 2 % of HCPs still use G-CSF in all GSD Ib patients. One third (33 %) recommends G-CSF in neutropenic patients, 27 % in patients with neutropenic symptoms, and 65 % in patients in whom empagliflozin treatment is not sufficiently effective. Six percent report that they never use G-CSF in their GSD Ib patients.

3.5.2. Ketotic GSDs

In patients with ketotic GSDs, regular vitamin D supplementation is recommended for all patients by 29 % of respondents irrespective of the vitamin status, while 69 % of HCPs start vitamin supplementation only in patients with vitamin D deficiency.

3.6. Liver transplantation

In principle, liver transplantation leads to normalized glycemic and metabolic control. While normalization of the fasting tolerance allows discontinuation of a strict dietary treatment in most GSD types, patients with GSD IIIa still need limitation of carbohydrate intake for the sake of their (still abnormally functioning) muscles. Only 9 % of the respondents consider liver transplantation an option for all their GSD I patients, while 88 % consider it in patients with liver adenoma that do not respond to dietary adaptations. Improvement of quality of life is considered a potential transplant indication for 34 % of HCPs. Five percent do not consider liver transplant an option for GSD I at all.

3.7. Emergency letters and psychosocial support

Eigthy-9 % of respondents report that all their GSD patients are provided with an emergency letter. Since a few years, a generic emergency protocol for liver GSDs that has been developed by an international consortium of metabolic and genetic specialists within the framework of the MetabERN network, is available at the website www.emergencyprotocol.net [11]. Seventy-two percent of the HCPs are aware of this website, but only 30 % use it regularly to create emergency letters for their patients.

Liver GSDs are associated with a high disease burden. However, not all patients or patient families receive psychological support. About half of the HCPs report that they can offer psychological support to all their patients, while 35 % can only offer it to a subset of patients, and 12 % cannot provide psychological support at all in their institutions.

Patient support groups can also provide peer contact and psychosocial support for patients and their families. Sixty-one percent of repondents report to refer all their liver GSD patients to the national patient support groups, while 8 % do not. Seventeen percent of HCPs mentioned that there are no national patient support groups in their respective countries.

4. Discussion

Liver GSDs are a group of inherited disorders of carbohydrate metabolism displaying a multisystem involvement requiring multidisciplinary care and raising substantial organizational, logistic, and financial burden for affected families and HCPs. To minimize such obstacles, expert opinion guidelines have been developed for the majority of liver GSD subtypes [4–9]. We hereby report current state-of-the-art clinical practice for management of patients with liver GSDs assessed by an international survey study among HCPs from 28 countries. We observed considerable differences in monitoring and treatment of individuals with liver GSDs worldwide. These differences likely reflect the local availability of managements tools and treatment options, the rarity of the different GSD subtypes, the different experience of HCPs, the geographical distribution of genetic variants and the existence of extreme phenotypes. Additionally, the diversity of practices may also be influenced by the lack of supportive evidence in the absence of natural history data for liver GSDs. As this diversity may cause significant and unwanted variations in diagnosis, treatment and outcomes, standardization of clinical care options and FAIR data availability are paramount to ensure the most favourable outcome for every affected individual. These topics relate to the recent European Health Data Space regulation, which aims to establish a common framework for using and exchanging personal electronic health data across the EU [12].

The need to standardize and uniform management has recently been identified as a top research priority by both HCPs and persons with hepatic GSDs and their caregivers [10]. This need is counterbalanced by the continuous development of novel diagnostic and treatment options. Particularly, the growing number of individuals with atypical/milder phenotypes identified through molecular testing techniques such as whole exome or genome sequencing raises new questions. Defining the clinical significance of genetic variants can be challenging. While the current approach and consensus is to treat the phenotype rather than the genotype, it is increasingly recognized that further development of functional studies is required to address this challenge and better characterize new genetic variants. This may also be important when genetic newborn screening (NBS) becomes practice. In this respect, in vivo tracer studies have the potential to translate to a clinically applicable tool [13].

CGM has become widely available for the monitoring of GSD patients

within the last decade [14], but it can still only be used off label. CGM has been demonstrated to allow refined detection and prevention of hypoglycemias (i.e. nocturnal hypoglycemia or hypoglycemia during physical activity) as well as a better long term metabolic control and thereby, possibly, the reduction of long-term complications [14–17]. It may also be helpful to prevent overtreatment. However, collected data revealed large differences regarding its mode use (e.g. continuous versus intermittent use) and indications among different centres. Similarly, while the recommended glucose target range appears to overlap between GSD I and ketotic GSD types, there is no agreement on whether this target should be adjusted depending on specific individual variables (e.g. GSD subtype, metabolic stability, age, patients' needs). These findings highlight the need to develop consensus guidelines for the use of CGM in liver GSD patients. In addition, it has to be taken into account, that target values for CGM may differ from those for glucose concentrations in capillary blood, whole blood, or plasma due to different matrix and assessment techniques, among others.

Data herein presented also shed light on specific issues requiring further investigation, such as breastfeeding in GSD I and starch therapy in GSD Ib. Information in the literature on breast-feeding in GSD I is scarce as is experience among HCPs, as most patients are only diagnosed during or after weaning from breast feeding. The current approach is mainly based on historical studies and pathophysiological considerations in which galactose restriction was indicated due to impaired gluconeogenesis and thus conversion to glucose [18–20]. Indeed, it remains to be ascertained whether exogenous galactose results in metabolic imbalance in breastfed infants with GSD I.

Glycosade®, a hydrothermally processed high amylopectin cornstarch, is used by many GSD patients as an alternative for uncooked cornstarch. In the past, Glycosade® has been considered contraindicated by many experts for the treatment of GSD Ib patients due to the inflammatory bowel disease associated with the neutropenia and neutrophil dysfunction in this patient group. It is noteworthy, that this is changing, and Glycosade® now seems to be widely used in GSD Ib without major problems, but experimental studies are lacking. This can most likely be attributed to the introduction of SGLT2 inhibitor treatment in recent years, which has led to a significant improvement in chronic inflammatory bowel disease and gastrointestinal symptoms in many GSD Ib patients [6,21,22].

Overall, there are considerable differences in the management of individuals with liver GSDs. This variability is expected to further increase as novel monitoring and treatment options arise, which may not be equally available to all individuals and HCPs within the GSD community. Hence, it is paramount to create a standard outcome set as a reference for both daily care and the evaluation of the effect of treatments for liver GSDs. This activity is especially warranted to monitor safety and efficacy of (novel) therapies that are in development for liver GSDs, such as dietary interventions, liver transplantation, drug repurposing, gene transfer and mRNA therapy.

5. Conclusion

Despite the progress that has occurred over the past decades, management practices for liver GSDs differ among clinical centers. This may depend on the local and/or national availability of monitoring tools, treatment options and also the patients' phenotype. It is important to adress and reduce the disparities in treatment and monitoring options among patients in different regions/countries. The role that patient organizations, professional organizations and European Reference Networks can play in this process should be explored. The creation of a standard outcome set as a reference for both daily care and the evaluation of safety and efficacy of current and future therapies for liver GSDs is a compelling need.

CRediT authorship contribution statement

Sarah C. Grünert: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Terry G.J. Derks:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Alessandro Rossi:** Writing – review & editing, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

SCG: reports no conflicts of interest relevant to this work. She has received honoraria for educational lectures from Vitaflo GmbH and Ultragenyx Pharmaceutical Inc. as well as for the creation of patient information material for Danone Deutschland GmBH, and received support for attending metabolic expert meetings from Nutricia Metabolics GmbH. She participated in an advisory board for Ultragenyx Pharmaceutical, Inc. TGJD: There are confidentiality agreements with third parties. In the past 36 months, there have been consultation agreements (with Danone S.A., Ultragenyx Pharmaceutical Inc., Moderna Inc., and Beam Therapeutics Inc.), contracts for financial research support for investigator-initiated research (NCT04311307) and sponsor-initiated research (NCT03517085, NCT03970278, NCT05139316, and NCT05196165), honoraria for lectures or presentations (by MEDTalks, Prelum, and Danone S.A.), and participations in a Data Safety Monitoring Board (NCT05095727) and Advisory Boards (Ultragenyx Pharmaceutical Inc., Moderna Inc., and Beam Therapeutics Inc.). For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG. AR: There are confidentiality agreements with third parties. In the past 36 months there have been consultation agreements or honoraria for lectures or presentations with Nestlé, Danone S.A. and Ultragenyx Pharmaceutical Inc.

GSD Collaboration group: A.S.L.-H. reports support of scientific meetings by Danone GmbH (Nutricia metabolics). J.M. reports involvement as PI in the phase II and phase III DTX401 studies by Ultragenyx. D.W. reports consulting agreements with the following companies: Ultragenyx, Beam Therapeutics, Prime Medicine, Moderna, Covert Therapeutics, CTI, Abata Therapeutics, Alltrna, Siren Biotechnology, Danone/Nutricia, Cometa Therapeutics, Golden Heart Flower, Ltd., ZipBio, Chaim Medicine, Vitaflo / Nestle, WIRB-Copernicus Group, SOLA Biotherapeutics. R.S. is a subinvestigator for the Ultragenyx gene therapy study (DTX401-CL301) for GSD Ia. All other authors declare no conflict of interests.

Acknowledgements

We thank Skadi Beblo, Georg F. Hoffman and Eva Morava for the fruitful discussion. P.W. was funded by the Fonds Wetenschappelijk Onderzoek-Vlaanderen (Fundamenteel Klinisch Mandaat 18B4322N).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2025.109129.

Data availability

Data will be made available on request.

References

[1] D.S. Bali, Y.-T. Chen, S. Austin, J.L. Goldstein, Glycogen storage disease type I, in: M.P. Adam, H.H. Ardinger, R.A. Pagon, S.E. Wallace, L.J. Bean, K. Stephens, A. Amemiya (Eds.), GeneReviews®, University of Washington, Seattle, Seattle (WA), 1993. http://www.ncbi.nlm.nih.gov/books/NBK1312/ (accessed April 21, 2020).

[2] A.B. Schreuder, A. Rossi, S.C. Grünert, T.G. Derks, Glycogen storage disease type III, in: M.P. Adam, J. Feldman, G.M. Mirzaa, R.A. Pagon, S.E. Wallace, L.J. Bean, K.

W. Gripp, A. Amemiya (Eds.), GeneReviews®, University of Washington, Seattle, Seattle (WA), 1993. http://www.ncbi.nlm.nih.gov/books/NBK26372/ (accessed June 25, 2024).
[3] M.A. Chen, D.A. Weinstein, Glyogen storage diseases: diagnosis, treatment and outcome, Transl. Sci. Rare Dis. 1 (2016) 45–72.
[4] P.S. Kishnani, J. Goldstein, S.L. Austin, P. Arn, B. Bachrach, D.S. Bali, W.K. Chung, A. El-Gharbawy, L.M. Brown, S. Kahler, S. Pendyal, K.M. Ross, L. Tsilianidis, D. A. Weinstein, M.S. Watson, ACMG Work Group on Diagnosis and Management of Glycogen Storage Diseases Type VI and IX, Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG), Genet. Med. 21 (2019) 772–789, https://doi.org/10.1038/s41436-018-0364-2.
[5] P.S. Kishnani, S.L. Austin, J.E. Abdenur, P. Arn, D.S. Bali, A. Boney, W.K. Chung, A. I. Dagli, D. Dale, D. Koeberl, M.J. Somers, S.B. Wechsler, D.A. Weinstein, J. I. Wolfsdorf, M.S. Watson, American College of Medical Genetics and Genomics, diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics, Genet. Med. 16 (2014) e1, https://doi.org/10.1038/gim.2014.128.
[6] S.C. Grünert, T.G.J. Derks, H. Mundy, R.N. Dalton, J. Donadieu, P. Hofbauer, N. Jones, S.K. Uçar, J. LaFreniere, E.L. Contreras, S. Pendyal, A. Rossi, B. Schneider, R. Spiegel, K.M. Stepien, D. Wesol-Kucharska, M. Veiga-da-Cunha, S. B. Wortmann, Treatment recommendations for glycogen storage disease type IB-associated neutropenia and neutrophil dysfunction with empagliflozin: consensus from an international workshop, Mol. Genet. Metab. 141 (2024) 108144, https://doi.org/10.1016/j.ymgme.2024.108144.
[7] P.S. Kishnani, S.L. Austin, P. Arn, D.S. Bali, A. Boney, L.E. Case, W.K. Chung, D. M. Desai, A. El-Gharbawy, R. Haller, G.P.A. Smit, A.D. Smith, L.D. Hobson-Webb, S. B. Wechsler, D.A. Weinstein, M.S. Watson, ACMG, glycogen storage disease type III diagnosis and management guidelines, Genet. Med. 12 (2010) 446–463, https://doi.org/10.1097/GIM.0b013e3181e655b6.
[8] J.P. Rake, G. Visser, P. Labrune, J.V. Leonard, K. Ullrich, G.P.A. Smit, European study on glycogen storage disease type I (ESGSD I), guidelines for management of glycogen storage disease type I - European study on glycogen storage disease type I (ESGSD I), Eur. J. Pediatr. 161 (Suppl. 1) (2002) S112–S119, https://doi.org/10.1007/s00431-002-1016-7.
[9] G. Visser, J.P. Rake, P. Labrune, J.V. Leonard, S. Moses, K. Ullrich, U. Wendel, G.P. A. Smit, European study on glycogen storage disease type I, consensus guidelines for management of glycogen storage disease type 1b - European study on glycogen storage disease type 1, Eur. J. Pediatr. 161 (Suppl. 1) (2002) S120–S123, https://doi.org/10.1007/s00431-002-1017-6.
[10] F. Peeks, W.F. Boonstra, L. de Baere, C. Carøe, T. Casswall, D. Cohen, K. Cowan, I. Ferrecchia, A. Ferriani, C. Gimbert, M. Landgren, N.L. Maldonado, J. McMillan, A. Nemeth, N. Seidita, U. Stachelhaus-Theimer, D.A. Weinstein, T.G.J. Derks, Research priorities for liver glycogen storage disease: an international priority setting partnership with the James Lind Alliance, J. Inherit. Metab. Dis. 43 (2020) 279–289, https://doi.org/10.1002/jimd.12178.
[11] A. Rossi, I.J. Hoogeveen, C.M.A. Lubout, F. de Boer, M.J. Fokkert-Wilts, I. L. Rodenburg, E. van Dam, S.C. Grünert, D. Martinelli, M. Scarpa, H. Dekker, S. T. Te Boekhorst, F.J. van Spronsen, T.G.J. Derks, CONNECT MetabERN Collaboration Group, A generic emergency protocol for patients with inborn errors of metabolism causing fasting intolerance: a retrospective, single-center study and the generation of www.emergencyprotocol.net, J. Inherit. Metab. Dis. 44 (2021) 1124–1135, https://doi.org/10.1002/jimd.12386.
[12] https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space-regulation-ehds_en.
[13] A. Rossi, M.G.S. Rutten, T.H. van Dijk, B.M. Bakker, D.-J. Reijngoud, M. H. Oosterveer, T.G.J. Derks, Dynamic methods for childhood hypoglycemia phenotyping: a narrative review, Front. Endocrinol. (Lausanne) 13 (2022) 858832, https://doi.org/10.3389/fendo.2022.858832.
[14] A. Rossi, A. Venema, P. Haarsma, L. Feldbrugge, R. Burghard, D. Rodriguez-Buritica, G. Parenti, M.H. Oosterveer, T.G.J. Derks, A prospective study on continuous glucose monitoring in glycogen storage disease type Ia: toward glycemic targets, J. Clin. Endocrinol. Metab. 107 (2022) e3612–e3623, https://doi.org/10.1210/clinem/dgac411.
[15] N. Kaiser, M. Gautschi, L. Bosanska, F. Meienberg, M.R. Baumgartner, G.A. Spinas, M. Hochuli, Glycemic control and complications in glycogen storage disease type I: results from the Swiss registry, Mol. Genet. Metab. 126 (2019) 355–361, https://doi.org/10.1016/j.ymgme.2019.02.008.
[16] R.J. Overduin, A. Venema, C.M.A. Lubout, M.J. Fokkert-Wilts, F. De Boer, A. B. Schreuder, A. Rossi, T.G.J. Derks, Continuous glucose monitoring metrics in people with liver glycogen storage disease and idiopathic ketotic hypoglycemia: a single-center, retrospective, observational study, Mol. Genet. Metab. 143 (2024) 108573, https://doi.org/10.1016/j.ymgme.2024.108573.
[17] M. Herbert, S. Pendyal, M. Rairikar, C. Halaby, R.W. Benjamin, P.S. Kishnani, Role of continuous glucose monitoring in the management of glycogen storage disorders, J. Inher. Metab. Dis. 41 (2018) 917–927, https://doi.org/10.1007/s10545-018-0200-5.
[18] R. Schwartz, J. Ashmore, A.E. Renold, Galactose tolerance in glycogen storage disease, Pediatrics 19 (1957) 585–595.
[19] J. Fernandes, The effect of disaccharides on the hyperlactacidaemia of glucose-6-phosphatase-deficient children, Acta Paediatr. Scand. 63 (1974) 695–698, https://doi.org/10.1111/j.1651-2227.1974.tb16992.x.
[20] K.M. Ross, I.A. Ferrecchia, K.R. Dahlberg, M. Dambska, P.T. Ryan, D.A. Weinstein, Dietary management of the glycogen storage diseases: evolution of treatment and ongoing controversies, Adv. Nutr. 11 (2020) 439–446, https://doi.org/10.1093/advances/nmz092.
[21] S.C. Grünert, T.G.J. Derks, K. Adrian, K. Al-Thihli, D. Ballhausen, J. Bidiuk, A. Bordugo, M. Boyer, D. Bratkovic, M. Brunner-Krainz, A. Burlina, A. Chakrapani, W. Corpeleijn, A. Cozens, C. Dawson, H. Dhamko, M.D. Milosevic, H. Eiroa, Y. Finezilber, C.F. Moura de Souza, M.C. Garcia-Jiménez, S. Gasperini, D. Haas, J. Häberle, R. Halligan, L.H. Fung, A. Hörbe-Blindt, L.M. Horka, M. Huemer, S. K. Uçar, B. Kecman, S. Kilavuz, G. Kriván, M. Lindner, N. Lüsebrink, K. Makrilakis, A. Mei-Kwun Kwok, E.M. Maier, A. Maiorana, S.E. McCandless, J.J. Mitchell, H. Mizumoto, H. Mundy, C. Ochoa, K. Pierce, P.Q. Fraile, D. Regier, A. Rossi, R. Santer, H.C. Schuman, P. Sobieraj, J. Spenger, R. Spiegel, K.M. Stepien, G. Tal, M.Z. Tanšek, A.D. Torkar, M. Tchan, S. Thyagu, S.A. Schrier Vergano, E. Vucko, N. Weinhold, P. Zsidegh, S.B. Wortmann, Efficacy and safety of empagliflozin in glycogen storage disease type Ib: data from an international questionnaire, Genet. Med. 24 (2022) 1781–1788, https://doi.org/10.1016/j.gim.2022.04.001.
[22] S.C. Grünert, M. Gautschi, J. Baker, M. Boyer, A. Burlina, T. Casswall, W. Corpeleijn, K. Çıki, M. Cotter, E. Crushell, T.G.J. Derks, D. Haas, S. Kilavuz, S.D. K. Kingma, S.H. Korman, A. Kozek, C. de Laet, H. Mundy, M.C. Nassogne, V. Quintero, A. Rossi, J. Spenger, R. Spiegel, X. Stephenne, D. Stojkov, G. Tal, M. Veiga-da Cunha, S.B. Wortmann, Empagliflozin for treating neutropenia and neutrophil dysfunction in 21 infants with glycogen storage disease 1b, Mol. Genet. Metab. 142 (2024) 108486, https://doi.org/10.1016/j.ymgme.2024.108486.