ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Dietary Fiber Supplementation in Type I Glycogen Storage Disease; Could it Contribute to a Better Metabolic Control?

Tip I Glikojen Depo Hastalığında Diyet Lifi Takviyesi; Daha İyi Bir Metabolik Kontrole Katkıda Bulunabilir Mi?

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Abstract

Introduction: Glycogen storage disease type I (GSD I) is one of rare inborn error of metabolic disorder inherited with autosomal recessively. It has a key role both in glycogenolysis and gluconeogenesis. Infants exhibit hypoglycemic episodes, developmental delay, growth retardation, hepatomegaly accompanying with increased blood concentrations of lactic acid, triglycerides, cholesterol, and uric acid. The major treatment is frequent feeding containing slow release carbohydrate supplementation. In this study we aimed to investigate the effects of adequate fiber supplementation to metabolic controls of patients with GSD I.

Materials and Methods: Patients followed up in our clinic with GSD I were enrolled to the study. Fiber amounts to be supplemented for each induvidual were calculated according to 3 day diet dairy and daily recommended amounts. Patients were subjected to 6 day continuous glucose monitorization and their biochemical metabolic parameters were reqruited before and at the end of 6 week fiber supplementation.

Results: Mean, lowest and highest glucose values insignificantly decreased, however HbA1c levels significantly increased. Lactate, cholesterol, LDL, AST, and uric acid mean values also decreased, however the differences were not statistically significant. In addition, decreased mean levels of triglyceride, GGT were statistically significant.

Conclusion: The results of this study suggest the improvment of glucose homeostasis and biochemical parameters which encourage for the use of adequate fiber supplementation in terms of contributing metabolic control in GSD I patients. However, randomized, double blinded controlled prospective long-term trials with expanded number of patients are required to investigate the effects of fiber supplementation perspectively.

Keywords
Dietary fiber, glycogen storage disease, hyperlactatemia, hyperlipidemia, hypoglycemia

Öz

Giriş: Glikojen depo hastalığı tip I (GSD I), otozomal resesif geçişli metabolik bozukluğun nadir doğuştan gelen hatalarından biridir.Hem glikojenoliz hem de glukoneogenezde anahtar role sahiptir. Bebeklerde hipoglisemik ataklar, gelişimsel gecikme, büyüme geriliği, hepatomegali ile birlikte laktik asit, trigliseritler, kolesterol ve ürik asit konsantrasyonlarının artması görülür. Ana tedavi, yavaş salınımlı karbonhidrat takviyesi içeren sık beslenmedir. Bu çalışmada, GSD I'li hastaların metabolik kontrollerine yeterli lif desteğinin etkilerini araştırmayı amaçladık.

Anahtar kelimeler
Diyet lifi, glikojen depo hastalığı, hiperlaktatemi, hiperlipidemi, hipoglisemi

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Gereç ve Yöntem: Kliniğimizde GSD I ile takip edilen hastalar çalışmaya alındı. Her bir endüstri için takviye edilecek lif miktarları 3 günlük diyet, süt ve günlük önerilen miktarlara göre hesaplanmıştır. Hastalar 6 günlük sürekli glukoz monitörizasyonuna tabi tutuldu ve 6 haftalık lif takviyesi öncesi ve sonunda biyokimyasal metabolik parametreleri sorgulandı.
Bulgular: Ortalama, en düşük ve en yüksek glukoz değerleri önemsiz ölçüde azalmış, ancak HbA1c düzeyleri anlamlı olarak artmıştır. Laktat, kolesterol, LDL, AST ve ürik asit ortalama değerleri de azaldı, ancak farklılıklar istatistiksel olarak anlamlı değildi. Ek olarak, ortalama trigliserit düzeylerinde azalma, GGT istatistiksel olarak anlamlı bulundu.
Sonuç: Bu çalışmanın sonuçları, GSD I hastalarında metabolik kontrole katkıda bulunmak açısından yeterli lif takviyesinin kullanımını teşvik eden glukoz homeostazı ve biyokimyasal parametrelerin iyileştirildiğini göstermektedir. Bununla birlikte, lif takviyesinin etkilerini perspektif olarak araştırmak için randomize, çift kör kontrollü prospektif uzun süreli çalışmaların artan sayıda hasta ile yapılması gerekmektedir.

Introduction

Glycogen storage disease type I (GSD I) is one of rare inborn errors of metabolic disorder inherited with autosomal recessively occurring with an incidence of approximately 1/100,000. GSD Ia is caused by deficiency of glucose-6-phosphatase and GSD Ib by deficiency of the endoplasmic reticulum trans-membrane glucose-6- phosphate transport protein, G-6-P translocase. Since glucose-6-phosphatase involves in the last step of both glycogenolysis and gluconeogenesis, low activity leads to deficient endogenous glucose production. Severe hypoglycemia may occur within 3-4 h of a meal. Infants exhibit hypoglycemic episodes, developmental delay, hepatomegaly, and growth retardation. Glucose-6-phosphate concentrations increase from glycogenolysis, and its accumulation leads to increase concentrations of lactic acid, triglycerides, cholesterol, and uric acid due to shunting into alternative pathways (1).

Essential management method of GSD I is dietary that includes consists of regular feeding, rather containing slowly release carbohydrates such as uncooked cornstarch at frequent intervals, and restriction of simple carbohydrates such as fructose, sucrose, and lactose intake (2). Treatment efficacy is monitored by following growth and biochemical parameters, in addition to abdominal ultrasound for assessment of liver volume and nodules. Strict dietary consistency decreases the risk of long-term complications including short stature, osteoporosis or osteopenia, renal disorders, hepatocellular adenomas, pancreatitis associated with hypertriglyceridemia. However, starch supplementation has some limitations. Some patients require large amounts of uncooked cornstarch, and this may result in high carbohydrate intake within a target >65% and limiting of protein and fat intake. Starch supplementation also leads to more energy intake and risk of obesity and type II diabetes, or it may cause appetite loss and less energy intake which may result in micronutrient deficiencies. In addition, patients with GSD Ib may have malabsorption and poor weight gain due to inflammatory bowel disease (3).

Dietary fiber is a complex carbohydrate resistant to digestion in the small intestine and requires microbial fermentation in the large intestine (4). It has been consumed for centuries for its beneficial health effects. Guar gum is a water-soluble polysaccharide mainly consists of galactomannan. It has been used in food processing as a thickener and emulsion stabilizer. Because guar gum is extremely viscous, it is partially hydrolyzed to obtain a physiological effect. Partially hydrolyzed guar gum (PHGG) is completely water soluble, invisible in solution, taste-free and known as a prebiotic fiber. PHGG reduces blood cholesterol and stabilizes blood sugar levels (5).

The primary target in management of GSD I is to maintain normal blood glucose levels. However, uncooked cornstarch may be sometimes disappointing and has some side effects. Therefore, we hypothesized that because the ingestion of high amount of cornstarch, dietary fiber intake of patients with GSD I was inadequate, and consumption of adequate dietary fiber could contribute to improve metabolic control as maintaining normal blood glucose and reducing triglyceride and cholesterol levels. In this study we aimed to evaluate the effects of fiber as PHGG on glucose homeostasis, and blood concentrations of lipid, lactate, uric acid and transaminases.

Materials and Methods

This study was an open label, prospective study conducted on children with GSD I followed up in our outpatient clinic. The study was approved by the Gazi University Faculty of Medicine Ethics Committee (approval no: 2021.03.252, decided: 08 March 2021). Written informed consent was obtained from the patients and their parents/legal guardians/next of kin to participate in the study. Inclusion criteria were presence of GSD Ia/b, absence of additional disease, ages between 2-18 years, on dietary treatment for minimum of one year, willingness of wearing a medical device for six days and consistence of consumption of fiber supplementation regularly.

Three-day diet diary data was collected from patients. They were then analyzed for fiber composition using BeBis 8.2 Version (6). Mean daily fiber intakes were calculated. Recommended daily fiber intake values by age were determined according to American Academy of Pediatrics and amounts to be supplemented were calculated for each individual (7). Before the fiber supplementation, patients were subjected to continuous glucose monitorization (CGM) for 6 days using Medtronic enlite sensor as described in the study of Kasapkara et al. (8).

Patients' physical examinations, body weight, height measurements, body mass index (BMI) calculation and biochemical analysis were obtained before the onset of fiber supplementation. Guar gum was ingested as fiber supplementation for 6 weeks. Calculated fiber powder dispensed as to be mixed with 100 mL of water divided twice a day and consumed within 30 minutes of a meal. CGM during last six days of the study, anthropometric measurements, and biochemical analysis at the end of the study were repeated.

Statistical Analysis

Standard deviation, median, lowest, highest frequency and ratio values were used for descriptive statistics of the data. The distribution of variables was measured with Kolmogorov-Smirnov test. Wilcoxon test was used in the analysis of dependent quantitative data. SPSS 27.0 program was used in the analysis.

Results

Nine patients were involved in the study. Two patients were excluded from the study due to irregular use of dietary fiber supplementation. Seven patients completed the study. The age ranges of patients were 6-13,5 years (median age was 9 and mean was 9.6 years). Female/male ratio was 4/3. Demographic and daily feeding features of patients were shown in Tables 1 and 2 respectively. All patients were on galactose and sucrose restricted and carbohydrate rich diet supplemented with uncooked cornstarch every 3-4 hours. Daily energy intake of patients was adequate by the ages. Uncooked cornstarch addition had been adjusted consistent with their metabolic control and tolerance levels. Daily fiber intake of all patients was under recommended amounts. Two patients' weight for age z-score was >2, two patients' height for age z-score was >2. BMI z-score was determined >2 in only one patient. Patients were classified by metabolic control according to the criteria based on the European Study on GSD I (ESGSD I): blood glucose > 63 mg/dL, triglycerides <530 mg/dL, uric acid <7 mg/dL, BMI between 0 and + 2 standard deviations (SD), and lactate > 2.5 mmol/L (Table 1) (3).

All patients fully completed the CGMS without any complication. Neither local adverse events such as redness, hypersensitivity and minor subcutaneous hemorrhage nor device failure sensor dislodgement

Table 1. Demographic features of patients with GSD I

Patient no	Age (y)/sex/age at diagnosis (m)	GSD subtype	Metabolic control	Weight (kg) Z score	Height (cm)/Z score	BMI/Z score
I	7,1/F/6	Ia	Good	19/-1.3	109/-2.54	15.49/0.59
II	11,6/M/5	Ia	Good	34/2,08	123/-0.41	22/1
III	6,5/F/5	Ia	Poor	34,5/2.73	122/0.82	23.1/2.57
IV	6/M/4	Ib	Poor	21/0.09	111,5/-0.99	16.8/0,9
V	13,5/M/5	Ia	Poor	38/-1.74	134/-3.6	21.1/0.28
VI	13/F/ 7	Ia	Poor	67/1.94	168/1.66	23.7/1.21
VII	9/F/4	Ia	Poor	41/1.79	130/-0.4	24.2/1.31

were recorded. All determined hypoglycemic levels by the CGM were asymptomatic. None of the patients had any side effects of fiber supplementation such as bloating, flatus, abdominal/stomach cramping, or fecal incontinence. Nobody experienced weight or appetite loss during the study.

Basal laboratory findings and 6-day CGM results were shown in Table 3. Mean, lowest and highest glucose values insignificantly decreased, however HbA1c levels significantly increased. Lactate, cholesterol, LDL, AST, and uric acid mean values also decreased, nevertheless the differences were not statistically significant. However, the decreased mean levels of triglyceride, GGT and increased levels of HbA1C were statistically significant. Laboratory alterations before and after fiber supplementation for each individual were shown in Table 3.

Table 2. Feeding features of patients with GSD I

Patient no	Daily mean energy intake (kcal)	Daily cornstarch intake (gr/kg)	Daily mean fiber intake (gr/day)	Recommended Daily fiber intake (gr) (16)
I	1805	5,5	14	25
II	2278	5,8	21	31
III	1897	4,3	9	25
IV	1680	5,7	11	25
V	2394	3,2	16	31
VI	2345	3,1	15	26
VII	1886	3,9	16	26

Table 3. Alterations of biochemical findings after fiber supplementation

		Min.-Max.			Median	Mean ± SS			↓	↑	=	p	
Lactate (umol/l)	B	2,8	-	12,3	5,2	6,3	±	3,9	4	2	1	0,116	W
	A	2,9	-	7,3	3,9	4,3	±	1,5					
AST (IU/L)	B	42,0	-	344,0	103,0	169,3	±	131,5	5	2	0	0,310	W
	A	22,0	-	444,0	72,0	163,6	±	163,2					
ALT (IU/L)	B	39,0	-	331,0	87,0	139,4	±	122,3	3	3	1	0,600	W
	A	24,0	-	414,0	103,0	148,4	±	146,7					
GGT (IU/L)	B	35,0	-	349,0	121,0	147,3	±	106,7	5	0	2	**0,043**	W
	A	35,0	-	320,0	117,0	133,6	±	99,2					
Uric acid (mg/dL)	B	4,5	-	8,2	5,5	5,9	±	30,7	4	3	0	0,611	W
	A	3,8	-	6,6	5,8	5,7	±	0,9					
Triglyceride (mg/dL)	B	312,0	-	970,0	617,0	610,4	±	226,2	6	1	0	**0,043**	W
	A	230,0	-	578,0	349,0	393,9	±	145,7					
Cholesterol (mg/dL)	B	149,0	-	341,0	267,0	258,4	±	68,7	6	1	0	0,091	W
	A	144,0	-	365,0	243,0	244,3	±	74,6					
LDL (mg/dL)	B	58,0	-	431,0	178,0	200,1	±	115,0	4	3	0	0,237	W
	A	70,0	-	234,0	141,0	142,9	±	63,0					
HbA1c (%)	B	4,7	-	5,3	4,8	5,0	±	0,3	1	6	0	**0,042**	W
	A	3,8	-	6,6	5,8	5,7	±	0,9					
Biotinidase activity (%)	B	146,0	-	186,0	178,0	170,9	±	13,9	2	5	0	0,446	W
	A	130,0	-	199,4	182,4	173,1	±	25,6					

B= before, A=after, ↓= number of patients with decreased value, ↑= number of patients with increased value, min=minimum, max=maximum

Discussion

This is an open label prospective study evaluating the use of adequate fiber supplementation for 6 weeks in children with GSD I. The study revealed PHGG supplementation produced an improvement in metabolic control of patients. Since infants with GSD I are avoided to have hypoglycemia, they are delayed in introducing additional solid foods and continue to be fed with formula for a long time. Thus, patients may have poor feeding habits, they may refuse to try solid foods and to provide a well-balanced diet might be challenging. Consequently, dietary restrictions, poor feeding habits, poor compliance, social and developmental issues may cause patients not to be fed well-balanced and they are likely to develop nutritional deficiencies. Apparently one of them is fiber which has some similar properties to uncooked cornstarch. Fiber provides delayed gastric transit as uncooked cornstarch in turn contributes to mainstay of normal blood glucose concentrations.

Soluble dietary fiber raises viscosity of the stomach content which causes prolonged gastric emptying, reduced transit time through the small intestine and lowered rate of starch digestion and glucose absorption, resulting in changes in blood glucose and cholesterol concentrations (9). Reduced postprandial glucose, insulin levels and improved glycemic control in diabetic and healthy individuals were observed after guar gum ingestion in different studies (5,10). The mechanism of these properties is to slow down gastric emptying and possibly limiting diffusion towards the absorbative mucosal surface. Leeds et al. (11) showed that 14,5 gr guar flours supplementation to a LUNDH type meal increased the transit time from mouth to caecum by 1-1,25 times.

Guar gum and other types of gel-forming dietary fiber have already been shown to reduce serum cholesterol concentration. Their lipid-lowering effects are associated with reducing intestinal cholesterol absorption. In addition, guar gum also decreases bile acid uptake in the gut which leads to be used more cholesterol to reproduce adequate bile acids, in turn reducing circulating blood cholesterol. Therefore, guar gum reduces total cholesterol levels as well. Furthermore, its use is noticeably safe (12). The effects of guar gum on serum triglyceride levels are controversial. Suziki and Hara (13) investigated the effects of hydrolyzed guar gum on glucose intolerance and hypertriglyceridemia in rats on high-fructose diets and observed dietary addition of hydrolyzed guar gum to rats improved the glucose intolerance and hypertriglyceridemia induced by a high-fructose diet. They suggested these beneficial effects might be associated with short chain fatty acids produced by microbial fermentation of hydrolyzed guar gum in large intestine. Whereas Oda et al. (14) showed, guar gum did not influence triglyceride concentrations in diet induced hypertriglyceridemic rats. In the study of Niv et al. (5) guar gum was ingested to type II hyperlipidemic patients for two weeks and no significant effect on triglyceride levels was observed. Similarly, Groop et al. (10) preceded guar gum to type II diabetic patients for 8 weeks and they observed improved glycemic control and cholesterol concentrations, whereas no difference in triglyceride levels were obtained.

The main target in management of GSD I is maintain the blood glucose levels in normal ranges. Otherwise, impaired gluconeogenesis and glycogenolysis may cause biochemical and clinical alterations. Dietary addition of PHGG resulted in decline in all glucose parameters involving average, lowest and highest in our patients. However, HbA1c levels increased significantly. Although the decrease in highest, lowest, and average glucose values in the patients seems a negative result at first glance, increased HbA1c levels indicates hypo and hyperglycemia periods were reduced, that is, the fluctuations decreased, and glycemic control improved.

Hyperlipidemia, particularly hypertriglyceridemia is one of the most frequent complications and may lead to pancreatitis episodes and hepatic steatosis in GSD I patients. The main cause of hyperlipidemia is impaired gluconeogenesis. Accumulated glucose 6 phosphate increases de novo lipogenesis. Additionally, there may be a reduction in lipid clearance (15). With fiber supplementation LDL and total cholesterol levels decreased in 4 and 6 patients respectively. Furthermore, decreased serum triglyceride levels were statistically significant. In the literature different studies suggested dietary guar gum supplementation had more beneficial effects on cholesterol concentration rather than triglyceride. However, in our study despite significantly decreased triglyceride levels, reducing cholesterol and LDL concentrations were not statistically significant.

This might be due to the small number of patients and/or short duration of the study.

Glucose 6 phosphate accumulation also results in increased flux through the pentose phosphate pathway which causes hyperuricemia. Patients may require the use of allopurinol to prevent complications such as gouty arthritis and urolithiasis (16). After the supplementation, patients' uric acid levels decreased in 4 and increased in 3. However, the mean uric acid levels decreased insignificantly.

Liver function tests show some abnormality in patients with GSD I. The failure of glucose dephosphorylation to release free glucose from glucose 6 phosphate severely inhibits hepatic glycogen breakdown resulting in excessive glycogen storage and hepatomegaly. Accumulation of glycogen impairs the ability of liver to function normally (17). There was no significant difference in AST and ALT values in our patients, whereas GGT levels decreased significantly. This may be explained with reduced total cholesterol and LDL levels because decreasing of them may improve liver injury and ultimately result in lower GGT.

Hyperlactatemia occurs as a consequence of the disruption of gluconeogenesis and increases with fasting. Since lactate may be used in the brain as an alternative energy source, patients are protected from the adverse effects of hypoglycemia. In patients with poor metabolic control, increased lactate levels may cause lactic acidosis and chronic lactatemia leads to bone resorption that results in hypercalcemia, osteopenia/osteoporosis, and growth retardation consequently (18-20). In our study all patients had high blood lactate levels before the fiber supplementation. Its reduction was not statistically significant; however, this may be associated with the small number of participants. Mean lactate levels decreased which may be related to decreased need of gluconeogenesis due to improved glycemic control.

The enzyme biotinidase (BTD) catalyzes the hydrolysis of biocytin to biotin and is mostly produced in the liver. Serum levels in patients with GSDI showed elevations in many studies, however the correlation between the activity of BTD and age or dietary control was inconsistent. Therefore, it was suggested that it had little value as a potential biomarker. Consistently, in our patients no significant difference was observed in serum biotinidase levels at the end of the study (21-25).

Consequently, this is the first study assessing the effects of adequate fiber supplementation in patients with GSD I. Dietary adequate fiber supplementation for 6 weeks resulted in decreased mean lactate, AST, ALT, cholesterol, LDL, uric acid levels insignificantly and decreased triglyceride, GGT concentrations and increased HbA1c values significantly. Apparently, it could have beneficial effects on glycemic and metabolic control. The alterations in biochemical parameters were more prominent in patients with poor metabolic control and consuming low starch amount per kilogram. Currently, the only way to achieve metabolic control is frequent feeding and consuming large amounts of uncooked cornstarch every 3-4 hours. However, to ensure patients consume adequate cornstarch for long term is challenging, and most patients cannot tolerate excessive starch intake. Thus, it becomes more difficult to provide good metabolic control for patients. Since there are some evidences that long term optimal metabolic control with normoglycemia and no secondary metabolic disturbances reduces the risk of development of long term complications, we can contribute to a better metabolic control with fiber supplementation for patients with inadequate fiber intake due to high cornstarch consumption (26).

Study Limitations

The study had some limitations. These were to be the open label nature of the study, small number of patients and relatively short duration of treatment. These limitations may have obscured the significance of some insignificant biochemical changes, and because of the short duration of the study we could not evaluate the alterations in glycogen storage and liver size with ultrasound.

Conclusion

The results of this study seem encouraging for the use of adequate fiber supplementation in terms of improving metabolic control in GSD I patients. However, randomized, double blinded controlled prospective long-term trials with expanded number of patients are required to investigate the effects of fiber supplementation in perspective.

Ethics

Ethics Committee Approval: The study was approved by the Gazi University Faculty of Medicine Ethics Committee (approval no: 2021.03.252, decided: 08 March 2021).

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Correia CE, Bhattacharya K, Lee PJ, Shuster JJ, Theriaque DW, Shankar MN, et al. Use of modified cornstarch therapy to extend fasting in glycogen storage disease types Ia and Ib. Am J Clin Nutr 2008;88:1272-6.
2. Froissart R, Piraud M, Boudjemline AM, Vianey-Saban C, Petit F, Hubert-Buron A, et al. Glucose-6-phosphatase deficiency. Orphanet J Rare Dis 2011;6:27.
3. Bhattacharya K. Dietary dilemmas in the management of glycogen storage disease type I. J Inherit Metab Dis 2011;34:621-9.
4. Lattimer JM, Haub MD. Effects of dietary fiber and its components on metabolic health. Nutrients 2010;2:1266-89.
5. Niv E, Halak A, Tiommny E, Yanai H, Strul H, Naftali T, et al. Randomized clinical study: Partially hydrolyzed guar gum (PHGG) versus placebo in the treatment of patients with irritable bowel syndrome. Nutr Metab (Lond) 2016;13:10.
6. Bundeslebensmittelschluessel; German Food Code and Nutrient Data Base; Version 3.01B [http://www.bfr.bund.de/cd/801
7. Kleinmen RE (ed). Pediatirc Nutrition Handbook (6thed.) İllimois: Amarican Academy of Pediatrics, 2009.
8. Kasapkara ÇS, Cinasal Demir G, Hasanoğlu A, Tümer L. Continuous glucose monitoring in children with glycogen storage disease type I. Eur J Clin Nutr 2014;68:101-5.
9. Dikeman CL, Murphy MR, Fahey GC Jr. Dietary fibers affect viscosity of solutions and simulated human gastric and small intestinal digesta. J Nutr 2006;136:913-9.
10. Groop PH, Aro A, Stenman S, Groop L. Long-term effects of guar gum in subjects with non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1993;58:513-8.
11. Leeds AR, Gassull MA, Metz GL, Jenkins DJ. Letter: Food: influence of form on absorption. Lancet 1975;2:1213.
12. Lin J, Sun Y, Santos HO, Găman MA, Bhat LT, Cui Y. Effects of guar gum supplementation on the lipid profile: A systematic review and meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2021;31:3271-81.
13. Suzuki T, Hara H. Ingestion of guar gum hydrolysate, a soluble and fermentable nondigestible saccharide, improves glucose intolerance and prevents hypertriglyceridemia in rats fed fructose. J Nutr 2004;134:1942-7.
14. Oda T, Aoe S, Imanishi S, Kanazawa Y, Sanada H, Ayano Y. Effects of dietary oat, barley, and guar gums on serum and liver lipid concentrations in diet-induced hypertriglyceridemic rats. J Nutr Sci Vitaminol (Tokyo) 1994;40:213-7.
15. Bandsma RH, Prinsen BH, van Der Velden Mde S, Rake JP, Boer T, Smit GP, et al. Increased de novo lipogenesis and delayed conversion of large VLDL into intermediate density lipoprotein particles contribute to hyperlipidemia in glycogen storage disease type 1a. Pediatr Res 2008;63:702-7.
16. Roe TF, Kogut MD. The pathogenesis of hyperuricemia in glycogen storage disease, type I. Pediatr Res 1977;11:664-9.
17. Ozen H. Glycogen storage diseases: new perspectives. World J Gastroenterol 2007;13:2541-53.
18. MAHLER R. Glycogen storage diseases J. clin. Path 1969;22(Suppl 2):32-41.
19. Cabrera-Abreu J, Crabtree NJ, Elias E, Fraser W, Cramb R, Alger S. Bone mineral density and markers of bone turnover in patients with glycogen storage disease types I, III and IX. J Inherit Metab Dis 2004;27:1-9.
20. Krieger NS, Sessler NE, Bushinsky DA. Acidosis inhibits osteoblastic and stimulates osteoclastic activity in vitro. Am J Physiol 1992;262:F442-8.
21. Paesold-Burda P, Baumgartner MR, Santer R, Bosshard NU, Steinmann B. Elevated serum biotinidase activity in hepatic glycogen storage disorders--a convenient biomarker. J Inherit Metab Dis 2007;30:896-902.
22. Angaroni CJ, Giner-Ayala AN, Hill LP, Guelbert NB, Paschini-Capra AE, Dodelson de Kremer R. Evaluation of the biotinidase activity in hepatic glycogen storage disease patients. Undescribed genetic finding associated with atypical enzymatic behavior: an outlook. J Inherit Metab Dis 2010;33(Suppl 2):S289-94.
23. Hug G, Chuck G, Tsoras M. Increased Serum Biotinidase Activity in Glycogen-Storage-Disease Type-Ia. In Proceedings of the Pediatric Research; Williams & Wilkins: Baltimore, MD, USA 1994;35:A203.
24. Burlina AB, Dermikol M, Mantau A, Piovan S, Grazian L, Zacchello F, et al. Increased plasma biotinidase activity in patients with glycogen storage disease type Ia: effect of biotin supplementation. J Inherit Metab Dis 1996;19:209-12.
25. Wolf B, Freehauf CL, Thomas JA, Gordon PL, Greene CL, Ward JC. Markedly elevated serum biotinidase activity may indicate glycogen storage disease type Ia. J Inherit Metab Dis 2003;26:805-9.
26. Däublin G, Schwahn B, Wendel U. Type I glycogen storage disease: favourable outcome on a strict management regimen avoiding increased lactate production during childhood and adolescence. Eur J Pediatr 2002;161 Suppl 1:S40-5.