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# Modified Atkins ketogenic diet improves heart and skeletal muscle function in glycogen storage disease type III

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**Glycogen storage disease type III (GSDIII) management in adult patients includes a high-protein diet with cornstarch supplementation to maintain a normal level of glucose in the blood. This regimen can prevent hypoglycaemia but does not seem to improve skeletal muscle and heart function. A 34 years-old patient with GSD IIIa with hypertrophic cardiomyopathy was then treated with a modified Atkins ketogenic diet. After 12 months of treatment ejection fraction raised from 30 to 45%, liver enzymes were reduced and CK plasma level dropped from 568 to 327 U/l. Physical activity increased from about 1300 to 2800 steps per day and health-related quality of life assessment ameliorated. An increase in uric acid triglycerides plasma level was observed. This data obtained in an adult patient confirm previous reports evidencing the effectiveness of ketogenic diets in improving cardiac and muscular manifestations in children with GSDIII.**

**Key words:** glycogen storage disease type III, ketogenic diet, hypertrophic cardiomyopathy

## Introduction

Glycogen storage disease type III (GSD-III), also known as Cori's disease, is a rare, autosomal recessive disorder of metabolism due to the deficiency of glycogen debranching enzyme. GSD types IIIa and IIIc mainly affect the liver and muscles, while GSD types IIIb and IIId typically affect only the liver (1, 2). The abnormal accumulation of limit dextrin results in frequent hypoglycaemia and both striated muscle and liver symptoms. In childhood, the phenotype is mainly characterized by hepatomegaly, short stature, hypoglycaemia and minimal skeletal muscle involvement that can worsen in adulthood. Heart involvement is rare in GSD3 children but in adult patients hypertrophic cardiomyopathy may happens.

Currently, the only treatment to limit glycogen storage is the diet. High-carbohydrate diet prevent fasting hypoglycemia but increases glycogen storage and does not slow the progression of cardiac and muscular manifestations. Ketogenic diets (KDs) are high-fat diets with an important carbohydrate reduction. Classic KDs are typically composed of a 4:1 or 3:1 ratio of fat (in grams) to protein plus carbohydrates (in grams). To improve compliance, other types of KDs have been proposed. Modified Atkins diet (MAD) is a high-fat and high-protein diet providing up to 20 g carbohydrate per day which is roughly equivalent to a ratio of 1-2:1 of fat to protein plus carbohydrates and does not require weighing of food portions (3). In this paper we report a case of a adult patient with GSD-IIIa treated with MAD.

## Patient and methods

We observed a 34-year-old patients who was diagnosed GSD IIIa at the age of 9 months. He showed motor retardation, myopathy and hepatomegaly and then high-carbohydrate diet supplemented with uncooked cornstarch over night was started. At the age of 15 he was diagnosed with liver cirrhosis. Muscle involvement worsened with age causing distal weakness and exercise intolerance. Atthe age of 25 years hypertrophic cardiomyopathy was find and a high-protein diet providing 2.5 g protein/kg/d was initiated. At presentation to our outpatient clinic, cardiac function and general clinical picture had worsened despite the dietary treatment. Cardiac ultrasound showed increased left ventricle size, increase of parietal and septum thickness with diffuse hypokinesia. Ejection fraction was 30% and the patient had underwent diuretic therapy with furosemide, 300 mg/d, metolazone, 5 mg/d and spironolactone, 100 mg/d. Given the

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lack of efficacy of previous dietary approaches, a MAD with carbohydrates limited to 20 g per day was started. Food rich in fat and in protein like meat, fish, eggs, nuts were allowed ad libitum. Olive oil and medium chain triglycerides (MCTs) were recommended as seasoning fats. Vitamins and minerals were supplemented according to dietary recommendations. Uncooked cornstarch was prescribed only in case of hypoglycaemia.

Clinical and biological assessments took place before the start of the diet and every three months including: body weight, fasting plasma level of glucose, lactate, urea, beta2-microglobulin, creatinine, creatine kinase (CK), CK-muscle/brain (MB) mass and CK activity, uric acid, folates, vitamin B12, 25 OH-vitamin D, parathyroid hormone (PTH), N-terminal pro b-type natriuretic peptide (NTproBNP), plasma lipid profile, liver enzymes, echocardiography and liver ultrasonography. Urinary ketones were measured once daily by semi-quantitative test strips. To assess the amount of physical activity the daily step count was evaluated using a pedometer (Garmin Vivofit 3).

We assessed the patient's health-related quality of life (HRQoL) through the Italian version of the Short Form Health Survey (SF-36) questionnaire (4). The SF-36 contains eight domains;four domains assess the physical component (PC) of HRQoL (physical functioning, physical role, body pain, and general health) and four domains assess the mental component (MC) of HRQoL (vitality, social functioning, emotional role, and mental health). A score of 50 is regarded as the normal. For individual results, T-scores < 45 indicate impaired functioning in the domain.

## Results

After 12 month of treatment MAD was well tolerated and the patient did not experience symptomatic hypoglycemia. Uncooked cornstarch or slow-release carbohydrates were never used during MAD. Semi-quantitative test strips showed high levels of KB in urines throughout the diet period. Body weight decreased from 67 to 64 kg. Echocardiography examination evidenced an increase of EF from 30 to 45%.CK plasma level dropped from 568 to 327 U/l, with a reduction both of CK-MB mass and CK-MB activity. NT-proBNP fell from 3010 to 2570 pg/ml. Furosemide was reduced from 300 mg/d to 75 mg/dand metolazone was suspended. Urea and beta-2 microglobulin decrease to almost normalize. Glomerular filtration, calculate according CKD-EPI creatinine equation (5) rise from 78 to 123 ml/min. Liver enzymes improved while C-LDL and triglycerides slightly increased (Table 1). Uric acid plasma level raised from 5.5 to 9.7 mg/dl and for this reason treatment with allopurinol 100 mg/d was started. Liver size did not change during the study.

**Table 1.** Biochemical and clinical patient data before and after 12 months of MAD treatment.

| | T0 | 12 months |
|---|---|---|
| Weight (kg) | 67 | 64 |
| Plasma glucose g/dl | 82 | 59 |
| C-LDL g/dl | 129 | 154 |
| C-HDL g/dl | 30 | 35 |
| TG g/dl | 111 | 134 |
| Plasma uric acid g/dl | 5.5 | 9.7 |
| CK U/l | 508 | 327 |
| CK mass U/l | 10.4 | 7.2 |
| CK activity U/l | 27 | 19 |
| NT-proBNP pg/ml | 3010 | 2570 |
| AST U/l | 122 | 87 |
| ALT U/l | 111 | 85 |
| GGT U/l | 133 | 38 |
| LDH U/l | 745 | 518 |
| ALP U/l | 234 | 129 |
| PTH pg/ml | 107 | 111 |
| Plasma creatinine g/dl | 1.2 | 0.7 |
| Plasma urea g/dl | 47 | 22 |
| GFR ml/min/$m^2$ | 78 | 123 |
| EF % | 30 | 45 |
| Steps /24h | 1300 | 2800 |
| Hr-QoL Physical component | 42/100 | 58/100 |
| Hr-QoL Mental component | 48/100 | 52/100 |

Vitamin B12, 25 OH-vitamin D, parathyroid hormone (PTH) did not show notable variations.

Daily step count a increased from about 1300 daily steps before MAD to 2800 daily steps after 12 months of treatment. Before MAD HRQoL assessment showed a SF-36 PC subscore of 42/100 and a MC subscore of 48/100. After 12 months of MAD PS and MC subscores reached 58/100 and 52/100, respectively. The results are summarized in Table 2.

## Discussion

In our patient MAD was able to induce and maintain ketosis without symptomatic hypoglycemia despite the very low intake of carbohydrates, probably due to gluconeogenesis from aminoacids and to higher plasma KBs availability. MAD significantly improved the clinical picture. The increase of FE and the reduction of heart failure laboratory tests evidenced the amelioration of cardiac function.

Renal function, which before MAD was impaired probably due to cardiomyopathy, improved and diuretics were reduced. The physical activity level assessed using the daily step count more than doubled compared

**Table 2.** Outcome data from case reports on KD in GSDIII for: author, patient number, age, length of follow-up, heart function and liver function effect, side effects.

| Study | No. patients/age | Diet | Follow-up | Heart function | Liver function | Side effects |
|---|---|---|---|---|---|---|
| Valayannopoulos V [6] (2011) | 1 (2 mo) | 2:1 KD plus 3OHB | 24 months | Improved | Stable | None |
| Brambilla A [5] (2014) | 2 (5,7 y) | High-fat high-protein low-CHO | 12 months | Improved | Improved | None |
| Mayorandan S [18] (2014) | 2 (9,11 y) | MAD | 32-26 months | Improved | Not reported | Transient asymptomatic hypoglycemia |
| Francini F | 1 (34 y) | MAD | 12 months | Improved | Improved | Increase of uric acid plasma level and C-LDL |

to the levelmeasured before MADand the quality of life improved above all in the physical component. The rise in uric acid plasma level was the main metabolic adverse effect observed during the MAD period and it required a pharmacological therapy.. Lipid profile showed a little rise of triglycerides and C-LDL with a reduction of C-HDL/ C-LDL ratio. Worsening of cardiovascular risk is one of the main concern about the long-term treatment with KDs because of their high fat content. However, the studies employing long-term KDs demonstrated their relatively safety, the most common adverse effects including gastrointestinal disturbances, hyperlipidemia and hyperuricemia (6). Alterations of lipid profile does not necessarily lead to an increased cardiovascular risk because the low-carbohydrate diets cause an enlargement of LDL size and a reduction of more atherogenic small-LDL (7). Moreover, our patient was recommended to take olive oil and MCTs as seasoning fats as the former reduce cardiovascular risk, and the latter have not atherogenic effect and promote KDs synthesis (8). KD reduced transaminases plasma level and stabilized the liver size, likely due to a lesser limit-dextrin accumulation in hepatocytes.

This is the first case of adult GSDIIIa patient treated with KD. Previously, Dagli et al. (9) described a 22-year-old patient in whom a diet providing 30% of energy as protein with a low cornstarch supplementation (1.36 g/kg/d) improved cardiac function and normalized ventricular mass index. However, authors failed to report the exact amount of fat and CHO in the diet and the ketosis status was not evaluated.Valayannopoulos et al. (10) treated a 2-month-old infant with GSD III complicated by cardiomyopathy with a 2:1 KD supplemented with 3OHB up to 800 mg/kg/d. After 24 months the onset of this treatment, cardiomyopathy improved and motor development and somatic growth were normal. Brambilla et al. (11) reported a case of two siblings, 7- and 5- year-old, affected with GSD IIIa who developed a severe cardiomyopathy. They were first treated with frequent diurnal and nocturnal hyperproteic meals followed by uncooked cornstarch supplementation. Because a rapid worsening of cardiomyopathy a MAD-like diet (fat 60, 25%, carbohydrate 15%) was started at age seven for the girl and five for the boy. After 12 months exertion dyspnea improved, CK and NT-proBNP reduced and echocardiograms showed a marked improvement of cardiomyopathy.

Mayorandan et al. (12) treated two 9 and 11-year-old boys with GSD IIIa with a MAD (10 g carbohydrate per day, protein and fatty acids ad libitum) over a period of 32 and 26 months, respectively. At the end of observation CK plasma levels dropped and cardiac function markedly improved in the patient with severe cardiomyopathy. LDL-cholesterol levels were in the normal range and triglycerides slightly increased in one patient.

Increase of KBs plasma level during KDs could partly explain their efficacy in cardiomyopathy. Plasma KBs level raises in patients with severe heart congestive failure and the role of KBs as an alternative fuel in the failing human heart has recently been shown (13).

In conclusion, MAD showed a good efficacy in GSDIIIa treatment, improving physical activity, quality of life and overall cardiomyopathy, unlike the classic dietary approach. A part the low carbohydrates provision, the cases reporting a treatment with KDs in GSDIII differ with respect to the remaining dietary macronutrient. In our opinion, MAD has advantages over other diets because does not require calculating and weighing of protein and fat foods. Further studies are needed in order to investigate the long-term efficacy and safety of these diets.

## Conflict of interest

The Authors declare to have no conflict of interest.

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