Novel monitoring and management strategies for hepatic glycogen storage diseases

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DOI:
10.33612/diss.202010693

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Rossi, A. (2022). Novel monitoring and management strategies for hepatic glycogen storage diseases. University of Groningen. https://doi.org/10.33612/diss.202010693

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Chapter 4

Dietary lipids in glycogen storage disease type III: a systematic literature study, case studies, and future recommendations

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Journal of Inherited Metabolic Disease 2020; 43(4):770-777

PMID: 32064649
ABSTRACT

A potential role of dietary lipids in the management of hepatic glycogen storage diseases (GSDs) has been proposed, but no consensus on management guidelines exists. The aim of this study was to describe current experiences with dietary lipid manipulations in hepatic GSD patients. An international study was set up to identify published and unpublished cases describing hepatic GSD patients with a dietary lipid manipulation. A literature search was performed according to the Cochrane Collaboration methodology through PubMed and EMBASE (up to December 2018). All delegates who attended the dietetics session at the IGSD2017, Groningen were invited to share unpublished cases. Due to multiple biases, only data on GSDIII were presented. A total of 28 cases with GSDIII and a dietary lipid manipulation were identified. Main indications were cardiomyopathy and/or myopathy. A high fat diet was the most common dietary lipid manipulation. A decline in creatine kinase concentrations (n = 19, P < .001) and a decrease in cardiac hypertrophy in paediatric GSDIIIa patients (n = 7, P < .01) were observed after the introduction with a high fat diet. This study presents an international cohort of GSDIII patients with different dietary lipid manipulations. High fat diet may be beneficial in paediatric GSDIIIa patients with cardiac hypertrophy, but careful long-term monitoring for potential complications is warranted, such as growth restriction, liver inflammation, and hepatocellular carcinoma development.
INTRODUCTION

Glycogen storage diseases (GSD) are inborn errors of glycogen synthesis or degradation. Although a wide spectrum of clinical and biochemical presentation is observed, GSD are usually classified into hepatic and muscle GSD. Primary manifestations of the hepatic GSD subtypes 0, I, III, VI, IX, and XI are fasting intolerance associated hypoglycaemia, hepatomegaly and failure to thrive. In addition, GSDIII patients also show a myopathic phenotype with skeletal muscle involvement and/or cardiomyopathy.1

Management guidelines have been published for GSD subtypes Ia2,3, Ib4, III5, and VI and IX together6 Dietary management is the cornerstone of treatment for hepatic GSD patients to maintain normoglycaemia, prevent secondary metabolic derangements and long-term complications. Strict dietary management and compliance has significantly improved the outcomes for many GSD patients.7,8 Traditionally, dietary carbohydrates and protein have received most interest, whereas lipids usually have been restricted. Several case reports have described beneficial effects of dietary lipid manipulations in hepatic GSD patients, including (modified) ketogenic diets and medium-chain triglyceride (MCT) enrichment9-13. However, the role of dietary lipids as a third macronutrient in dietary management is still controversial14.

The aim of this study was to describe current experiences with dietary lipid manipulations in hepatic GSD patients. We performed a systematic literature study of all published cases describing hepatic GSD patients with a dietary lipid manipulation. Thereafter, an international, observational, retrospective study was performed to include unpublished cases. The subsequent discussion provides recommendations for future patient care and research.

METHODS

Systematic literature study

Published cases were retrieved by a systematic literature search conducted according to the Cochrane Collaboration methodology on December 31, 2018. PubMed and EMBASE were searched using both MeSH terms and free text. A flowchart of the detailed search strategy can be found in Supplementary File S1. Initially, all hepatic GSD patients with a dietary lipid manipulation were identified. However, the majority of cases describing GSD type I and VI patients were published before the introduction of management guidelines and lacked important clinical information15-18. Therefore, these data were not included, and further data analysis was solely focused on GSDIII. All reports about GSDIII patients receiving dietary lipid manipulation were included. Inclusion criteria were GSDIII diagnosis based on biochemical or molecular evaluation and English language. Exclusion criteria were no individual data presentation and/or absence of follow-up data. Two independent reviewers (I.J.H., V.B.B.) performed title, abstract screening and subsequently full-text assessment. After selection of eligible full-text papers and conference abstracts, case information was collected in a data table specifically designed for the purpose of this study, including patient’s age at start dietary intervention, gender, GSDIII subtype, indication to start dietary intervention, specifications of diet, duration of the intervention and follow-up, and outcome measures (laboratory results, imaging tests, and clinical picture).
Case studies

Unpublished cases were retrieved via the International GSD Conference 2017, organised in Groningen, The Netherlands on June 15 to 17, 2017. All metabolic dieticians were invited to join a networking session on the role of MCT in hepatic GSD. In October 2017, after the IGSD2017, all delegates who had attended the networking session received an invitation by email to share unpublished data of hepatic GSD patients with a dietary lipid manipulation. Data were collected through the same table used for published cases.

Data synthesis and analysis

Data on macronutrients were presented as energy percentage (E-%) of total caloric intake, or if otherwise noted in the legend. MCT supplementation was defined as regular GSD diet enriched in MCT. MCT replacement was defined as long-chain triglycerides substituted with MCT. High fat diet was defined as a diet in which lipids were the main macronutrient based on E-% values. Ketogenic diets were also categorised as high fat even in the absence of E-% values. Standard deviations of BMI were calculated using standard growth charts established by the CDC/2000. Age specific outcomes were presented as Z-scores or in subgroups (i.e., child and adult). The cut-off value for adulthood was set at 16 years of age. Laboratory parameters were presented as range (minimum-maximum value) before and after the dietary intervention, respectively. For each parameter, individual differences (Δ) were presented as percentage difference between mean values before and after the dietary intervention, respectively. Concentrations were considered increased when Δ > +10%, decreased when Δ < −10% and stable if Δ between −10% and +10%. Z-scores were calculated for interventricular septum dimensions (IVSd) to normalise for the body surface area. For Z-score calculation, the regression equation by Pettersen was used. The Haycock formula was used for BSA calculation.

Statistical analysis

Data were analysed using Prism 7 software (GraphPad Software, Inc. La Jolla, California) and Statistical Package for Social Sciences, version 23.0 (SPSS, IBM Corp., Armonk, New York). Differences in outcome measures before and after dietary lipid manipulation were analysed with a paired t test if data were normally distributed (assessed by the Shapiro-Wilk test). Data were analysed with Wilcoxon signed ranks test in case of non-normally distributed data after log-transformation. Pearson's or Spearman's correlations tests were used to define relationships between dietary parameters and changes in laboratory outcomes. Statistical significance was defined as $P < .05$

RESULTS

Cases

Literature search revealed four full text articles and five conference abstracts describing 14 GSDIII patients (Supplementary File S2), whereas 14 unpublished cases were collected from six metabolic centres from three different countries (Supplementary File S3). Therefore, a total of 28 cases with GSDIII and a dietary lipid manipulation were collected.
Patients features, indication to start the diet and compliance

Main features of GSDIII patients receiving a dietary lipid manipulation are presented in Table 1. The main indication to start the dietary intervention was cardiomyopathy and/or myopathy. Four patients (cases 9, 19, 26, 27) did not follow the modified diet regimen regularly: either poor compliance was reported, or the diet was discontinued several times.

| Cases, n                              |            |
|---------------------------------------|------------|
| Published                             | 14         |
| Unpublished                           | 14         |
| Total                                 | 28         |

| Gender, n (%)                         |            |
|---------------------------------------|------------|
| Male                                  | 11 (39%)   |
| Female                                | 15 (54%)   |
| Unknown                               | 2 (7%)     |

| Agea, years                           | Median [range] 7 [0-41] |
|---------------------------------------|-------------------------|

| Indication, n (%)                     |            |
|---------------------------------------|------------|
| Hyperlipidemia                        | 2 (7%)     |
| Poor metabolic control                | 7 (25%)    |
| Muscle involvement                    | 19 (68%)   |
| -Skeletal muscle weakness             | 3          |
| -Cardiomyopathy                       | 6          |
| -Skeletal and cardiac muscle involvement | 9         |
| -Hypotonia                            | 1          |

| Intervention, n (%)                   |            |
|---------------------------------------|------------|
| High fat diet                         | 26b (93%)  |
| MCT supplementation/replacement       | 6 (21%)    |
| Atkins, ketogenic diet                 | 5 (18%)    |
| Corn oil supplementation              | 1 (4%)     |

| Months of dietary intervention        | Median [range] 18 [1-60] |
|---------------------------------------|-------------------------|

Table 1. Features of published and unpublished cases with GSDIII and a dietary lipid manipulation (n = 28).

aAge at start dietary intervention.
bFour patients received both MCT and a high fat diet (cases 15, 16, 20, and 21), five patients received a ketogenic diet which was also categorised as high fat diet (cases 2 and 8-11), one patient received a high fat diet with corn oil substitution (case 14), and one patient received a high fat diet supplemented with D,L-3-hydroxybutyrate (case 12).

Abbreviation: MCT, medium-chain triglyceride.
Diet composition

Most common lipid manipulation was high fat diet (Table 1). Figure 1A presents the diet composition before and after dietary intervention in GSDIII patients receiving a high fat diet. Lipid intake ranged from 0.9 to 8.0 g/kg/day (2.9-8.0 g/kg/day in children, 0.9-2.7 g/kg/day in adults) (Figure 1B). Less common interventions included corn oil supplementation together with high fat diet (case 14) and MCT supplementation alone (cases 6 and 7) (Supplementary File S2).

Figure 1. Dietary features of GSDIII patients. A, Diet composition in GSDIII patients before (n = 10) and after (n = 24) high fat diet. B, Lipid intake in GSDIII patients receiving high fat diet (n = 18, patients on high fat diet also receiving MCT supplementation were included). Data are presented as median [range]. CH, carbohydrates

Laboratory results

The changes in laboratory parameters in GSDIII patients receiving high fat diet are presented in Figure 2 and Supplementary File S4.

Creatine kinase (CK) concentrations were available in 73% (19/26) of GSDIII patients receiving high fat diet (Figure 2A). Mean CK concentrations were lower after receiving high fat diet in 89% (17/19) of GSDIII patients (2070 U/L ± 1634 vs 1078 U/L ± 1148, P < .001). One previously unreported patient showed an increase in CK concentrations (case 25); however, CK concentrations remained within the reference range. Another patient showed stable CK concentrations (case 26). No correlations between ΔCK and changes in macronutrients were found.

Liver transaminases (ALT/AST) were documented in 58% (15/26) of GSDIII patients on a high fat diet (Figure 2B, C). In adult GSDIII patients, ALT concentrations decreased in all cases (n = 6); AST concentrations decreased in five patients (83%) and were stable in the sixth patient. In paediatric GSDIII patients, ALT concentrations increased in four patients (44%), decreased in one patient (11%) and were stable in four patients (44%); AST concentrations increased in five patients (56%), decreased in two patients (22%), and were stable in two patients (22%).
Figure 2. Changes in laboratory parameters by dietary lipid manipulation in GSDIII. A, Relation between CK concentrations before intervention and change in CK concentration of 19 individual patients with GSDIII with high fat diet, including patients with combined high fat diet and MCT supplementation (n = 4). Spearman’s rho correlation coefficient = −0.40, P > .05. Grey square: GSDIII patient, black square: GSDIII patient receiving combined high fat diet and MCT supplementation, white square: GSDIII patient showing CK concentrations within age-related reference values before and after dietary lipid manipulation. B, Measured blood ALT concentrations in GSDIII patients before (circle) and after (square) the introduction of a high fat diet. C, Measured blood AST concentrations in GSDIII patients before (circle) and after (square) the introduction of a high fat diet.

Imaging and clinical outcomes

IVSd Z-scores decreased in paediatric GSDIII patients with a high fat diet (n = 7, P < .01; Figure 3), but not in adult GSDIII patients (n = 4, Supplementary File S3). There were no correlations between the change in IVSd Z-scores and changes in macronutrients. Data on muscle ultrasound and muscle function tests were available in two adult GSDIIIa patients on a high fat diet with MCT replacement (cases 15 and 16). There was no effect on muscle density. Muscle strength as assessed by dynamometry improved only for case 15. Subjective improvements of exercise tolerance and/or muscle strength were reported in 78% (14/18) of paediatric GSDIII patients and 50% (4/8) of adult
GSDIII patients on high fat diet. Among paediatric GSDIII patients receiving a high fat diet 18% (2/11) showed improved height SDS, 64% (7/11) showed stable height SDS and 18% (2/11) showed decreased height SDS. All paediatric patients showed normal BMI (60% stable, 40% normalised). BMI was stable in all adult GSDIII patients.

Figure 3. Effect of high fat diet on interventricular septum dimension in paediatric GSDIIla patients (n = 7). Measurements are displayed as Z-scores. GSDIIla subjects are noted with symbols according to E-% of fat. Grey column represents range of normal Z-scores.

Side effects

Side effects were reported in two patients. Hypoglycaemia is an intrinsic symptom of hepatic GSD and was reported in two GSDIII patients on a high fat diet. Specifically, one paediatric GSDIIla patient (case 18) reported isolated hypoglycaemia 3 years after the start of a high fat diet, and one paediatric GSDIIla patient (case 19) presented with an isolated hypoglycaemia 1 year before and 2 years after starting with a high fat diet.

DISCUSSION

Complex carbohydrates and, for ketotic GSD patients, protein enrichment are the cornerstones of dietary management in hepatic GSD. The role of lipids has not been systematically assessed and the current guidelines do not provide clear indications for their use. This systematic literature study and retrospective international multicentre cohort study presents that a high fat diet could be considered in paediatric GSDIII patients with cardiomyopathy. The significant reduction in blood CK concentrations and subjective improvement in muscle strength reported in GSDIII patients necessitates further quantification of the effect of a high fat diet on muscle quality and function. Also,
liver function, morphology, and growth should be carefully monitored under a high fat regimen given the potential impact on underlying liver disease.

Before discussing the results, some methodological issues need to be addressed. The analysis and interpretation of the data were hampered by large variation in age, dietary intervention (e.g., lipid amount, high fat diet alone or together with lipid supplementation), duration of intervention, and outcome parameters. Initially, this study was set up to describe all hepatic GSD types. Most of the data on GSDI and GSDVI were limited and/or historical\textsuperscript{10,12,15,16,18,23}, whereas metabolic control has improved with increasing knowledge on dietary management/glycaemic control and the introduction of management guidelines, as demonstrated for GSDIa patients\textsuperscript{24}. Therefore, in this article, we only included data from GSDIII patients. The published cases presented in this study \((n = 14)\) were retrieved from case reports or small cohort studies (describing less than five patients); these data were potentially affected by selection and publication bias. Also, the possible beneficial role of a more compliant dietary scheme during dietary intervention should be considered. Finally, ascertainment bias extends to healthcare professionals attending a GSD conference.

The main indications to start with a dietary lipid manipulation in GSDIII patients were cardiomyopathy, skeletal myopathy or a combination of both. Lipids became the main macronutrient in GSDIII patients at the expense of carbohydrates. Interestingly, cardiac hypertrophy, as quantified by IVSd Z-scores, decreased only in paediatric GSDIIIa patients. We hypothesize that an early switch to high fat diet can reverse—or at least decrease—the cardiac glycogen storage. Moreover, results showed decreased CK concentrations in 89\% of GSDIII patients in accordance with literature\textsuperscript{9,11,13} and improved subjective strength in most of the patients. Increased blood CK concentrations reflect muscle damage which may partially be influenced by exercise. Whether the beneficial effect of a high fat diet on CK concentrations is caused by a lower carbohydrate intake—and thus less accumulation of abnormal glycogen in muscle tissue—or due to the properties of fat to supply alternative energy substrate for muscle remains to be investigated. Notably, most of the GSDIII patients included in the present study received a combination of a high fat and high protein diet. Therefore, these changes in macronutrient composition could also partly account for the beneficial effect on cardiomyopathy and CK concentrations. Nevertheless, protein intake was comparable before and after intervention in GSDIII patients in the present study (Figure 1A).

The development of chronic liver disease is an important concern in ageing GSDIII patients. Although the prevalence of hepatocellular carcinoma was low in the International Study on GSDIII\textsuperscript{25}, severe and progressive liver fibrosis has been described at early ages\textsuperscript{26}. Only one publication describing high fat diet in two GSDIIIa patients documented data on liver transaminases (cases 4 and 5\textsuperscript{9}). Interestingly, we found that ALT concentrations increased in 44\% (4/9) of paediatric GSDIII patients but decreased in all adult GSDIII patients. After dietary lipid manipulation, the concomitant decrease in carbohydrate intake would theoretically lead to less glycogen accumulation in the liver. It remains speculative if these age-specific effects are part of the natural history or influenced by dietary lipid manipulations. However, under these circumstances, careful monitoring and follow-up is warranted for liver complications such as hepatosteatosis, liver inflammation, and hepatocellular carcinoma\textsuperscript{27}.

Side effects were reported in two patients, consisting in isolated (and mostly mild) hypoglycaemia, an intrinsic symptom in GSD patients\textsuperscript{28}. ‘Side effects’ were not a specific parameter in our data table,
and therefore the side effects reported in this study could be an underrepresentation. Previously mentioned concerns regarding MCT in GSD patients are the unknown consequence towards the elongation of fatty acids or gluconeogenesis pathway\textsuperscript{14}. Increased triglycerides concentrations after introduction of MCT have been reported in GSDIII patients\textsuperscript{29}. However, in the present study, the majority of GSDIII patients received a high fat diet rather than MCT supplementation or replacement. As high fat diets have been associated with an increased risk of osteoporosis\textsuperscript{30} combined with the reduced bone mineral density in GSDIII patients\textsuperscript{31} the long-term effect of dietary lipid manipulations on bone status should be carefully monitored.

Recommendations for future dietary intervention studies and follow-up of GSDIII patients who start with a high fat diet are summarised in Supplementary File S5. The present study also provides insight in important outcome parameters when assessing the effect of a dietary intervention in hepatic GSD patients. Several additional outcome measures are proposed including muscle\textsuperscript{32-34}, bone\textsuperscript{31}, mitochondrial\textsuperscript{12,35}, and enzymatic\textsuperscript{36} markers. Prospective, long-term follow-up studies are warranted to confirm efficacy and safety of dietary lipid manipulations in the international GSDIII and further hepatic GSD cohort.
Chapter 4

FUNDING

This project was funded by Junior Scientific Masterclass by University Medical Center Groningen (MD-PhD 15-16 grant to I.J.H. and Dr T.G.J.D.). The stay of A.R. at University of Groningen was financially supported by University of Naples “Federico II” and Compagnia di San Paolo, in the frame of Programme STAR.

ACKNOWLEDGMENTS

The authors would like to thank Margreet van Rijn, metabolic dietician from Groningen who was involved in the initiation of this project. The authors would also like to acknowledge Ellen Wagenaar who was responsible for the organisation of the dietary networking session at the IGSD2017. M.R., S.G., and R.P. gratefully acknowledge Roberta Pretese, metabolic dietician in Monza, who thoroughly followed all GSDIII patients of the centre.
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Chapter 4

SUPPLEMENTARY MATERIAL

Supplementary File S1
Supplementary File S1. Prisma flowchart of search strategy. PubMed and Embase were searched using both MeSH terms and free text: a. PubMed search: ‘("Glycogen Storage Disease"[Mesh] OR glycogen storage[tiab] OR glycogenos*[tiab]) AND ("Ketogenic Diet"[Mesh] OR "Diet, Carbohydrate-Restricted"[Mesh] OR ((fat[tiab] OR fatty*[tiab] OR oil*[tiab] OR atkins[tiab] OR ketogen*[tiab]) AND (diet[tiab] OR diets[tiab] OR dietary[tiab] OR dieting[tiab])) OR "triheptanoin" [Supplementary Concept] OR "Triglycerides"[Mesh] OR "Dietary Fats"[Mesh] OR "Fish Oils"[Mesh] OR medium chain triglycerid*[tiab] OR MCT[tiab] OR triheptanoin*[tiab] OR omega-3-fatty acid*[tiab] OR fish oil*[tiab]) NOT ((("Animal*[Mesh] NOT "Humans*[Mesh] OR animal*[ti] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] ) OR (diet OR diets OR dietary OR dieting)) OR ("Triacylglycerol" OR "fat intake") OR ("medium chain triglycerid" OR MCT OR triheptanoin* OR omega-3-fatty acid" OR "fish oil"); ab,ti) AND ("ketogenic diet" OR "low carbohydrate diet") OR ((fat OR fatty* OR oil* OR atkins OR ketogen*) AND (diet OR diets OR dietary OR dieting)); ab,ti OR "triheptanoin" OR "fat intake" OR "medium chain triglycerid" OR MCT OR triheptanoin* OR omega-3-fatty acid" OR "fish oil"; ab,ti) NOT ((("animal" OR "nonhuman") OR (animal OR rat OR rats OR mouse OR mice)); ti). The search was conducted on the 31th of December 2018. The PubMed search revealed 179 articles whereas the Embase search resulted in 388 articles. After the duplicate check a total of 455 articles could be included for the search strategy. *From one of these cases missing data were collected during the retrospective study part; this case was included as unpublished case (case 21) in Supplementary File S3.
Chapter 4

Supplementary File S2
| Patient number | Reference | Age at start (years), gender (M/F) and GSD type | Indication to start the dietary intervention | Dietary intervention and Diet composition | Duration of intervention (months) | Outcome parameters: laboratory results (glucose/lactate/Ketones/acetoacetate/BOHB/TC/TG/HDL/LDL: mmol/L, insulin: mU/L, uric acid: mg/dL, AST/ALT/CK: U/L,FFA: µmol/L,TnT/NT-proBNP: ng/L,Mb: µmol/L) | Outcome parameters: diagnostic imaging | Outcome parameters: Clinical picture, side effects |
|----------------|-----------|-----------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| 1              | White et al, J Inherit Metab Dis. 2018 ABSTRACT | 0.42 F IIIa                                  | High glucose demand, seizure                 | High-fat, high protein diet 20% carbohydrates, 60% lipids, 20% protein | 7                               | Glucose: >2.8 mmol/L Ketones: 0.5 - 2.4 mmol/L Insulin, TC, TG, CK: n/a Other: n/a | Cardiac US: hypertrophic cardiomyopathy fully resolved. | Increased fasting tolerance. |
| 2              | Groselj et al, J Inborn Errors Metab Screen 2017 ABSTRACT | 12 F IIIa                                    | Severe hypertrophic cardiomyopathy, hepatomegaly, myopathy. | Ketogenic diet. Ketogenic ratios of meals were from 2.5:1 to 4:1. 2% carbohydrates, 87% lipids, 11% protein | 18                              | Glucose: no hypoglycemia Ketones, insulin, TC, TG, CK: n/a Other: lipid levels improved significantly. | Liver US: significant improvement of hepatomegaly Cardiac MRI: normalization of left ventricular parameters and mass (from 70 g to 35 g), without residual outflow obstruction. | Exertion dyspnea disappeared. Capacity for oxygen consumption almost doubled |
| 3              | Kumru et al, J Inherit Metab Dis. 2016 ABSTRACT | 6 M IIIa                                     | Hypertrophic cardiomyopathy Fatigue          | High-fat, high protein diet. 30% carbohydrates, 50% lipids,20% protein. | 18                              | Glucose, ketones, insulin, TC, TG: n/a CK: from 1628 to 1125 Other: n/a | Cardiac US: left ventricular outflow gradient reduced from 35 to 20 mmHg; IVS thickness reduced from 21 to 10 mm; posterior wall thickness reduced from 18 to 11 mm | Fatigue resolved |
| Case | Name | Age | Gender | CMA | Diagnosis | Diet prescribed | Diet withdrawal | Additional protein sources | Biochemical changes | Cardiac US | Clinical changes |
|------|------|-----|--------|-----|------------|----------------|-----------------|--------------------------|-------------------|-----------|-----------------|
| 4    | Brambilla et al., J Inherit Metab Dis. Rep. 2014 | 7 | F | IIIa | Severe cardiomyopathy, muscle weakness | High-fat high protein diet 1120 Kcal/day, 15% carbohydrates, 59% lipids, 26% proteins UCCS progressively withdrawn Polyunsaturated fatty acids preferred Only extra-virgin olive oil as relish Additional protein powders to increase protein intake | | | Glucose, lactate: no significant difference (normal) Insulin: n/a Ketones: n/a TG: TG: no significant difference (normal) CK: significant decrease Other: NT-proBNP, Mb, ALT: significant decrease; AST: slight decrease; TnT: no significant difference (normal) | Cardiac US: IVS thickness, posterior wall thickness and outflow tract obstruction significantly reduced | Increased strength and reduced exertion dyspnea. No significant impact on growth (normal) and liver size (increased) |
| 5    | Brambilla et al., J Inherit Metab Dis. Rep. 2014 | 5 | M | IIIa | Severe cardiomyopathy, muscle weakness | High-fat high protein diet 1050 Kcal/day, 15% carbohydrates, 60% lipids, 25% proteins UCCS progressively withdrawn Polyunsaturated fatty acids preferred Only extra-virgin olive oil as relish Additional protein powders to increase protein intake | | | Glucose, lactate: no significant difference (normal) Insulin: n/a Ketones: n/a TG: no significant difference (normal) TG: slight increase CK: significant decrease Other: NT-proBNP, Myoglobin, ALT, AST: significant decrease; TnT: no significant difference (normal) | Cardiac US: IVS thickness, posterior wall thickness and outflow tract obstruction significantly reduced | Increased strength No significant impact on growth (normal) and liver size (increased) |
| No. | Authors | M | GSD Type | Diet | UCCS | Metabolic Control | Adverse Effects | Other | Cardiac US | Other Effects |
|-----|---------|---|----------|------|------|------------------|----------------|-------|------------|---------------|
| 6   | El-Gharbawy et al, Mol Genet Metab. 2014 | 3.5 | IIIa | Poor metabolic control | MCT supplementation UCCS progressively withdrawn | Glucose, insulin, TC, TG: no significant difference Ketones: no evidence of ketosis CK: significant decrease Other: ALT, AST: modest decrease | n/a | Improved energy levels |
| 7   | El-Gharbawy et al, Mol Genet Metab. 2014 | 2 | IIIa | Poor metabolic control | MCT supplementation UCCS progressively withdrawn | Glucose, insulin, TC, TG: no significant difference Ketones: no evidence of ketosis CK: significant decrease Other: ALT, AST: modest decrease | n/a | Improved energy levels |
| 8   | Mayorandan et al, Orphanet J Rare Dis. 2014 | 9 | IIIa | Severe cardiomyopathy, muscle weakness | High-fat high protein diet UCCS progressively withdrawn Modified Atkins diet 0.4 g/Kg/day carbohydrates, 8 g/Kg/day lipids, 7 g/Kg/day proteins | Glucose, insulin: n/a; occasional hypoglycemia during the first weeks Ketones: increased TC: n/a TG: slight increase CK: significant decrease Other: NT-proBNP: significant decrease; LDL: no significant difference (normal) | Cardiac US: IVS thickness and left ventricular outflow tract-gradient significantly reduced | Increased stamina No significant impact on growth (normal) |
| 9   | Mayorandan et al, Orphanet J Rare Dis. 2014 | 11 | IIIa | cardiomyopathy, muscle weakness, chest pain, nausea after exercise | High-fat high protein diet UCCS progressively withdrawn Modified Atkins diet 0.5 g/Kg/day carbohydrates, 6 g/Kg/day lipids, 5 g/Kg/day lipids | Glucose, insulin: n/a Ketones: increased TC: n/a TG: no significant difference (normal) CK: significant decrease Other: LDL: no significant difference (normal) Increase in CK levels and lost ketosis upon diet discontinuation. CK levels fell again and ketosis was re-established when the diet resumed | Cardiac US: Hypertrophic cardiomyopathy disappeared | Chest pain, nausea and weakness disappeared Increased stamina Chest pain and weakness reappeared upon diet discontinuation and reverted again when the diet was resumed |
| Page | Authors | Year | Gender | Diagnosis | Diet | Glucose, insulin | Ketones, TC, TG | CK | Cardiac function | Physical strength |
|------|---------|------|--------|-----------|------|----------------|----------------|-----|----------------|------------------|
| 10   | Meyer et al, J Inherit Metab Dis. 2013 | 9 | M | IIIa | Poor metabolic control | High-fat high protein diet | Atkins diet | 12 | Glucose, insulin: n/a | Cardiac function stabilised | Improved physical strength |
| 11   | Meyer et al, J Inherit Metab Dis. 2013 | 11 | M | IIIa | Poor metabolic control | High-fat high protein diet | Atkins diet | 12 | Glucose, insulin: n/a | Cardiac function stabilised | Improved physical strength |
| 12   | Valayannopoulos et al, Pediatr Res. 2011 | 0.17 | M | III | Severe cardiomyopathy | High-fat high protein diet | 20% carbohydrates, 65% lipids, 15% proteins + BHB (400-800 mg/Kg/day) | 24 | Glucose, insulin: significant decrease (normal) | Cardiac US: IVS thickness significantly decreased | Normal muscle tone and strength, growth and development | Liver size increased within the first 6 months and then remained stable | Diet and BHB treatment well tolerated: no further hypoglycemia |
|   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |   |
| 13 | Fernandes et al, Am J Clin Nutr. 1969 | 1 | F | III | Hyperlipidemia | High fat low carbohydrate diet | Period 1: 39% carbohydrates, 50% lipids (32% corn oil, 18% milk fat), 11% proteins | Period 2: 39% carbohydrates, 50% lipids (32% olive oil, 18% milk fat), 11% proteins | Period 3: 39% carbohydrates, 50% lipids (32% coconut oil, 18% milk fat), 11% proteins | Period 4: 39% carbohydrates, 50% lipids (MCT), 11% proteins | Glucose, insulin, ketones, TG, CK: n/a | Period 1: TC no significant difference (high) | FFA: significant decrease | Period 2: TC, FFA: no significant difference | Period 3: TC no significant difference, FFA: high fluctuation | Period 4: TC, FFA: significant increase | n/a | n/a |
| 14 | Fernandes et al, Am J Clin Nutr. 1969 | 5 | F | III | Hyperlipidemia | High fat low carbohydrate diet | 35% carbohydrates, 48% lipids (corn oil), 17% proteins | 1.4 | Glucose, insulin, ketones, TG, CK: n/a | Marked fluctuations in TC and FFA levels | n/a | n/a | n/a |

Supplementary file S2. Table published cases.

**ACs:** serum acylcarnitines, **ALT:** alanine aminotransferase, **AST:** aspartate aminotransferase, **BHB:** beta-hydroxybutyrate, **CK:** creatine kinase, **CK-MB:** creatine kinase isoenzyme MB, **FFA:** free fatty acids, **HDL:** High-density lipoprotein, **IVS:** interventricular septum, **LCT:** long-chain triglycerides, **LD:** liver longitudinal diameter, **LDL:** Low-density lipoprotein, **LVW:** left ventricular wall, **Mb:** myoglobin, **MCT:** medium-chain triglycerides, **MRI:** magnetic resonance imaging, **NT-proBNP:** N-terminal prohormone of brain natriuretic peptide, **UCCS:** uncooked corn starch, **TC:** total cholesterol, **TG:** triglycerides, **TnT:** Troponin T, **US:** ultrasound, **ω-3FA:** omega-3 fatty acids.
Chapter 4

Supplementary File S3.
| Patient number | Age at start (years) | Gender (M/F) and GSD type | Genotype gene (allele 1/ allele 2) OR Enzyme test | Indication to start dietary intervention | Dietary intervention and diet composition (amount of MCT/fat per day, amount of carbo per day (specify amount of UCCS), amount of protein per day (% of total daily intake, daily g)) | Duration (months) | Outcome parameters: laboratory results (glucose/lactate/Ketones/acetoacetate/BHB/TC/TG/HDL/LDL: mmol/L, insulin: mU/L, uric acid: mg/dL, AST/ALT/CK: U/L, CK-MB: ng/mLFFA: µmol/L, TnT/NT-proBNP: ng/L, Mb: µmol/L) | Outcome parameters: diagnostic imaging | Outcome parameters: Clinical picture, side effects | Clinical picture, side effects |
|----------------|----------------------|---------------------------|--------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| 15             | 37                   | F                         | Illa                                             | Exercise intolerance, Overweight, Cardiomyopathy | MCT replacement UCCS replaced with MCT-emulsion Period 1. 1400 Kcal/day, 12.8% carbohydrates, 63.5% lipids (60% MCT), 24.1% proteins Period 2. 1900 Kcal/day, 11% carbohydrates, 47% lipids (60% MCT), 41% proteins | 31               | Glucose: 4.5  Insulin: n/a  Acetoacetate: 0.02  BHB: 0.2  TC: 2.3  TG: 0.5  CK: 1010  Other: AST:191-196, ALT: 60-119, HDL: 0.8-12, LDL: 1.1-1.8, FFA: n/a, CK-MB: 68-118, TnT, NT-proBNP: n/a | Glucose: 5-6.5  Insulin: 4.1-23.8  Acetoacetate: 0.02-0.2  BHB: 0.02-0.25  TC: 3.2-3.9  TG: 0.69-1.23  CK: 775-2480  Other: AST:88-126, ALT: 53-86, HDL: 1-1.3, LDL: 1.5-2, FFA:74-807, CK-MB: 35-60, TnT: n/a, NT-proBNP: 3230-4899 | BEFORE Liver US: hepatomegaly (CC:16 cm), no adenoma  Cardiac US: IVS thickness: 14 , LVW thickness: 17.6 , EF: 50%. Mitral insufficiency gr III. Hypertrophic cardiomyopathy with impaired diastolic function. ECG: normal | AFTER Liver US: hepatomegaly (CC: 16 cm), no adenoma. Cardiac US: IVS thickness: 14, LVW thickness: 18.3, EF: 50%. Mitral insufficiency in situ. Hypertrophic restricted cardiomyopathy. ECG: left axis deviation. | BEFORE Weight: 98 Height: 172 BMI: 33 (+ 3.0 SD)  AFTER Weight: 99 Height: 171 (+0.04 SD) BMI: 33.9 (+3.13 SD). Overall muscle strength improved during period 2 when measured with dynamometry. No difference on muscle ultrasound density. |
| Chapter 4 |
|-----------|
| 16 | 35 | F | IIIa | AGL, c.4529dup (p.Tyr1510Ter*) | Muscle weakness Not liking UCCS Overweight | MCT replacement UCCS replaced with MCT-emulsion 2614 Kcal/day, 15% carbohydrates, 66% lipids (75% MCT), 19% proteins | 36 | Glucose: 4-5 Insulin: n/a Acetoacetate: 0-0.02 BHB: 0-0.2 TG: 4.20-5.7 TG: 0.76-1.63 CK: 898-3408 Other: AST:123-338, ALT: 94-215, HDL:1.2-2.1, LDL: 2.3-3.3, FFA: n/a, CK-MB, TnT, NT-proBNP: n/a | Glucose: 4.5-6.8 Insulin: 2-4.87 Acetoacetate: 0.02-0.81 BHB: 0.03-2.57 TG: 4.1-4.6 TG: 0.73-1.05 CK: 749-1173 Other: AST: 99-118, ALT: 86-118, HDL:1.2-1.6, LDL: 2.5-2.8, FFA: 154-463, CK-MB, TnT: n/a, NT-proBNP: 84-125 | BEFORE Liver US: hepatomegaly (CC:20 cm), no adenoma. Cardiac US: IVS thickness: 12 , LVW thickness: 13.1 , EF: 60%. Minimal left ventricle hypertrophy. ECG: normal. AFTER Liver US: hepatomegaly (CC:18 cm), no adenoma. Cardiac US: IVS thickness: 13 , LVW thickness: 11.2 , EF:55-60% , Minimal left ventricle hypertrophy. |
| 17 | 6 | M | IIIa | AGL, c.3235C>T (p.Gln1079Ter*) | Severe cardiomyopathy | High fat diet UCCS withdrawn 1726 Kcal/day, 9% (37 g/day) carbohydrates, 77% (147 g/day) lipids, 14% (62 g/day) proteins | 39 | Glucose: 3-5.5 Insulin: n/a Ketones: 0.0 TG: 3.9-5.3 TG: 1.6-4.6 CK: 145-534 Other: AST: 126-437, ALT: 139-539, HDL: 0.5-0.7, LDL: 1.4-4.1, FFA, CK-MB, TnT, NT-proBNP: n/a | Glucose: 3.4-5.5 Insulin:0.5-22.6 Ketones: 0-0.2 TG: 4-4.8 TG: 2-3 CK:58-449 Other: AST: 124-510, ALT: 145-598, HDL: 0.5-0.8, LDL: 2.7-3.7 mg/dL, FFA, CK-MB, TnT, NT-proBNP: n/a | BEFORE Liver US: hepatomegaly, fatty liver Cardiac US: IVS 10-19, left ventricular mass +4SD Severe hypertrophic cardiomyopathy with intraventricular and subaortic obstruction, diastolic dysfunction grade III ECG, n/a | AFTER Liver US: hepatomegaly, fatty liver Cardiac US: IVS 8.2, left ventricular mass +1.5 SD Improvement of cardiomyopathy with |
| BEFORE | Weight: 81.3 Height: 178 BMI: 25.7 AFTER | Weight: 79.5 Height: 178 BMI: 25.1 (+1.21 SD). Muscle dynamometry showed a progressive myopathy affecting especially the proximal muscles. Worsening of muscle weakness when on MCT diet. Muscle ultrasound showed decrease in muscle mass and increase in muscle density. | BEFORE Weight 25 (1 SD) Height 116 (-0.3 SD) BMI: 18.6 (1.6 SD) Muscle strength: n/a | AFTER | Weight 34.4 (0.7 SD) Height 144 (1.2 SD) BMI 16.6 (0.1 SD) Muscle strength: n/a |
| No | Age | Sex | Mutation | Phenotype | Treatment | Baseline | 8 weeks | Baseline | 8 weeks |
|----|-----|-----|----------|-----------|-----------|----------|---------|----------|---------|
| 18 | 4   | F   | AGL, arf[GRCh37] 1p21.2(10027499 4_100623922)x1 pat/ c.4202G>A (p.Trp1401Ter*) | Cardiomyopathy | High fat diet UCCS withdrawn 1770 Kcal/day, 13% (57 g/day) carbohydrates, 68% (134 g/day) lipids, 19% (83 g/day) proteins | Glucose: 4-4.9 Insulin: 1.42-5.48 Ketones: 0-0.1 TC: 6.4-7.9 TG: 4.2-4.4 CK: 878-1305 Other: AST: 179-438, ALT: 226-522, HDL: 0.59-0.60, LDL: 4.4-5.8, FFA, CK-MB, TnT, NT-proBNP: n/a | Glucose: 2.6-5.2 Insulin: 0.5-5.25 Ketones: 0.1-0.9 TC: 6.2-9.5 TG: 2.4-9.8 CK: 133-711 Other: AST: 197-420, ALT: 248-560, HDL: 0.75-1.11, LDL: 2.7-8.7, FFA, CK-MB, TnT, NT-proBNP: n/a | BEFORE Liver US: hepatomegaly, fatty liver, no adenoma Cardiac US: IVS:10, mild hypertrophic cardiomyopathy ECG: n/a AFTER Liver US: hepatomegaly, fatty liver, no adenoma Cardiac US: IVS: 4.8, regression of hypertrophic cardiomyopathy ECG: n/a | BEFORE Weight 15.9 (0.3 SD) Height 93 (-1.5 SD) BMI: 18.3 (1.8 SD) Muscle strength: n/a AFTER Weight 20.8 (-1.2 SD) Height: 108 (-3.5 SD) BMI 17.8 (0.9 SD) Muscle strength: n/a |
| 19 | 5   | F   | AGL, c.3988G>A/c.4332 insAA (p.Trp1330*/p.Gly 1445Lysfs*27) | Cardiomyopathy Myopathy | High fat diet UCCS withdrawn 1536 Kcal/day, 12% (43 g/day) carbohydrates, 65% (111 g/day) lipids, 23% (89 g/day) proteins | Glucose: 2.4-5.6 Insulin: n/a Ketones: n/a TC: 4-4.9mg/dL TG: 2.3-4.9 CK: 622-2938 Other: AST: 236-509, ALT: 283-531, HDL: 0.6-0.75, LDL: 1.5-3.6, FFA, CK-MB, TnT, NT-proBNP: n/a | Glucose: 2.8-4.2 Insulin: 0.5-1.35 Ketones: 0.2-0.3 TC: 4.75-6.8 TG: 2.1-4.3 CK:643-1692 Other: AST: 694-1382, ALT: 489-824, HDL: 0.7-0.9, LDL: 3.3-5.9, FFA, CK-MB, TnT, NT-proBNP: n/a | BEFORE Liver US: hepatomegaly, fatty liver Cardiac US: IVS 8.5mm, moderate hypertrophic cardiomyopathy ECG: n/a AFTER Liver US: hepatomegaly, fatty liver Cardiac US: IVS 6.1mm, regression of hypertrophic cardiomyopathy ECG: n/a | BEFORE Weight 18.5 (0.6 SD) Height 100 (-1 SD) BMI: 18.3 (1.8 SD) Muscle strength: n/a AFTER Weight 24.8 (0.8 SD) Height: 116 (-0.5 SD) BMI 18.4 (1.4 SD) Muscle strength: n/a |
| Page |符号 | 疾病 | 控制 | 饮食 | 参数 |
|------|------|------|------|------|------|
| 20   | III  | Amylo-1,6-glucosidase: 0 | Poor metabolic control | MCT supplementation Low carbohydrate diet enriched in MCT. UCCS withdrawn. 2575 Kcal/day, 10% carbohydrates, 62% lipids (11% MCT, 20 g/day), 19% proteins | Glucose: 4.2-4.9 Insulin: 1.2-2.3 Ketones: n/a TC: 6.6-7.2 TG: 2-3.3 CK: 2933-3032 Other: AST: 9-111, ALT: 32-195, HDL: 0.8-0.9, LDL: 2.1-2.8, FFA, CK-MB, TnT, NT-proBNP: n/a |
| 21   | IIIa | Amylo-1,6-glucosidase: 0 | Severe cardiomyopathy Poor metabolic control | MCT supplementation Low carbohydrate diet enriched in MCT. UCCS withdrawn. 2005 Kcal/day, 25% carbohydrates, 50% lipids (20% MCT, 20 g/day), 25% proteins | Glucose: 4.2-5.1 Insulin: 0.8-5.8 Ketones: n/a TC: 3.3-4.7 TG: 1.5-2.6 CK: 803-3887 Other: AST: 118-377, ALT: 112-501, HDL: 0.5-0.9, LDL: 2.7-3.3, FFA, CK-MB, TnT: n/a, NT-proBNP: 1260-5850 |
| 22   | IIIa | AGL, c.2147delG | Fatigue Exercise intolerance Refusal of night meals and UCCS | High fat diet UCCS withdrawn 1770 Kcal/day, 6% carbohydrates, 76% lipids, 18% proteins | Glucose: 3 Insulin: n/a Ketones: n/a TC: 5.4 TG: 1.1 CK: 867-1918 Other: AST: 111-144, ALT: 143-190, HDL: 1.08, LDL: 3.7, FFA, CK-MB, TnT, NT-proBNP: n/a |
|      |      |      |      |      | Glucose: 2.8-3.9 Insulin: n/a Ketones: 0.2-1.4 TC: 4.5 TG: 1.1 CK: 244-511 Other: AST: 61-82, ALT: 48-78, HDL: 1.16, LDL: 2.8, FFA, CK-MB, TnT, NT-proBNP: n/a |
|      |      |      |      |      | BEFORE Liver ultrasound: hepatomegaly, fatty liver Cardiac US: IVS thickness: 11 ECG: normal AFTER Liver ultrasound: hepatomegaly, no fatty liver Cardiac US: IVS thickness 11 ECG: normal |
|      |      |      |      |      | BEFORE Liver US: hepatomegaly, fatty liver Cardiac US: IVS thickness: 17, LVW thickness: 12, EF:27% ECG: n/a AFTER Liver US: hepatomegaly, fatty liver Cardiac US: IVS thickness: normal ECG: n/a |
|      |      |      |      |      | BEFORE Liver US: hepatomegaly, fatty liver Cardiac US: IVS thickness: 17, LVW thickness: 12, EF:27% ECG: n/a AFTER Liver US: hepatomegaly, fatty liver Cardiac US: IVS thickness: normal ECG: n/a |
|      |      |      |      |      | BEFORE Liver US: hepatomegaly, fatty liver Cardiac US: IVS thickness: 17, LVW thickness: 12, EF:27% ECG: n/a AFTER Liver US: hepatomegaly, fatty liver Cardiac US: IVS thickness: normal ECG: n/a |

**BEFORE**

- Weight: 66 (0.7 SD)
- Height: 171 (1.2 SD)
- BMI: 22.6 (0.2 SD)

**AFTER**

- Weight: 66 (0.7 SD)
- Height: 171 (1.2 SD)
- BMI: 22.6 (0.2 SD)
- Muscle strength: n/a
### Dietary lipids in GSDIII

| Patient | Age | Sex | Mutation | Exercise Intolerance | Fatigue | Cardiomyopathy | Dietary Lipids | Weight | Height | BMI | Changes |
|---------|-----|-----|----------|----------------------|---------|----------------|---------------|--------|--------|-----|---------|
| 23      | 7 F Ilia | AGL c.3444T>A/4347-1G>T | Cardiomyopathy | High fat diet | Glucose 3.4-6.2 | Insulin n/a | Ketones (plasma) n/a | 1550 Kcal/day, 18% carbohydrates, 54% lipids, 28% proteins | UCCS withdrawn. | 1800 Kcal/day, 16% carbohydrates, 60% lipids, 23% proteins | Glucose 4-6.2 | Insulin n/a | Ketones (plasma) n/a | Cardiomyopathy, severe fatty liver, pericolecistic areas of hypechoegenicity. | Liver US: hepatomegaly (LD:110), fatty liver. | BEFORE Liver US: hepatomegaly (LD:150), fatty liver. | AFTER Liver US: hepatomegaly, moderate fatty liver, no focal areas of hypechoegenicity. | BEFORE Liver US: hepatomegaly, LD:110, fatty liver. | AFTER Liver US: hepatomegaly, LD:150, fatty liver. |
| 24      | 41 M Ilia | AGL c.2919_2920insTT GG / c.2936delG | Fatigue | High fat diet | Glucose 3.9-5.6 | Insulin n/a | Ketones n/a | 1800 Kcal/day, 16% carbohydrates, 60% lipids, 23% proteins | Lost to follow-up | Cardiomyopathy | Glucose 4-5.4 | Insulin n/a | Ketones n/a | Cardiomyopathy, exercise intolerance | Cardiomyopathy, severe fatty liver, pericolecistic areas of hypechoegenicity. | BEFORE Liver US: hepatomegaly, severe fatty liver, pericolecistic areas of hypechoegenicity. | AFTER Liver US: hepatomegaly, severe fatty liver, pericolecistic areas of hypechoegenicity. | BEFORE Liver US: hepatomegaly, severe fatty liver, pericolecistic areas of hypechoegenicity. | AFTER Liver US: hepatomegaly, severe fatty liver, pericolecistic areas of hypechoegenicity. |

**Liver US**

BEFORE

- Hepatomegaly (LD:150), fatty liver.
- Cardiomyopathy: mild ventricular hypertrophy; IVS thickness: 9, LVW thickness: 7
- ECG: biventricular hypertrophy

AFTER

- Hepatomegaly (LD:150), fatty liver.
- Cardiomyopathy: no ventricular hypertrophy; IVS thickness: 6.2, LVW thickness: 6.2
- ECG: mild ventricular hypertrophy

**Cardiac US**

BEFORE

- Mild ventricular hypertrophy

AFTER

- No ventricular hypertrophy

**ECG**

BEFORE

- Biventricular hypertrophy

AFTER

- Normal sinus rhythm

**BMI**

BEFORE

- 1.3 SD

AFTER

- 1.9 SD

**Subjective Changes**

BEFORE

- Pubertal delay

AFTER

- Mild improvement on physical activity.
| Chapter 4 |
|-----------|
| 25        |
| 1         |
| F         |
| III       |
| AGL, c.3911dupA (p.Asn1304Lysfs*) |
| Severe hypotonia, Delayed motor skills Developmental delay |
| High fat diet UCCS withdrawn 1600 Kcal/day, 14-25% carbohydrates, 40-50% lipids, 23-30% proteins |
| 60        |
| Glucose: 2.4-4.3 |
| Insulin: n/a |
| Ketones (plasma): n/a |
| TG: 5.1-5.9 |
| TG: 3.5-5.2 |
| CK: 63-72 |
| Other: AST: 222-534, ALT: 246-498, HDL: LDL, FFA, CK-MB, TnT, NT-proBNP: n/a |
| Glucose: 3.5 |
| Insulin: n/a |
| Ketones (plasma): n/a |
| TG: 5.9-7.5 |
| TG: 4.5-8.1 |
| CK: 86-91 |
| Other: AST: 237-2818, ALT: 334-1030, HDL: LDL, FFA, CK-MB, TnT, NT-proBNP: n/a |
| ECG: Left ventricular hypertrophy |
| BEFORE |
| Liver US: hepatomegaly, moderate-severe fatty liver |
| Cardiac US: normal |
| ECG: normal. |
| BEFORE |
| Weight: n/a (-0.7 SD) |
| Height: n/a (-2.1 SD) |
| BMI: n/a |
| AFTER |
| Weight: n/a (-0.7 SD) |
| Height: n/a (-2.1 SD) |
| BMI: n/a |
| Mild improvement on physical activity. The family was not able to increase lipids over 50%. |

| 26        |
| 4         |
| M         |
| III       |
| AGL, c.2590C>T (p.Arg864Ter*) |
| Poor metabolic control |
| High fat diet UCCS withdrawn 1300 Kcal/day, 18-20% carbohydrates, 55-60% lipids, 25-28% proteins |
| 36 Poor complianc e Lost to follow-up |
| Glucose: 2.6-4.7 |
| Insulin: 2.9-7.9 |
| Ketones: n/a |
| TG: 0.3-7.7 |
| TG: 5.4-9.3 |
| CK: 85-171 |
| Other: AST: 469-1020, ALT: 366-475, HDL: 0.6, LDL: n/a, FFA, CK-MB, TnT, NT-proBNP: n/a |
| Glucose: 3.2-3.8 |
| Insulin: n/a |
| Ketones: n/a |
| TG: 5.8-6.9 |
| TG: 4.5-9 |
| CK: 133 |
| Other: AST: 439-1446, ALT: 426-766, HDL: 0.5-0.7, LDL: 3.5, FFA, CK-MB, TnT, NT-proBNP: n/a |
| ECG: normal. |
| BEFORE |
| Liver US: severe hepatomegaly, fatty liver |
| Cardiac US: normal |
| ECG: normal. |
| AFTER |
| Weight: 14.7 (0.3 SD) |
| Height: 84 (-3 SD) |
| BMI: 20.8 (3 SD) |
| AFTER |
| Weight: 19.5 (-1.6 SD) |
| Height: 108.5 (-3 SD) |
| BMI: 16.6 (0.5 SD) |
| Muscle strength: n/a |

| 27        |
| 36        |
| F         |
| IIIa      |
| AGL, c.2681+1G>T |
| Muscle weakness Exercise intolerance |
| High fat diet 1300-1500 Kcal/day, 34% (110-137 g/day) carbohydrates, 36-37% (52-62 g/day) lipids, 29-30% (95-108 g/day) proteins |
| 60 Poor complianc e |
| Glucose: 3.7-6.2 |
| Insulin: 2.9-7.9 |
| Ketones: n/a |
| TG: 2.6-5.1 |
| TG: 1.2-1.7 |
| CK: 792-2616 |
| Other: AST: 65-114, ALT: 42-71, HDL: 1.1-1.5, LDL: 2.6-3.1, FFA, CK-MB, TnT, NT-proBNP: n/a |
| Glucose: 3.9-6.4 |
| Insulin: 2.9-7.9 |
| Ketones: n/a |
| TG: 4-5.3 |
| TG: 1.3-1.7 |
| CK: 587-1400 |
| Other: AST: 54-112, ALT: 31-67, HDL: 1-1.4, LDL: 2.5-3.8, FFA, CK-MB, TnT, NT-proBNP: n/a |
| ECG: normal. |
| BEFORE |
| Liver US: hepatomegaly, fatty liver, cirrhosis |
| Cardiac US: normal |
| ECG: n/a |
| AFTER |
| Weight: 66.7 (0.7 SD) |
| Height: 166 (0.4 SD) |
| BMI: 24.2 (0.6 SD) |
| AFTER |
| Weight: 73 (1.2 SD) |
| Height: 166 (0.4 SD) |
| BMI: 26.5 (1 SD) |
| Muscle strength: n/a |
| Refused to further increase lipid intake |
### Dietary lipids in GSDIII

|   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|
| 28 | 1 | F | IIIa | Cardiomyopathy | High fat diet | Never taken UCCS | 710 Kcal/day, 11% carbohydrates, 70% lipids, 19% proteins | 12 | Lost to follow-up | Glucose: 2.3-5.4 | Insulin: 0.3-6.6 | Ketones: n/a | TC: 4.2 | TG: 3.9 | CK: 430 |
|   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |

**BEFORE**

Liver US: hepatomegaly, fatty liver
Cardiac US: obstructive hypertrophy; IVS thickness: 4.5, LVW thickness: 4.2
ECG: n/a

**AFTER**

Liver US: hepatomegaly, fatty liver
Cardiac US: reduced hypertrophy (no more obstructive); IVS thickness: 4.2, LVW thickness: 4.4
ECG: n/a

**Supplementary File S3.** Table unpublished cases.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BHB: beta-hydroxybutyrate, CK: creatine kinase, CK-MB: creatine kinase isoenzyme MB, ECG: electrocardiogram, FFA: free fatty acids, HDL: High-density lipoprotein, IVS: interventricular septum, LCT: long-chain triglycerides, LD: liver longitudinal diameter, LDL: Low-density lipoprotein, LVW: left ventricular wall, Mb: myoglobin, MCT: medium-chain triglycerides, MRI: magnetic resonance imaging, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, UCCS: uncooked corn starch, TC: total cholesterol, TG: triglycerides, TnT: Troponin T, US: ultrasound, ω-3FA: omega-3 fatty acids.
Chapter 4

Supplementary file S4
|     | Δ Glucose (%) | Δ Insulin (%) | Δ Ketones (%) | Δ Total Cholesterol (%) | Δ Triglycerides (%) | Δ AST (%) | Δ ALT (%) | Δ CK (%) |
|-----|---------------|---------------|---------------|-------------------------|---------------------|-----------|-----------|----------|
| P1  | -             | -             | +            | -                       | -                   | -         | -         | -        |
| P2  | -             | -             | +            | -                       | -                   | -         | -         | -        |
| P3  | -             | -             | -            | -                       | -                   | -         | -         | -43      |
| P4  | +6            | -             | -            | +24                     | -1                  | -21       | -6        | -88      |
| P5  | +7            | -             | -            | -9                      | +30                 | -71       | -37       | -51      |
| P8  | -             | -             | +2800        | -                       | +39                 | -         | -         | -77      |
| P9  | -             | -             | +6000        | -                       | -                   | -         | -         | -27      |
| P10 | -             | -             | -            | -                       | -                   | -         | -         | -        |
| P11 | -             | -             | -            | -                       | -                   | -         | -         | -        |
| P12 | -16           | -55           | +1000        | 0                       | 0                   | 0         | 0         | -43      |
| P13 | -             | -             | -            | 0#                      | 0                   | -         | -         | -        |
| P14 | -             | -             | -            | -                       | -                   | -         | -         | -        |
| P15*| +28           | -             | +463         | +33                     | +26                 | -25       | -22       | -33      |
| P16*| +24           | -             | +2600        | -12                     | -18                 | -53       | -34       | -41      |
| P17 | +7            | -             | +250         | -5                      | -20                 | +13       | 10        | -38      |
| P18 | -16           | -35           | +450         | +9                      | +41                 | +0        | +8        | -65      |
| P19 | -4            | -             | +29          | -11                     | +179                | +61       | -20       |         |
| P20*| -2            | 0             | -            | -3                      | +4                  | -         | -         | -65      |
| P21*| -6            | -32           | -            | +7                      | -42                 | -60       | -68       | -66      |
| P22 | +12           | -             | -17          | 0                       | -44                 | -63       | -73       |         |
| P23 | +9            | -             | +9           | +22                     | +15                 | +39       | -31       |         |
| P24 | 0             | -             | +9           | +93                     | -19                 | -19       | -22       |         |
| P25 | +21           | -             | +22          | +42                     | +304                | +83       | +32*      |         |
| P26 | +2            | -             | +915         | -10                     | +27                 | +42       | 0*        |         |
| P27 | +4            | 0             | +31          | 0                       | -7                  | -13       | -36       |         |
| P28 | +23           | +580          | -            | +12                     | +85                 | -9        | +10       | -45      |
| Stable (%) | 59 | 33 | 50 | 37 | 29 | 31 | 5 |
| Increased (%) | 29 | 17 | 100 | 39 | 42 | 29 | 31 | 5 |
| Decreased (%) | 12 | 50 | 0 | 11 | 21 | 41 | 38 | 90 |

**Supplemental file S4**, Individual percentual changes in laboratory parameters of metabolic control for all GSDIII patients.  
* High fat diet + MCT supplementation, # increased after MCT supplementation,* within the reference range, + increased, no raw data available, ^ decreased, no raw data available.
Recommendations for clinical follow-up of dietary lipid manipulations in patients with glycogen storage diseases type III.

Based on: ‘Dietary lipids in glycogen storage disease type III: a systematic literature study, case studies and future recommendations.’

Introduction

Prospectively designed dietary intervention studies are strongly needed to strengthen our knowledge on dietary management in hepatic GSD. With this recommendations document we aim to provide guidance to clinicians and researchers in the field of metabolic disease who intend to study a dietary lipid manipulation, either in clinical management or in the setting of a clinical trial.

Target audience

The present recommendation document is addressed to all health care professionals (physicians and dieticians) who take care of hepatic GSD patients.

Disclaimer

Recommendations are derived from retrospective data collection. Recommendations only refer to dietary lipid manipulations in GSD type IIIa. However, general principles provided here could help arranging a dietary lipid manipulation in all hepatic GSD.

To date, recommendations on dietary management from international management guidelines are still the key in management in hepatic GSD patients.

Index

A – General study recommendations
B – Recommendation sheet lipid manipulation in GSDIIIa patients
A- General study recommendations

I. Patient selection

1) Reasons to start dietary lipid manipulation
Development of cardiomyopathy and/or muscle weakness despite optimal dietary regimen.

2) Rationale to start dietary lipid manipulation
Reverse/improve cardiomyopathy and/or myopathy

3) Check contra-indications
-Liver and/or kidney dysfunction
-Osteoporosis
-Current pregnancy, or breastfeeding
-Diabetes mellitus (excluding isolated insulin-resistance)

II. Dietary intervention

- Interventions should be standardized. The amount of fat should be uniform (e.g. high-fat diet, ketogenic diet) as well as the type of fat administered (e.g. high-fat only, high-fat + MCT) and duration of the supplementation.
- Three-day food diaries are recommended to study dietary compliance and analyze exact distributions of macronutrients.
- Amount and duration herein suggested are based on the results of the present study (median value among patients showing beneficial effect)

1 Guidelines recommend a minimal protein intake of 3 grams per kilogram bodyweight in pediatric GSDIIIa patients.
III. Outcome measures

Outcome measures should be uniform and blood samples should be taken under similar conditions (i.e. specific number of hours after meal and/or specific time during the day). Standard outcome markers should be assessed to make future studies comparable. Taking into account the results of the present study, specific markers are suggested on the next pages.

Improvement should be defined if:

- [CK] decreased by 10% (or more) or normalized
- IVSd Z-scores decreased or normalized

IV. Recommendations on safety

In compliance with Good Clinical Practice (GCP) all adverse events should carefully be assessed and documented.

Possible adverse events:

- Hypoglycemia
- Gastrointestinal symptoms
B- Lipid manipulation in GSDIIIa patients

Dietary intervention: high fat diet

Amount: lipids 60% of daily E-% (children 6 g/kg/day, adults 1.7 g/kg/day)

Minimal duration of intervention: 24 months [range: 3 – 60]

Outcome measures:

Clinical markers: height SDS, weight SDS, BMI, clinical picture (e.g. fatigue, exercise intolerance, dyspnea, muscle strength), comorbidities, QoL questionnaire, International physical activity questionnaire.

Biochemical markers:

- Blood glucose homeostasis: home site continuous glucose monitoring. Number of hypoglycemia (n), mean [range] glucose concentration, percentage of the day [glucose] < 4.0 mmol/L, percentage of the day [glucose] > 8.0 mmol/L. Mean morning ketone concentrations (mmol/L) as assessed with handheld device.

- Blood markers: beta-hydroxybutyrate, acetoacetate, triglycerides, total cholesterol, HDL, LDL, FFA, insulin, AST, ALT, CK, CK-MB, NT-proBNP, TnT, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, calcitonin, osteocalcin, vitamin D, prealbumin, creatinine, estimated glomerular filtration rate, vitamins*, minerals*

- urine: proteinuria, microalbuminuria

- Metabolic investigations: plasma acylcarnitines, plasma biotinidase, urine organic acids, urine glucose tetrasaccharide

Imaging markers: liver ultrasound (liver size in cm, liver longitudinal diameter), cardiac ultrasound (IVS thickness, SF, outflow obstruction, diastolic function parameters, left ventricular mass), muscle ultrasound, bone mineral density (DXA), liver/heart/muscle MRI*

Muscle markers: six-minute walking test, muscle ultrasound (muscle density for all muscle groups), dynamometry (strength Z-scores according to references) *

Dietary markers: diet composition (total Kcal/day, E-% and exact amount (g/kg/day) for each macronutrient. Dietary compliance; three-day food diary.

Frequency of follow-up:

Check clinical, blood, and dietary markers monthly for the first 3 months. According to individual outcomes frequency of follow-up can be expanded to every 6 months. Specific metabolic investigations, muscle markers and imaging measures should be at least assessed at the beginning and at the end of the intervention.

* consider

Supplementary File S5. Recommendations for clinical follow-up of dietary lipid manipulations in patients with glycogen storage diseases type III.
