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Glycogen storage disease type III: a mixed-methods study to assess the burden of disease

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Ayla Evins, Jill Mayhew, Tricia Cimms, Julie Whyte, Kathy Vong, Elizabeth Hribal, Christopher J. Evans and Andrew Grimm

Abstract

Background: Glycogen storage disease type III (GSD III) is a rare inherited disorder that results from a glycogen debranching enzyme deficiency.

Objectives: The purpose of this research was to collect data on the signs, symptoms, and impacts of GSD III from the perspective of adult patients and caregivers of individuals with GSD III.

Design: Online survey and qualitative interviews.

Methods: Following institutional review board approval, adult patients and caregivers of children with GSD III were recruited through advocacy networks and clinical sites. If eligible, participants were consented, screened, and sent a survey and/or participated in a 60-min interview. The survey and interview included questions about family history, diagnosis, signs and symptoms, impacts, and management of GSD III. Conceptual models were developed following the analysis of results.

Results: In all, 29 adults and 46 caregivers completed the online survey and/or the interviews with 73 survey and 19 interview respondents. Adults and caregivers reported digestive, musculoskeletal, growth and physical appearance, and cardiac signs and symptoms. Liver conditions were reported by most respondents (83%). Adults and caregivers frequently reported impacts such as difficulty keeping up with peers (77%) and difficulty exercising/difficulty with physical activity (53%). Hypoglycemia was frequently reported in both adults and children, with more than half reporting hospitalizations due to hypoglycemia. Caregivers focused on hypoglycemia when reporting signs/symptoms that most interfere with their child's life and prevention of hypoglycemia as a desired outcome for an effective therapy. Adults most often reported muscle weakness as a top interfering symptom and the most important goal of a potential therapy. Impacts were also reported in activities of daily living, cognitive, emotional, work/school, and sleep domains.

Conclusion: Individuals with GSD III experience a broad spectrum of symptoms and disease impacts. There is an unmet need for therapies that improve metabolic control, reduce the burden of dietary management, reduce fatigue and liver problems, and improve muscle strength and function.

Keywords: conceptual model, glycogen storage disease type III, mixed methods, qualitative research, rare disease

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Correspondence to:
Ayla Evins
Ultragenyx Pharmaceutical Inc., 60 Leveroni Court, Novato, CA, 94949 USA
aevins@ultragenyx.com

Jill Mayhew
Tricia Cimms
Andrew Grimm
Ultragenyx Pharmaceutical Inc., Novato, CA, USA

Julie Whyte
Kathy Vong
Elizabeth Hribal
Christopher J. Evans
Endpoint Outcomes, A Lumanity Company, Boston, MA and Long Beach, CA, USA

Introduction

Glycogen storage disease type III (GSD III) is a rare inherited disorder that results from a glycogen debranching enzyme deficiency.[1] The prevalence of GSD III in the general US population and globally is not known. The incidence of GSD III is

approximately 1:100,000 in the United States, with higher incidences in some populations including the North African Jewish population (~1:5400) and in the Inuit population in Nunavik, Canada (~1:2500).[2–4] Two major subtypes of GSD III exist: GSD IIIa and GSD IIIb. Both subtypes are autosomal recessive allelic disorders and phenotype differences are explained in part, by tissue-specific expression. In GSD IIIa, the enzyme is deficient in both the liver and muscle, while in GSD IIIb, the enzyme is deficient only in the liver.[5]

GSD IIIa accounts for approximately 85% of cases.[6] There are two additional subtypes, GSD IIIc and GSD IIId but these subtypes are extremely rare.[7] Common signs and symptoms of GSD III include hepatomegaly, ketotic hypoglycemia, muscle weakness, and growth delay.[1]

While no approved medicines are available for GSD III, a medically prescribed diet can reduce the incidence and severity of hypoglycemia and hypertrophic cardiomyopathy.[1,8] This nutritional management typically includes high protein intake, avoidance of simple sugars, avoidance of fasting, and uncooked cornstarch supplementation.[8] Psychosocial effects may arise from such a diet, especially for children with GSD III; preserving a sense of normalcy can prevent patients from feeling isolated or pessimistic due to their diet.[8] Despite dietary management, patients with GSD III may continue to develop progressive hepatic fibrosis, skeletal myopathy, and cardiomyopathy, each of which can have severe impacts and lead to early mortality.

Due to a lack of published data documenting the humanistic burden of GSD III from the perspective of patients and caregivers, this research sought to develop a conceptual model in GSD III to characterize the burden of disease among patients and caregivers while highlighting the difference in signs, symptoms, and impacts between adults and children with GSD III. Two complementary methodologies were employed in a mixed-methods approach to document disease burden. A larger, mainly fixed-response online survey was used to document primary disease manifestations and this was supplemented with detailed interviews with patients and caregivers of individuals with GSD III to more fully characterize the experience of living with GSD III.

Methods

Online survey

The adult (patient) and caregiver surveys were drafted in English by the authors of this paper who have expertise in collecting patient experience data, survey development, and measurement methodology. After multiple rounds of review, the English language surveys were refined and finalized. Survey data were collected from 1 January 2020 to 30 March 2021.

The GSD III survey study protocol and associated study materials for the English language surveys were submitted to the Western Institutional Review Board (WIRB) for ethics review and approval prior to any contact with survey respondents. Once approved, the surveys were translated into Spanish by an external translation vendor for distribution in Latin America. All surveys were programmed into SurveyMonkey to be completed online.

Following WIRB approval, adults and caregivers of children with GSD III were recruited through clinical and nonclinical sites such as advocacy groups and social media. With the use of an IRB-approved recruitment flyer, interested respondents contacted the research team to be screened for eligibility. Eligible respondents provided written consent to participate and completed an online survey consisting of closed- and open-ended questions.

The main eligibility criteria for adults and caregivers included the following:

- Adult/caregiver consented to take part in the research study;
- Adult/caregiver was at least 18 years of age;
- Adult/caregiver confirmed that they/their child had been diagnosed with GSD III and not any other type of GSD;
- Adult/caregiver confirmed that they/their child was diagnosed using genetic testing or by a physician;
- Caregiver confirmed that their child was <18 years old; and
- Adult/caregiver confirmed they were able to read and complete an online survey in English or Spanish.

Interview

The GSD III interview study protocol and associated study materials were submitted to WIRB for ethics review and approval prior to any contact with study participants. Following WIRB approval, adults and caregivers of children with GSD III were recruited through nonclinical sites such as a patient advocacy group, social media, and those who participated in the online survey who were interested in participating in further research. With the use of an IRB-approved recruitment flyer, interested participants contacted the research team to be screened for eligibility. Eligible participants provided written consent to participate and completed a 60-min qualitative interview *via* telephone. Eligibility criteria for interview participants followed the same eligibility criteria for the online survey with the exception that participants must have been able to complete the interview in English. Interviews took place from 10 June 2020 to 12 April 2021.

Data analysis

Adult and caregiver data were analyzed separately. Spanish language data were translated into English prior to data analysis.

All survey data were analyzed descriptively [e.g. frequency, mean, standard deviation (SD), minimum (Min)–maximum (Max), etc.] for all survey respondents and subgroups of interest (e.g. English language *versus* Spanish language). Open-ended survey response items were analyzed using ATLAS.ti version 8.0 or higher (Atlas.ti GmbH, Berlin, Germany), a software program designed for qualitative data analysis.

Audio-recordings of the interviews were transcribed verbatim, anonymized, and analyzed using processes guided by established qualitative research methods, including grounded theory and constant comparison methods.[9–15] A coding scheme was applied and operationalized using ATLAS.ti version 8.0 or higher. Codes were applied to specific text within each transcript and then queried for frequency across transcripts. Intercoder reliability was evaluated using percent agreement, with greater than or equal to 90% agreement considered an acceptable threshold based on benchmarks outlined in the literature.[16]

Conceptual model development

Survey and interview data were combined by cohort (i.e. adult or caregiver) to develop conceptual models of the defining signs/symptoms and impacts associated with GSD III.

Results

Participant demographic and health information

In all, 28 adults and 45 caregivers of children with GSD III completed the online survey. Caregivers of children with GSD III reported on behalf of their children (including four adult children who were over the age of 18). One caregiver of a child over the age of 18 noted that their child was unable to complete the adult survey due to their intellectual disability and therefore the caregiver completed the caregiver survey on their behalf. The remaining three caregivers of a child over the age of 18 were located in Latin America and could not be contacted to determine if their adult child could complete the adult survey; therefore, their data were included in the analysis.

Nine adults and 10 caregivers of children with GSD III participated in qualitative interviews. There were eight adults and nine caregivers who completed both the survey and the interview. In total, data are presented for 29 unique adults and 46 unique caregivers of children with GSD III.

Adults were located in the following countries: United States ($n = 15$, 52%), United Kingdom ($n = 5$, 17%), Argentina ($n = 2$, 7%), Chile ($n = 2$, 7%), Canada ($n = 1$, 3%), Colombia ($n = 1$, 3%), Denmark ($n = 1$, 3%), Mexico ($n = 1$, 3%), and Norway ($n = 1$, 3%). Adults were on average 41.0 years old (SD = 13.0, min–max = 21.0–66.0, median = 44.0), and 21 (72%) adults identified as female.

Caregivers and their children were located in the following countries: Colombia ($n = 14$, 30%), the United States ($n = 10$, 22%), Mexico ($n = 5$, 11%), Chile ($n = 3$, 7%), the United Kingdom ($n = 3$, 7%), Brazil ($n = 2$, 4%), Argentina ($n = 1$, 2%), Canada ($n = 1$, 2%), Ecuador ($n = 1$, 2%), Guatemala ($n = 1$, 2%), Peru ($n = 1$, 2%), Spain ($n = 1$, 2%), and Venezuela ($n = 1$, 2%). Two caregivers ($n = 2$, 4%) had missing data. The children were on average 9.0 years old (SD = 6.0,

min–max = 1.0–20.0, median = 10.0), and 26 (57%) children identified as female. In all, 42 (91%) caregivers identified as the parent of the child with GSD III, two caregivers (4%) identified as a legal guardian, one caregiver (2%) identified as a foster mother, and one caregiver (2%) identified as a grandmother.

Signs/symptoms of GSD III

Signs and symptoms of GSD III were reported in both the survey and interviews. See Table 1 for a summary of signs and symptoms reported by at least $n = 4$ adults and/or caregivers.

Digestive

Liver. The majority of caregivers ($n = 37$ of 45, 82%) and adults ($n = 16$ of 28, 57%) who participated in the survey reported a liver problem. Across both the survey and interviews, the most commonly reported liver-related sign/symptom was an enlarged liver ($n = 62$ of 75, 83%). Almost all caregivers ($n = 44$ of 46, 96%) reported that their child experiences or has experienced an enlarged liver and over half of adults ($n = 18$ of 29, 62%) reported an enlarged liver.

Hypoglycemia-related. In total, 28 adults ($n = 28$ of 29, 97%) and 43 caregivers ($n = 43$ of 46, 93%) reported that they or their child experienced or has experienced hypoglycemia-related signs and symptoms. The majority of adults who had experienced a hypoglycemia-related sign or symptom in their lifetime ($n = 26$ of 28, 93%) reported experiencing at least one hypoglycemia-related sign or symptom as an adult.

Participants most often reported that they or their child has experienced a seizure in their lifetime ($n = 35$ of 75, 47%). Seizure ($n = 19$ of 29, 66%) was the most common sign/symptom of hypoglycemia among adults, while fatigue/tiredness ($n = 22$ of 46, 48%) was the most common sign/symptom among children as reported by their caregivers. Although seizure was the most commonly reported sign/symptom of hypoglycemia among adults, this includes both past and present experiences of seizures.

Gastrointestinal. The most commonly reported gastrointestinal sign/symptom was constipation ($n = 7$ of 75, 9%). Constipation was reported in both children and adults but more commonly in children ($n = 5$ of 46, 11%).

Musculoskeletal. Muscle weakness was the most commonly reported musculoskeletal sign/symptom among both adults and caregivers ($n = 60$ of 75, 80%). During interviews, participants generally described muscle weakness in terms of lack of strength and muscle fatigue. Carpal tunnel syndrome ($n = 10$ of 75, 13%) was only reported by adults.

Growth and physical appearance. Concerns related to growth and physical appearance included delayed growth ($n = 32$ of 75, 43%), a late growth spurt ($n = 25$ of 75, 33%), and protruding belly ($n = 25$ of 75, 33%). Delayed growth and a late growth spurt were reported more often by adults than caregivers. Skin-related issues ($n = 4$ of 75, 5%) were only reported by caregivers.

Cardiac. A cardiac condition was reported by 40% of participants overall and 13% ($n = 10$ of 75) reported irregular heart rhythm. Irregular heart rhythm was more frequently reported in adults.

Impacts of GSD III

Impacts of GSD III were reported in both the survey and interviews. See Table 2 for a summary of impacts reported by at least $n = 4$ adults and/or caregivers.

Physical. Difficulty exercising/difficulty with physical activity was the most commonly reported physical impact overall ($n = 40$ of 75, 53%). Caregivers most commonly ($n = 22$ of 46, 48%) reported that their child had difficulty exercising/difficulty with physical activity. Most adults reported difficulty walking ($n = 24$ of 29, 83%) and difficulty jumping/hopping ($n = 23$ of 29, 79%). Physical impacts were generally reported more often by adults than caregivers given that there were specific questions on the adult version of the survey dedicated to difficulty with physical activities.

Social. Difficulty keeping up with peers was the most commonly reported social impact overall ($n = 58$ of 75, 77%). All adults ($n = 29$ of 29, 100%) reported experiencing difficulty keeping up with peers. Over half of caregivers ($n = 29$ of 46, 63%) reported that their child had difficulty keeping up with peers.

Activities of daily living. Difficulty chewing was the most commonly reported activities of daily

Table 1. Signs/symptoms of GSD III reported by ⩾4 adults and/or caregivers.[a]

Sign/symptom	Adults (*n* = 29), *n* (%)	Caregivers (*n* = 46), *n* (%)	Total (*N* = 75), *n* (%)
Digestive			
Liver			
Enlarged liver	18 (62%)	44 (96%)	62 (83%)
Other liver conditions	22 (76%)	40 (87%)	62 (83%)
Hypoglycemia related[b]			
Seizures[c]	19 (66%)	16 (35%)	35 (47%)
Fatigue/tiredness	5 (17%)	22 (48%)	27 (36%)
Sweaty/clammy	6 (21%)	16 (35%)	22 (29%)
Shakiness	7 (24%)	12 (26%)	19 (25%)
Weakness[d]	–	19 (41%)	19 (25%)
Dizziness	7 (24%)	11 (24%)	18 (24%)
Irritability	5 (17%)	11 (24%)	16 (21%)
Nausea	3 (10%)	9 (20%)	12 (16%)
Hunger[e]	5 (17%)	4 (9%)	9 (12%)
Headache/migraine	5 (17%)	3 (7%)	8 (11%)
Anxiety[e]	2 (7%)	4 (9%)	6 (8%)
Blurred vision	3 (10%)	3 (7%)	6 (8%)
Vomiting	2 (7%)	4 (9%)	6 (8%)
Confusion[d]	–	5 (11%)	5 (7%)
Slurred speech[d]	–	5 (11%)	5 (7%)
High ketone levels	1 (3%)	3 (7%)	4 (5%)
Loss of consciousness	4 (14%)	–	4 (5%)
Pale skin[e]	2 (7%)	2 (4%)	4 (5%)
Gastrointestinal			
Constipation	2 (7%)	5 (11%)	7 (9%)
Vomiting	2 (7%)	4 (9%)	6 (8%)
Diarrhea[e]	2 (7%)	3 (7%)	5 (7%)
Nausea	3 (10%)	1 (2%)	4 (5%)
Musculoskeletal			
Muscle weakness	27 (93%)	33 (72%)	60 (80%)
Muscle pain	24 (83%)	22 (48%)	46 (61%)

(Continued)

Table 1. (Continued)

Sign/symptom	Adults (*n* = 29), *n* (%)	Caregivers (*n* = 46), *n* (%)	Total (*N* = 75), *n* (%)
Low muscle tone/hypotonia	21 (72%)	23 (50%)	44 (59%)
Fatigue/lack of energy	9 (31%)	10 (22%)	19 (25%)
Joint hypermobility	6 (21%)	9 (20%)	15 (20%)
Carpal tunnel syndrome[d]	10 (34%)	–	10 (13%)
Other bone conditions	7 (24%)	2 (4%)	9 (12%)
Muscle atrophy	2 (7%)	2 (4%)	4 (5%)
Growth and physical appearance			
Delayed growth	23 (79%)	9 (20%)	32 (43%)
Growth spurt to catch up to peers	23 (79%)	2 (4%)	25 (33%)
Protruding belly	15 (52%)	10 (22%)	25 (33%)
Stunted growth/shorter or smaller than peers[e]	5 (17%)	7 (15%)	12 (16%)
Thin arms/legs	7 (24%)	4 (9%)	11 (15%)
Late onset of puberty[e]	6 (21%)	2 (4%)	8 (11%)
Round cheeks	1 (3%)	4 (9%)	5 (7%)
Skin-related issues[d]	–	4 (9%)	4 (5%)
Cardiac			
Other cardiac conditions	13 (45%)	17 (37%)	30 (40%)
Irregular heart rhythm	6 (21%)	4 (9%)	10 (13%)

[a]Some signs/symptoms are reported more than once (e.g. fatigue) because they were also reported to be signs/symptoms specifically related to hypoglycemia.
[b]In all, 28 adults and 43 caregivers reported hypoglycemia-related signs/symptoms.
[c]Participants reported whether they had ever experienced seizures in their lifetime.
[d]Weakness, confusion, slurred speech, carpal tunnel syndrome, and skin-related issues were only reported in the survey.
[e]Hunger, anxiety, pale skin, diarrhea, stunted growth/shorter or smaller than peers, and late onset of puberty were only reported during interviews.
GSD III, glycogen storage disease type III.

living impact overall ($n = 7$ of 75, 9%). Adults most commonly reported that their GSD III affects their ability to get dressed ($n = 5$ of 29, 17%) and to run errands ($n = 5$ of 29, 17%) while caregivers most commonly reported diet-related impacts on their child's daily living, such as affects eating habits ($n = 5$ of 46, 11%) and the limitation to diet ($n = 4$ of 46, 9%). Affects ability to run errands and affects ability to bathe were only reported by adults.

Emotional. Feeling different from peers was the most commonly reported emotional impact overall ($n = 7$ of 75, 9%). Four caregivers ($n = 4$ of 46, 9%) reported that their child feels different from peers. Feeling anxious ($n = 4$ of 29, 14%) was the most commonly reported emotional impact among adults and was only reported by adults.

Work/school. The most commonly reported work/school impacts were being bullied in school

Table 2. Impacts of GSD III reported by ⩾4 adults and/or caregivers.

Impact	Adults (*n* = 29), *n* (%)	Caregivers (*n* = 46), *n* (%)	Total (*N* = 75), *n* (%)
Physical			
Difficulty exercising/difficulty with physical activity	18 (62%)	22 (48%)	40 (53%)
Difficulty walking	24 (83%)	4 (9%)	28 (37%)
Difficulty climbing stairs	22 (76%)	4 (9%)	26 (35%)
Difficulty jumping/hopping[a]	23 (79%)	3 (7%)	26 (35%)
Difficulty bending over	20 (69%)	2 (4%)	22 (29%)
Difficulty standing from sitting position[a]	19 (66%)	–	19 (25%)
Falling	17 (59%)	1 (2%)	18 (24%)
Difficulty raising arms/reaching for objects	17 (59%)	–	17 (23%)
Difficulty using hands	16 (55%)	1 (2%)	17 (23%)
Difficulty lifting heavy objects	10 (35%)	6 (13%)	16 (21%)
Difficulty playing sports	7 (24%)	8 (17%)	15 (20%)
Need to use walking aids/devices	11 (38%)	1 (2%)	12 (16%)
Affects balance/coordination[a]	4 (14%)	3 (7%)	7 (9%)
Difficulty standing	4 (14%)	–	4 (5%)
Social			
Difficulty keeping up with peers	29 (100%)	29 (63%)	58 (77%)
Limited social activities	4 (14%)	2 (4%)	6 (8%)
Disrupts scheduled activities[a]	1 (3%)	4 (9%)	5 (7%)
Receives unwanted attention[a]	1 (3%)	4 (9%)	5 (7%)
Activities of daily living			
Difficulty chewing[b]	4 (14%)	3 (7%)	7 (9%)
Affects the ability to get dressed[b]	5 (17%)	1 (2%)	6 (8%)
Affects eating habits	1 (3%)	5 (11%)	6 (8%)
Limitation to diet[b]	2 (7%)	4 (9%)	6 (8%)
Affects the ability to run errands[b]	5 (17%)	–	5 (7%)
Affects the ability to bathe[b]	4 (14%)	–	4 (5%)
Emotional			
Feels different from peers[b]	3 (10%)	4 (9%)	7 (9%)
Feels anxious[b]	4 (14%)	–	4 (5%)

(Continued)

Table 2. (Continued)

Impact	Adults (*n* = 29), *n* (%)	Caregivers (*n* = 46), *n* (%)	Total (*N* = 75), *n* (%)
Work/school			
Bullied in school[b]	3 (10%)	1 (2%)	4 (5%)
Has to leave class[b]	–	4 (9%)	4 (5%)
Sleep			
Unable to sleep comfortably through the night	3 (10%)	2 (4%)	5 (7%)
Cognitive			
Difficulty concentrating[b]	2 (7%)	2 (4%)	4 (5%)

[a]Difficulty jumping/hopping and difficulty standing from a sitting position were only reported in the survey.
[b]Difficulty chewing, affects the ability to get dressed, limitation to diet, affects the ability to run errands, affects the ability to bathe, affects balance/coordination, feels different from peers, disrupts scheduled activities, receives unwanted attention, feels anxious, bullied in school, having to leave class, and difficulty concentrating were only reported during interviews.
GSD III, glycogen storage disease type III.

(*n* = 4 of 75, 5%), which was reported by both adults and caregivers, and having to leave class (*n* = 4 of 75, 5%), which was only reported by caregivers.

Sleep. Five participants (*n* = 5 of 75, 7%) reported that they or their child were unable to sleep comfortably through the night. One caregiver noted that their child's inability to sleep comfortably through the night was due to their feeding schedule.

Cognitive. Four participants (*n* = 4 of 75, 5%) reported that they or their child had difficulty concentrating due to GSD III.

Bothersome/severity ratings (interviews)

During interviews, participants provided bothersome and severity ratings for signs/symptoms and impacts on a scale of 0 (not bothersome at all/no sign or symptom) to 10 (extremely bothersome/sign or symptom as bad as you can imagine); however, not all signs/symptoms and impacts reported received bothersome and/or severity ratings due to interviewer discretion or time constraints.

Signs/symptoms of GSD III. Of the signs/symptoms with bothersome/severity data from at least four participants overall, vomiting (7.8) received the highest bothersome rating on average and signs/symptoms of hypoglycemia (8.1) received the highest severity rating on average. Stunted growth/shorter or smaller than peers (9.0) received the highest median score for bothersomeness, followed by protruding belly (8.0) and vomiting (8.0). Fatigue/lack of energy and signs/symptoms of hypoglycemia received the highest median score for severity (8.0). Among adults, muscle weakness (7.3) received the highest bothersome rating on average and muscle pain (7.5) received the highest severity rating on average. Caregivers gave their child's signs/symptoms of hypoglycemia the highest bothersome rating (8.6) and highest severity rating (8.2) on average. See Table 3 for a summary of bothersome and severity ratings for signs/symptoms of GSD III provided by at least four participants overall.

Impacts of GSD III. Of the impacts with bothersome/severity data from at least three participants overall, having to use walking aids/devices (8.7) and feeling different from peers (8.3) received the highest bothersome ratings on average. In terms of median scores, limitation to diet (9.0) and feeling anxious (9.0) were the most bothersome impacts. Lack of appetite (9.0) received the highest severity rating on average. Among adults, having to use walking aids/devices (8.7) received the highest bothersome rating on average and difficulty exercising/difficulty with physical activity (9.0) received the highest severity rating on average. Caregivers gave their child's limitation to diet

Table 3. Bothersome and severity ratings for signs/symptoms of GSD III reported by ⩾4 participants.

Sign/symptom	Adults ($n = 9$)		Caregivers ($n = 10$)		Total ($n = 19$)	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Bothersomeness						
Vomiting	7.0 (n/a)	7.0	8.0 (2.2)	9.0	7.8 (1.9)	8.0
Signs/symptoms of hypoglycemia[a]	5.0 (2.4)	6.0	8.6 (1.9)	9.0	7.0 (2.8)	7.0
Low muscle tone/hypotonia	6.3 (1.5)	6.5	8.0 (n/a)	8.0	6.6 (1.5)	7.0
Protruding belly	7.0 (2.4)	8.0	6.0 (3.5)	8.0	6.5 (3.0)	8.0
Constipation	7.0 (2.0)	7.0	6.0 (1.0)	6.0	6.5 (1.7)	6.0
Stunted growth/shorter or smaller than peers	6.4 (4.5)	10.0	6.0 (4.3)	8.0	6.3 (4.4)	9.0
Enlarged liver	8.0 (0.8)	8.0	4.7 (3.4)	6.0	6.3 (3.0)	7.5
Muscle weakness	7.3 (2.2)	8.0	5.0 (2.4)	5.5	6.3 (2.5)	7.0
Muscle pain	6.7 (1.9)	8.0	5.5 (2.3)	6.0	6.0 (2.2)	7.0
Fatigue/lack of energy	6.6 (3.0)	7.0	5.0 (2.8)	7.0	5.9 (3.0)	7.0
Diarrhea	6.7 (1.6)	6.5	5.0 (3.4)	6.0	5.8 (2.8)	6.5
Heart problems[a]	5.8 (2.3)	6.0	0.0 (n/a)	0.0	4.8 (3.0)	5.5
Thin arms/legs	2.2 (2.0)	2.0	0.0 (n/a)	0.0	1.8 (2.0)	1.5
Severity						
Signs/symptoms of hypoglycemia[a]	8.0 (0.0)	8.0	8.2 (1.6)	8.0	8.1 (1.4)	8.0
Fatigue/lack of energy	7.3 (2.6)	8.0	6.8 (1.6)	7.0	7.1 (2.1)	8.0
Muscle pain	7.5 (0.5)	7.5	6.5 (1.1)	6.5	7.0 (1.0)	7.0
Enlarged liver	10.0 (n/a)	10.0	5.7 (2.1)	6.0	6.8 (2.6)	7.0
Heart problems[a]	7.3 (0.5)	7.0	5.0 (n/a)	5.0	6.8 (1.1)	7.0
Constipation	7.0 (0.0)	7.0	6.3 (0.8)	6.5	6.5 (0.8)	7.0
Muscle weakness	6.9 (2.5)	7.0	5.8 (1.8)	6.5	6.3 (2.2)	7.0
Stunted growth/shorter or smaller than peers	3.0 (2.0)	3.0	7.8 (2.3)	8.5	6.2 (3.1)	6.5
Low muscle tone/hypotonia	5.8 (1.1)	6.0	6.2 (2.6)	8.0	6.0 (2.1)	6.0
Protruding belly	3.0 (n/a)	3.0	5.7 (2.6)	5.0	5.3 (2.5)	5.0
Thin arms/legs	3.7 (2.5)	3.0	4.5 (2.5)	4.5	4.0 (2.5)	3.0

[a]Bothersome and severity ratings were not collected for specific hypoglycemia-related signs/symptoms (e.g. seizures) and specific heart problems (e.g. left ventricular hypertrophy).
GSD III, glycogen storage disease type III.

(9.3) the highest bothersome rating and their child's difficulty exercising/difficulty with physical activity (7.0) the highest severity rating on average. See Table 4 for a summary of bothersome and severity ratings for impacts of GSD III provided by at least three participants overall.

Table 4. Bothersome and severity ratings for impacts of GSD III reported by ⩾3 participants.

Impact	Adults ($n=9$)		Caregivers ($n=10$)		Total ($n=19$)	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Bothersomeness						
Uses walking aids/devices	8.7 (0.9)	8.0	n/a	n/a	8.7 (0.9)	8.0
Feels different from peers	9.0 (n/a)	9.0	8.0 (1.6)	8.0	8.3 (1.5)	8.5
Limitation to diet	3.0 (n/a)	3.0	9.3 (0.8)	9.5	8.0 (2.6)	9.0
Limited social activities	7.0 (n/a)	7.0	8.5 (0.5)	8.5	8.0 (0.8)	8.0
Feels anxious	7.7 (1.9)	9.0	n/a	n/a	7.7 (1.9)	9.0
Difficulty keeping up with peers	7.5 (1.5)	8.0	6.7 (3.5)	7.5	7.0 (2.9)	8.0
Trouble walking	8.2 (1.2)	8.0	1.0 (n/a)	1.0	7.0 (2.9)	7.5
Difficulty exercising/difficulty with physical activity	7.3 (1.1)	7.5	4.6 (2.9)	5.0	6.1 (2.5)	7.0
Difficulty lifting heavy objects	6.3 (1.2)	6.0	4.0 (n/a)	4.0	5.8 (1.5)	5.5
Trouble climbing stairs	7.3 (1.8)	7.0	2.5 (1.5)	2.5	5.7 (2.8)	6.0
Affects the ability to get dressed	5.3 (2.4)	7.0	0.0 (n/a)	0.0	4.0 (3.1)	4.5
Difficulty chewing	2.0 (n/a)	2.0	3.5 (2.5)	3.5	3.0 (2.2)	2.0
Severity						
Lack of appetite	8.0 (n/a)	8.0	9.5 (0.5)	9.5	9.0 (0.8)	9.0
Feels different from peers	7.5 (1.5)	7.5	8.0 (2.0)	8.0	7.8 (1.8)	7.5
Difficulty exercising/difficulty with physical activity	9.0 (n/a)	9.0	7.0 (2.5)	7.5	7.4 (2.4)	8.0
Difficulty lifting heavy objects	8.0 (n/a)	8.0	6.0 (1.0)	6.0	6.7 (1.2)	7.0
Difficulty keeping up with peers	7.0 (n/a)	7.0	6.5 (2.5)	6.5	6.6 (2.2)	7.0
Affects balance/coordination	5.0 (n/a)	5.0	6.0 (1.6)	6.0	5.8 (1.5)	5.5
Trouble climbing stairs	6.0 (n/a)	6.0	3.5 (1.5)	3.5	4.3 (1.7)	5.0

GSD III, glycogen storage disease type III.

Top symptoms or complications of GSD III (survey)

Over half of the survey participants ($n=36$ of 66, 55%) reported that hypoglycemia and related signs/symptoms interfered the most with their or their child's life. Caregivers most commonly reported that hypoglycemia and related signs/interfered the most with their child's life ($n=24$ of 39, 62%), whereas most adults reported that muscle weakness and related complications ($n=19$ of 27, 70%) interfered the most with one's life. Only caregivers reported growth and development issues as a top symptom or complication. See Table 5 for a summary of the top symptoms or complications that interfere with one's life reported by at least $n=4$ adults and/or caregivers.

Most important signs/symptoms to treat (interviews)

During interviews, participants were asked to consider the most important signs/symptoms of

Table 5. Top symptoms or complications that interfere with one's life reported by ⩾4 adults and/or caregivers.

Sign/symptom	Adults ($n=27$), *n* (%)	Caregivers ($n=39$), *n* (%)	Total ($n=66$), *n* (%)
Hypoglycemia and related symptoms	12 (44%)	24 (62%)	36 (55%)
Fatigue or exercise intolerance	11 (41%)	15 (39%)	26 (39%)
Muscle weakness and related complications	19 (70%)	7 (18%)	26 (39%)
Difficulty complying with diet/cornstarch regimen	5 (19%)	16 (41%)	21 (32%)
Muscle pain/cramping and related complications	7 (26%)	8 (21%)	15 (23%)
Enlarged liver	1 (4%)	7 (18%)	8 (12%)
Gastrointestinal symptoms	3 (11%)	5 (13%)	8 (12%)
Growth and development issues	–	4 (10%)	4 (6%)

Table 6. Meaningful goals of therapy reported by ⩾4 adults and/or caregivers.

Concept	Adults ($n=27$), *n* (%)	Caregivers ($n=39$), *n* (%)	Total ($n=66$), *n* (%)
Dietary liberalization	6 (22%)	19 (49%)	25 (38%)
Muscle strength and function	13 (48%)	5 (13%)	18 (27%)
Hypoglycemia prevention	4 (15%)	6 (15%)	10 (15%)
Curative therapy/vaccine	–	5 (13%)	5 (8%)

GSD III to treat. Adults commonly reported that muscle weakness ($n=5$ of 9, 56%) would be the most important to treat while caregivers commonly reported that both their child's muscle weakness ($n=4$ of 10, 40%) and signs/symptoms of hypoglycemia ($n=4$ of 10, 40%) would be the most important to treat.

Meaningful goals of therapy (survey)

Survey participants most often ($n=25$ of 66, 38%) reported that liberalization of their diet would be meaningful to them. Among caregivers, dietary liberalization was the most commonly reported goal of therapy ($n=19$ of 39, 49%) while adults most commonly reported that muscle strength and function ($n=13$ of 27, 48%) would be meaningful to them. See Table 6 for a summary of meaningful goals of therapy reported by at least $n=4$ adults and/or caregivers.

Hypoglycemia and glucose control

In the survey, the majority of adults reported experiencing hypoglycemia as an infant ($n=20$ of 28, 71%) and as a child ($n=24$ of 28, 86%). Three adults ($n=3$ of 28, 11%) reported they were unsure whether they experienced hypoglycemia as a child. Of the adults who experienced hypoglycemia as a child or were unsure, the majority ($n=26$ of 27, 96%) reported having experienced a hypoglycemia-related sign/symptom. The most common age at which adults first experienced hypoglycemia-related signs/symptoms was between 3 and 5 years old ($n=17$ of 26, 65%).

In the survey, of the adults who experienced hypoglycemia as a child or were unsure, more than half ($n=15$ of 27, 56%) reported being hospitalized due to hypoglycemia as a child. In addition, more than half of adults who experienced at least one hypoglycemia-related sign/symptom as

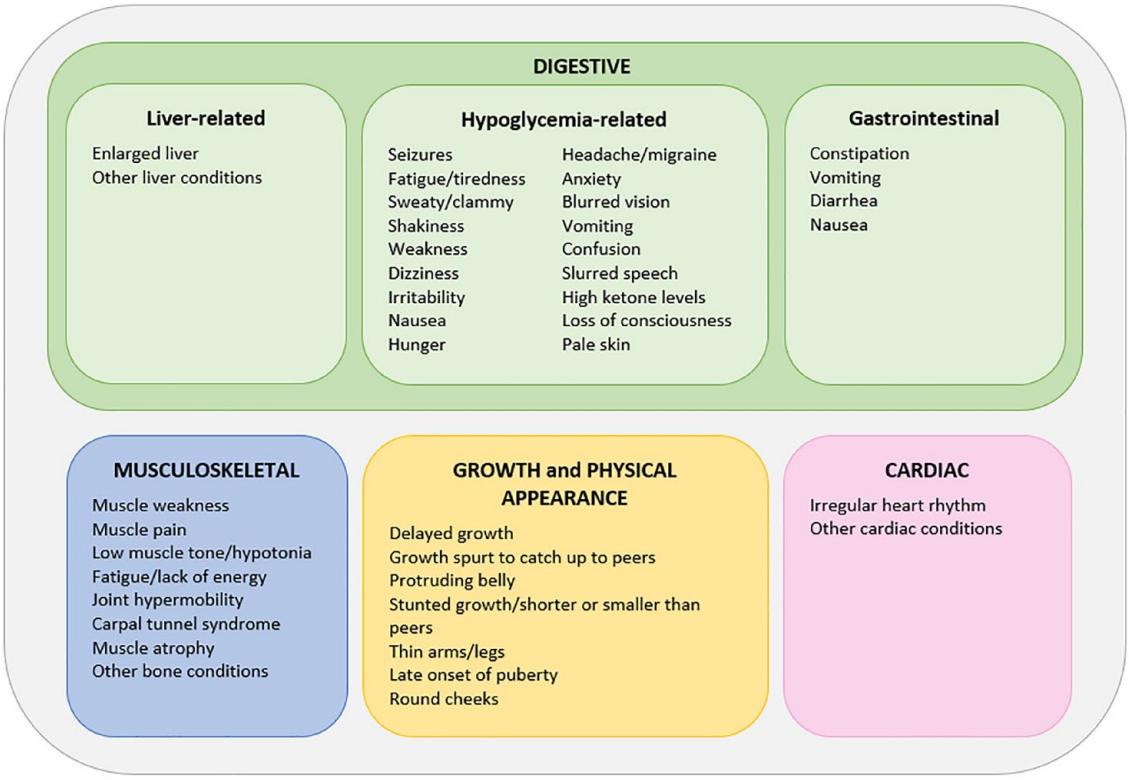

Figure 1. GSD III defining signs/symptoms conceptual model.
Some signs/symptoms are included under multiple organ systems.
GSD III, glycogen storage disease type III.

an adult ($n = 14$ of 26, 54%) reported having to go to the emergency room due to problems with GSD III in the past 5 years (as an adult). The average number of hospitalizations reported by adults on the survey was 6.4 times (SD = 9.8, median = 2.0, min–max = 1.0–34.0) as a child and 1.9 times (SD = 4.0, median = 0.5, min–max = 0.0–15.0) within the last 5 years (as an adult). During interviews, two adults ($n = 2$ of 9, 22%) reported that they had been hospitalized for hypoglycemia in their lifetime and reported an average of 1.9 hospitalizations per lifetime (SD = 0.9, median = 2.0, min–max = 1.0–25.0) due to their GSD III, including complications with hypoglycemia.

In the survey, most caregivers ($n = 41$ of 45, 91%) reported that their child had previously experienced hypoglycemia. Of these children, more than half ($n = 23$ of 41, 56%) experienced hypoglycemia in the past year. The average age at which children first experienced signs/symptoms of hypoglycemia was 1.3 years (SD = 1.4, median = 1.0, min–max = 0.1–6.4). During interviews, half of the caregivers ($n = 5$ of 10, 50%) reported that their child has been hospitalized for hypoglycemia in their lifetime and reported an average of 5.9 hospitalizations per lifetime (SD = 8.0, median = 3.5, min–max = 1.0–25.0) due to GSD III.

During interviews, some caregivers described burdens they experienced while caring for a child with GSD III, especially about their child's specific feeding schedule.

Conceptual model development

Based on the results of the interviews and survey, conceptual models were developed for the defining signs/symptoms and impacts of GSD III (see Figures 1 and 2). The signs/symptoms conceptual model includes digestive, musculoskeletal, growth and physical appearance, and cardiac signs/symptoms. The impacts conceptual model includes impacts reported across the following domains: physical, social, activities of daily living, emotional, work/school, sleep, and cognitive. Concepts reported by at least four (5%) adults

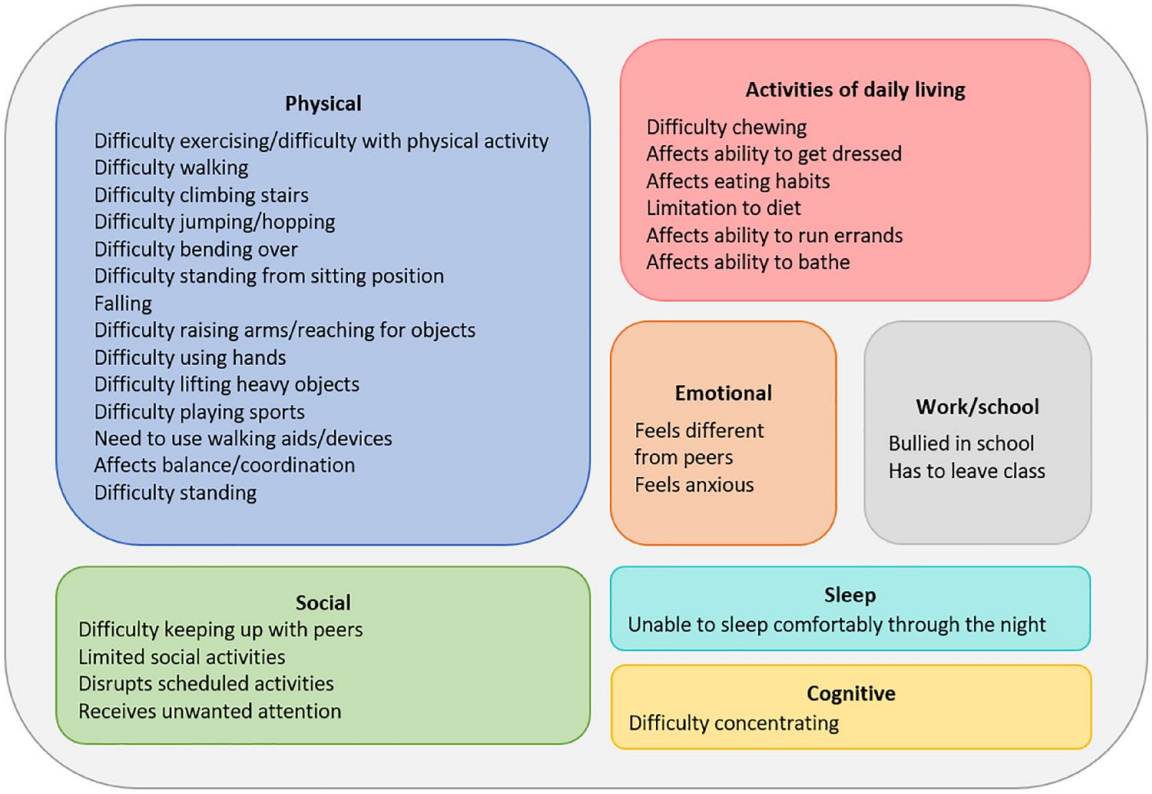

Figure 2. GSD III defining impacts conceptual model.
GSD III, glycogen storage disease type III.

and/or caregivers were included in the conceptual models.

Discussion

The objective of this research was to better understand GSD III and the experience of living with GSD III to develop a conceptual model. This conceptual model can be used to assist with the selection of appropriate existing measures to support endpoints in future clinical studies as well as a starting point for developing a disease-specific measure. Furthermore, this research increases our understanding of the burden of disease and the impact of GSD III on patients' and caregivers' lives. This research was conducted in line with draft FDA Guidance in Rare Diseases[13] as well as Patient-Focused Drug Development guidance on collecting comprehensive and representative input,[14] which highlight the importance of collecting patient experience data. Furthermore, this research aligns with the FDA Guidance for Industry in Patient Reported Outcome (PRO) measures,[15] which recommends the development of a conceptual model as the first step in PRO measure selection and/or development.

This research was a mixed-methods study that utilized both survey and interview responses from adult patients and caregivers of individuals with GSD III. This methodology allowed for direct reporting of both structured and open-ended responses, which is a key benefit of mixed-methods research.[19] In addition, collecting both survey and interview data resulted in a larger sample size which improved the generalizability of the results while also still providing valuable context with the qualitative interview data. Patient-Focused Drug Development guidance on methods to identify what is important to patients[17] encourages the use of mixed methods to harmonize or confirm results across research methods as well as supplement or clarify results from one method to another.

Fatigue/lack of energy, an enlarged liver, muscle weakness, delayed growth, and signs/symptoms of hypoglycemia were the predominant signs/symptoms of GSD III. These data appear to correlate

with findings in existing literature that report that GSDII commonly affects the liver, heart, and skeletal muscles and bones.[7,18] Both adults and caregivers considered fatigue/lack of energy as well as the signs/symptoms of hypoglycemia to be the most severe based on median scores. For adult patients, an enlarged liver and muscle weakness were reported as the most bothersome for them, on average. Caregivers reported signs/symptoms of hypoglycemia, low muscle tone/hypotonia, and vomiting as the most bothersome. Similarly, when asked about symptoms that interfere most with one's life, the majority of adult survey respondents indicated muscle weakness interferes the most while caregivers focused on hypoglycemia-related symptoms. This finding is in line with existing literature that reports that muscle involvement, specifically muscle weakness, seems to increase with age in patients with GSD IIIa and although minimal in childhood, may worsen with age.[19–21] In addition, this is not surprising given hospitalization rates due to hypoglycemia are three times greater in children than in adults, based on interview findings. When asked to consider the most important signs/symptoms of GSD III to treat, adults commonly reported muscle weakness and caregivers reported both hypoglycemia and muscle weakness as important to treat. These findings may reflect the concern that for patients with GSD III, management strategies are available for hypoglycemia and less so for muscle-related signs and symptoms.

Difficulty keeping up with peers, difficulty exercising/difficulty with physical activity, difficulty walking, difficulty climbing stairs, and difficulty jumping/hopping were the predominant impacts of GSD III. These data appear to correlate with findings in existing literature where commonly reported impacts due to GSDIII included exercise intolerance and difficulty climbing stairs.[19] Adults and caregivers considered difficulty exercising/difficulty with physical activity to be the most severe impact of GSD III. Having to use walking aids/devices and feeling different from peers were the most bothersome impacts on average, though limitation to diet and feeling anxious received the highest median bothersome ratings. Of note, having to use walking aids/devices was more commonly reported by adults, which may provide insight as to why adults commonly reported that trouble walking would be the most important impact to treat. In addition, existing literature has reported that older individuals with GSD IIIa tended to show more mobility limitations than younger adults.[21] Caregivers commonly reported that difficulty exercising/difficulty with physical activity would be the most important impact of GSD III to treat.

One limitation of this study is that adults and caregivers volunteered to participate in this research, and those who participated may not be an accurate representation of the total GSD III population. However, saturation was assessed for signs/symptoms and impacts reported during the interviews, and concepts spontaneously introduced in the last 25% of interviews were either distal concepts, related to other signs/symptoms, or had been reported earlier in the interview following probing. Therefore, under the principle of saturation,[22] the sample size for interviews was considered sufficient and these results are likely generalizable to the GSD III population. Another limitation of this study is that medical records were not reviewed to confirm the patient-reported signs/symptoms; however, this manuscript includes all patient and caregiver-reported concepts to fully illustrate the patient experience of GSD III. Furthermore, patients are experts when it comes to understanding the burden of disease, as evidenced by the FDA requirements for incorporating the patient voice into drug development.[23]

Ultimately, the findings of the survey and interviews suggest that there is a broad spectrum of sign/symptom presentation in GSD III. The majority of signs/symptoms were reported by a fairly even split of adults and caregivers; however, the data indicate that prevention of hypoglycemia is a greater challenge during childhood than in adulthood. The findings also suggest that GSD III can cause a variety of impacts, the most common being physical impacts and impacts on activities of daily living. Furthermore, limitation to diet received the highest median bothersome rating of the impacts of GSD III along with feeling anxious about one's health. This reinforces the need for an effective therapy for GSD III that improves outcomes and the burdens of dietary management.

These results and the development of the conceptual model could be considered when designing a measurement strategy for future clinical studies. Although the FDA Guidance in Rare Diseases[17] recommends utilizing existing PRO measures in rare diseases when possible, these results suggest

individuals with GSD III experience a wide range of impacts and have a unique diet to treat their GSD III. Therefore, this research could serve as the foundation for the development of a GSD III-specific impact and/or diet management measure.

Declarations

Ethics approval and consent to participate

This study was approved by the Western Institutional Review Board and all patients provided written informed consent. The ethics approval numbers are 20192949 for the survey study and 20201063 for the interview study.

Consent for publication

Participants were notified *via* the Informed Consent Form that if the results were published, results would be presented in aggregate and therefore they would not be identifiable.

Author contributions

Ayla Evins: Conceptualization; Methodology; Supervision; Writing – review & editing.

Jill Mayhew: Conceptualization; Methodology; Writing – review & editing.

Tricia Cimms: Conceptualization; Methodology; Writing – review & editing.

Julie Whyte: Conceptualization; Formal analysis; Methodology; Project administration; Resources; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Kathy Vong: Data curation; Formal analysis; Investigation; Resources; Visualization; Writing – original draft; Writing – review & editing.

Elizabeth Hribal: Data curation; Formal analysis; Investigation; Resources; Visualization; Writing – review & editing.

Christopher J. Evans: Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Andrew Grimm: Conceptualization; Writing – review & editing.

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Competing interests

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

ORCID iD

Julie Whyte https://orcid.org/0000-0002-9367-4201

Supplemental material

Supplemental material for this article is available online.

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