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Galactose supplementation in phosphoglucomutase-1 deficiency; review and outlook for a novel treatable CDG

Eva Morava, MD, PhD^{1,2}

¹Tulane University Medical Center, Department of Pediatrics, Hayward Genetics Center, New Orleans, LA, USA ²Department of Pediatrics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Abstract

We recently redefined phosphoglucomutase-1 deficiency not only as an enzyme defect, involved in normal glycogen metabolism, but also an inborn error of protein glycosylation.

Phosphoglucomutase-1 is a key enzyme in glycolysis and glycogenesis by catalyzing in the bidirectional transfer of phosphate from position 1 to 6 on glucose. Glucose-1-P and UDP-glucose are closely linked to galactose metabolism. Normal PGM1 activity is important for effective glycolysis during fasting. Activated glucose and galactose are essential for normal protein glycosylation. The complex defect involving abnormal concentrations of activated sugars leads to hypoglycemia and two major phenotypic presentations, one with primary muscle involvement and the other with severe multisystem disease. The multisystem phenotype includes growth delay and malformations, like cleft palate or uvula, and liver, endocrine and possible cardiomyopathy. The patients have normal intelligence.

Decreased transferrin galactosylation is a characteristic finding on mass spectrometry. Previous in vitro studies in patient fibroblasts showed an improvement of glycosylation on galactose supplements. Four patients with PGM1 deficiency have been trialed on D-galactose (compassionate use), and showed improvement of serum transferrin hypoglycosylation. There was a parallel improvement of liver function, endocrine abnormalities and a decrease in the frequency of hypoglycemic episodes. No side effects have been observed. Galactose supplementation didn't seem to resolve all clinical symptoms. Adding complex carbohydrates showed an additional clinical amelioration. Based on the available clinical data we suggest to consider the use of 0.5–1g/kg/day D-galactose and maximum 50g/day oral galactose therapy in PGM1-CDG.

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Correspondence: Tulane University Medical Center, Department of Pediatrics, Hayward Genetics Center, New Orleans, LA, USA. T: 1(504) 9885101. emoravakozicz@tulane.edu.

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The existing data on galactose therapy have to be viewed as preliminary observations. A prospective multicenter trial is ongoing to evaluate the efficacy and optimal D-galactose dose of galactose supplementation.

Keywords

Congenital disorder of glycosylation; CDG; PGM1; glycogenosis; galactose; UDP-galactose; hypoglycemia; muscle disease; rhabdomyolysis; D-galactose; therapy

Introduction

We recently defined a novel inborn error of glycosylation; phosphoglucomutase-1 deficiency (1). Phosphoglucomutase (EC 5.4.2.2: PGM1) is an enzyme that transfers a phosphate group on an alpha-D-glucose monomer from the 1' to the 6' position in the forward direction or the 6' to the 1' position in the reverse direction. Interestingly, the enzyme deficiency has been reported before in association with primary muscle disease, as glycogen storage disease XIV (GSD14; MIM 612964)(2). Glycosylation hasn't been evaluated in these cases (2). In a quite different clinical group of children with cleft palate, short stature, liver disease, hypoglycemia, cardiomyopathy, normal intelligence and abnormal transferrin isoelectric focusing PGM1 gene mutations were detected by next generation sequencing. This led to the discovery of a new type of CDG (PGM1-CDG) (1,3). The biochemical abnormalities affected several glycoproteins, leading to classic CDG-related features, (liver dysfunction, hypoglycemia, endocrine abnormalities, coagulation problems) and a mixed type 1 and type 2 pattern of serum transferrin isoelectric focusing (1,3,4). There is a clinical difference between PGM1 deficient cases diagnosed in young adults compared to children, since "adult" cases show predominantly symptoms of primary muscle disease. However, pediatric cases with multisystem disease may show significant muscle symptoms, even rhabdomyolysis in childhood. Later presenting cases might be missed, as glycosylation disorders (CDGs), although by closer evaluation endocrine disturbances or uvula bifida can be discovered in adult cases based on previous history.

Decreased transferrin galactosylation was shown by mass spectrometry (3). Increasing galactose concentrations in cell cultures of PGM1 deficient patient fibroblasts ameliorates hypogalactosylation and might rescue the biochemical phenotype (3). This led to the compassionate use of D-galactose, a freely available, over the counter dietary supplement in a few individual patients, showing biochemical and clinical improvement during oral treatment (3,5).

Biochemical background

Phosphoglucomutase-1 (Suppl. Fig. 1) is a key enzyme between glycolysis and glyconeogenesis. The enzyme participates in the bidirectional transfer of phosphate between position 1 to 6 of glucose. The first step in the forward reaction is the transfer of a phosphoryl group to glucose 1-phosphate, forming glucose 1,6-bisphosphate. The dephosphorylated form of the enzyme then undergoes a rapid diffusional reorientation and facilitates the transfer of a phosphoryl group from the glucose-1,6-bisphosphate intermediate

to the enzyme, regenerating phosphorylated phosphoglucomutase and yielding glucose 6-phosphate (7). The oxygen of the active-site serine residue at the active site becomes phosphorylated and dephosphorylated (8).

Phosphoglucomutase is important in the maintenance of normoglycemia. Hyperglycemia increases the flux through glucose 6-phosphate, glucose 1-phosphate and UDP-glucose to glycogen (via glycogen synthase) (Suppl. Fig. 1) (9,10). Glycogen phosphorylase acts in the other direction, during fasting. The phosphorolytic cleavage of a glucosyl residue from glycogen produces glucose-1-phosphate. Phosphoglucomutase then catalyzes the conversion of this glucose 1-phosphate to glucose 6-phosphate. The latter can be catabolized by glycolysis, or feed into the pentose phosphate pathway, or, in liver converted to glucose (9,10). Glucose-1-P is connected to galactose metabolism through UDP-glucose. UDP-glucose and UDP-galactose are in metabolic balance in healthy individuals, due to the enzyme UDP-galactose-4-epimerase (GALE). GALE deficiency leads to a rare form of galactosemia. Galactose, when ingested, is phosphorylated to galactose-1-phosphate, which is converted to UDP-galactose by galactose-1-phosphate uridyl transferase (GALT). UDP-galactose is then epimerized to UDP-glucose by GALE. UDP-glucose is converted to glucose-1-phosphate, and the latter to glucose-6-phosphate by PGM1. The ratio of glucose-1-phosphate to galactose-1-phosphate depends on the GALE activity and the galactose intake.

Phosphoglucomutase-1 deficiency and muscle disease

Initial case reports associated with PGM1 deficiency showed a primary muscle involvement associated with variable clinical symptoms and significant decrease (10–15% residual activity) in PGM activity in muscle biopsy or red blood cells. One of the earliest reports included a 5-month-old boy who had recurrent vomiting, lethargy, and poor weight gain, metabolic acidosis and nonketotic dicarboxylic aciduria, muscle carnitine deficiency and clinical improvement on oral carnitine administration. Muscle biopsy revealed a slight increase in intra-fiber lipid droplets and mild subsarcolemmal accumulation of glycogen. PGM deficiency was suggested to be secondary systemic carnitine deficiency (11). Another child presented with muscle fatigue and elevated creatine kinase levels, first branchial arch syndrome and growth hormone deficiency (4). Another patient had exercise-induced weakness of the extremities since the age of 20 years, moderate muscle weakness, clubbed fingers and low fasting plasma glucose levels (58 mg/dl). Venous concentration of lactate failed to rise after an ischemic forearm exercise test. Muscle biopsy demonstrated small amount of increase in subsarcolemmal glycogen. Sural nerve biopsy showed degeneration of myelinated and unmyelinated fibers, but there was no apparent accumulation of glycogen (12). A patient with phosphoglucomutase deficiency out of a series of 22 cases of metabolic myopathies had normal muscle histology (11). PGM1 deficiency has been also reported in adults in association with exercise intolerance, episodes of rhabdomyolysis, elevated creatine kinase levels and increased muscle glycogen content (2,11,13,14). Patients had exercise induced hyperammonia, decreased lactate increase during forearm ischemic tests, but no episodes of hypoglycemia, endocrine dysfunction or liver involvement (2). Glucose administration during exercise led to better exercise tolerance in this subgroup of adult PGM1 patients with primary muscle involvement (15).

Multisystem phenotype in PGM1 deficiency

Upon the recent, surprising discovery of recessive *PGM1* mutations in two undiagnosed patients with hypoglycemia, abnormal protein glycosylation and mild muscle symptoms, PGM1 deficiency was redefined as a congenital disorder of glycosylation (PGM1-CDG) (1,16). In the two original patients diagnosed with PGM1-CDG additional features included several known features of abnormal protein glycosylation; like liver disease, endocrine and coagulation disturbances, malignant hyperthermia and dilated cardiomyopathy. Special features included cleft palate or uvula and Pierre-Robin sequence (1). Evaluation of further patients led to the definition of a recognizable phenotype with variable degrees of midline facial defects, hypoglycemia, liver and muscle disease, short stature and progressive cardiac failure and hypoglycosylation of serum proteins (4,16,17). Further studies in patients fibroblasts showed elevated levels of Glucose-1-P and, to a lesser degree, of Galactose-1-P with an increased ratio of UDP-glucose over UDP-galactose. This relative decrease in the ratio of activated galactose/activated glucose molecules was thought to cause protein hypoglycosylation (3). In fact, tandem mass spectrometric analysis of serum glycans showed in all, so far discovered PGM1 deficient patients missing glycan chains, and also truncated glycans, with a significant decrease in the total galactose content of glycans (3).

As we mentioned previously, endocrine and coagulation abnormalities, liver disease, growth-delay, and in some of the cases cardiac dysfunction are also present in most cases of PGM1-CDG. The abnormal glycoproteins in PGM1 deficiency are most likely due to the decreased availability of UDP-Galactose compared to UDP glucose for the proper glycosylation, demonstrated by hypogalactosylation of transferrin on mass spectrometry (1). Clinical consequences include hypoadrenocorticism, growth delay due to decreased IGF1/3 levels, hypothyroidism, hyperinsulinism with hypoglycemia, increased liver transaminases, decreased antithrombin-III levels and increased thrombosis risk (3). PGM1 is not expressed in the central nervous system; therefore patients have no neurological symptoms and normal intelligence.

The cardiac involvement in PGM1 deficiency is not fully understood. Zasp (Z-band alternatively spliced PDZ-motif protein) is a Z-disc component in cardiac muscle. The protein anchors PGM1 to Z-disc under stress conditions, suggesting that an impaired binding of PGM1 might be involved in the pathogenesis of cardiomyopathy in PGM1 deficiency (3). Also, not fully understood is the Pierre Robin spectrum, cleft palate or bifid uvula, although malformations are quite common in glycosylation defects. One might hypothesize that the abnormal glycosylation, and abnormal signaling play a role in these embryologic abnormalities.

Hypoglycemia in PGM1 deficiency

The origin of hypoglycemia in PGM1 deficiency is complex, on the one hand insufficient glucose release from glycogen, on the other hand functional hyperinsulinism abnormal protein glycosylation (3,18). As in most glycogenoses, frequent feeding and complex carbohydrate therapy are beneficiary in the treatment of liver disease and hypoglycemia in PGM1-CDG. In severe cases dietary intervention (corn starch supplements in 1–2g/kg/day)

might need to be combined with Diazoxide therapy. In some cases even tube feeding might be necessary (3,18).

In a two year-old boy with Pierre-Robin anomaly, moderate hepatomegaly, daily hypoketotic hypoglycemic episodes, and short stature laboratory investigations showed increased serum transaminases, minimally elevated CK levels, and normal uric acid, triglyceride and cholesterol levels in blood. An oral glucose tolerance test (OGTT) led to persistent hyperglycemia with increase of insulin but not of lactate levels. Hypoglycemic episodes persisted on complex carbohydrate diet (5). Another patient with short stature, feeding problems and IGF3 deficiency showed similar biochemical abnormalities. The patient was started on complex carbohydrate treatment and additional bolus tube feeding, but also Diazoxide therapy for recurrent, persistent hypoglycemic episodes (18). Other patients however only showed fasting hypoglycemia with normal ketosis and insulin levels, supporting a pathomechanism more related to abnormal glycogen metabolism.

Galactose supplementation increases of protein glycosylation in patient fibroblasts

PGM1 deficient fibroblasts were cultured in the presence of additional galactose in the medium. They were labeled with ICAM-1, an antibody specific for N-linked glycosylation, which stains cell surface glycoproteins, and, in case of abnormal glycosylation, offers a sensitive screening method (3,5). Patient fibroblasts showed a significant decrease in ICAM-1 staining, compatible with a severe decrease of cell surface protein glycosylation in PGM1 deficiency. Galactose supplementation of cell cultures led to a significant improvement of glycosylation with restoration of staining, supporting the beneficiary effect of excess galactose in PGM1 defect (3,5,6).

D-Galactose

Galactose is present in dairy products, the pectin of some fruits, certain vegetables, chestnuts, and some herbs. Young children get most of their dietary galactose from milk. In children and young adults, depending on the dietary intake, D-galactose intake varies between 0.5–3.5g/kg/day. In addition, D-galactose is freely available in health food stores and is promoted for stimulating the immune system and improving gut motility in healthy individuals.

In clinical practice, galactose (1g/kg/day: maximum 50 g in one dose) has been used in the past for clinical loading tests (19). Oral and intravenous D-galactose have been used in the so called “galactose tolerance test” to determine the ability of the liver to convert galactose to glycogen. Galactose has been also safely used in clinical trials. D-galactose is known to bind to the focal segmental protein factor (FSPF) that causes focal segmental glomerulosclerosis (FSGS) and suggested to inactivate FSPF thereby stopping it from damaging the kidney. D-galactose has been safely used in clinical trials for FSGS in a dose of maximum 30g daily for a period of 4 months (20).

Investigators studied oral and intravenous administration of galactose 0.6 g/kg in eight subjects showed peak serum galactose levels of approximately 24 mg/dl after oral administration and 58 mg/dl after intravenous administration (21). In another study healthy young subjects received a single oral dose of galactose (0.5 g/kg body weight), while a second group was given a daily supplement of 0.5 g/kg galactose for 15 days. Blood galactose and galactitol were measured. On the first day of the study some subjects seemed to tolerate galactose less well than others. However, galactitol appeared in their plasmas, however, after 15 days of galactose intake, the subjects adapted, with decrease in blood galactose and the disappearance of urinary galactitol, supporting safety of long term high dose galactose administration (22).

In a performance trial evaluating the effect of monosaccharide ingestion during long lasting exercise, subjects were requested to cycle four times 1km and four times 4 km with maximal efforts. Before each trial 1 hour before the exercise 38 ± 3 g 6% glucose or 6% D-galactose was administered, followed by an intake at a rate of 37 ± 3 g/hour during exercise at. A 6% D-galactose drink did not lead to any side effects. Galactose ingestion did not enhance performance time, but improved intermediate self paced effort (23).

Dietary galactose supplementation

All patients so far treated with galactose a frequent feeding regimen and complex carbohydrate use was initiated previously. So far eight patients received either lactose or D-galactose supplements (personal communications), for variable length of administration as compassionate use, but not in formal prospective studies or in randomized trials. Also the patients showed highly variable compliance, and several patients tried out both lactose and galactose, even taking supplements parallel. Six of these patients have been already reported with significant improvement of protein glycosylation (Suppl. Table 1) after a few weeks of therapy. The regional ethical commissions approved D-Galactose supplementation. Lactose was used as a freely available common dietary supplement. The total daily galactose intake was within the limits of the normal daily dietary intake in all cases. Daily galactose intake varies in healthy children between 0.5–3.5 g/kg/day, according to age and preferred diet. Patients received 0.5g/kg/day up to 1g/kg/day oral D-galactose intake, divided into several doses. No patient received more than a maximum of 50g/day D-galactose. Compliance was variable but all together all six patient treated with either galactose or lactose received at least an average dose of 0.5g/kg/day galactose intake for a 6 months period (5,6). From the six reported cases two patients were trialed on alternating lactose (1g/kg for 6 months) and then galactose (0.5–1g/kg for 6 months) supplements. These patients showed rapid improvement of glycosylation within a few weeks of either lactose or galactose therapy (Suppl. Table 1).

In one of the two patients on only oral lactose supplementation only (1g/kg/day) one had mild biochemical improvement and no hypoglycemic episodes, but in the other hypoglycemic episodes persisted and the patient needed further tube feeding and Diazoxide therapy. However, growth, the transferrin IEF pattern and serum IGF3 levels improved gradually (18).

One patient was only trialed on D-galactose therapy. One patient had parallel galactose and lactose supplementation upon primarily being established on lactose supplements, in order to try to achieve further possible improvement of the treatment. In the total four patients on variable daily intake of D-galactose (0.5–1g/kg/day) no more hypoglycemic episodes occurred after the galactose supplements were started. Glycosylation of transferrin and several glycosylated proteins improved within weeks on mass spectrometry in all patients receiving extra galactose. The transferrin isoelectric focusing pattern has shown significant further improvement with time, but didn't restore fully, even in the single patient who only received galactose. ASAT levels remained mildly elevated in some patients, but ALAT, LDH, APTT and PT and lactate levels have been fully normalized after 8–10 months of galactose therapy (Suppl. Table 1). The liver size remained normal, no increase of glycogen content was suspected based on serial liver ultrasounds in any of the patients upon treatment. In the two patients with endocrine dysfunction and muscle involvement no more rhabdomyolytic episodes occurred on galactose treatment, and the hypogonadotropic hypogonadism resolved (3,5,6). Some of the patients were able to decrease complex carbohydrate intake significantly.

Discussion

PGM1 deficiency is an intriguing inborn error, showing both features of insufficient glycogen mobilization and protein hypoglycosylation (1,3). Normal PGM1 activity is important for several metabolic pathways, it has an essential role in effective glycolysis during fasting, its activity is important in the regulation of glycogen synthesis and it has a secondary role in the regulation of concentration of activated monosaccharides. Activated glucose and galactose are both essential for normal protein glycosylation, however protein glycosylation has a much higher demand on galactose residues, compared to glucose.

Recently found PGM1 deficient patients show a spectrum of symptoms; some of them have muscle involvement and hypoglycemia, as we see in many GSDs, others have a severe multisystem disease including liver involvement, endocrine disturbance (hypothyroidism, growth delay) and coagulation abnormalities, comparable to patients with CDG (3). Traditional treatment with frequent feedings and a complex carbohydrate diet seems to be insufficient to prevent hypoglycemic episodes, and has no effect on endocrine and coagulation anomalies, related to abnormal protein glycosylation. Recent studies of galactose supplements in vitro, and in a few patients, in vivo show promising results suggesting that galactose therapy has a beneficial effect on the biochemical and clinical phenotype in PGM1 deficient patients (3,5,6).

In all previously reported patients the dose of supplementary oral D-galactose supplementation was in the normal dietary range. Galactose could be added to normal food, and was well ingested, without any side effects, including gastrointestinal symptoms, or diarrhea, even on the highest dose (3g/kg/day) intake. No daily dose was used, however above the suggested maximal intake of 50g/day (13).

Hypoglycemia, a consistent feature in PGM1 patients is due to relative hyperinsulinism in some cases (18,24), but in older patients, normoketotic hypoglycemia as well as normal

insulin levels, and slightly elevated lactate levels have been observed. This observation suggests that hypoglycemia in PGM1 deficiency occurs due to different factors as a consequence of the complex metabolic abnormalities, and might be different of origin at different ages during the course of the disease (18).

PGM1 deficiency has an important role in glycogen metabolism, frequent feeding and the use of complex carbohydrates are most likely important in the treatment of phosphoglucomutase deficiency, even when galactose supplementation seems to be effective. Two patients with severe hypoglycemic episodes are currently still on partial tube feeding (3). In cases of severe hypoglycemia Diazoxid use might be needed as well (3,18). The optimal dose of galactose has still to be determined. An open question is whether adding uridine to the diet in order to facilitate galactose activation would improve glycosylation even more efficiently (3). In conclusion the existing data are preliminary observations and further prospective studies are needed to evaluate the efficacy and the optimal dose of galactose supplementation in PGM1-CDG, ideally upon the appearance of symptoms and early diagnosis.

Based on our own and others' experience D-galactose doses up to 50g/day seem to be safe. We suggest to combine this with frequent feedings, complex carbohydrate diet and in some cases, if needed, with Diazoxide treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ASAT	aspartate amino transferase
ALAT	alanine amino transferase
CDG	Congenital disorder of glycosylation
CK	Creatine kinase
GSD	Glycogen storage disease
GALT	galactose phosphate uridyl transferase
GALE	galactose phosphate 4 epimerase
OGTT	Oral glucose tolerance test
PGM1	Phosphoglucomutase 1

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Highlights

PGM1 deficiency is an intriguing inborn error with features of abnormal glycogen metabolism and defective protein glycosylation

A literature overview on the metabolic background and clinical features of PGM1 deficiency is presented.

We review the data on clinical experience in PGM1 deficient patients on dietary galactose supplementation

We emphasize the need for prospective dietary intervention trials to find the optimal nutritional intervention in PGM1 deficiency