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# Therapeutic approaches in Congenital Disorders of Glycosylation (CDG) involving N-linked glycosylation: an update

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## Abstract

Congenital disorders of glycosylation (CDG) are a group of clinically and genetically heterogeneous metabolic disorders. Over 150 CDG types have been described. Most CDG types are ultrarare disorders. CDG types affecting N-glycosylation are the most common type of CDG with emerging therapeutic possibilities. This review is an update on the available therapies for disorders affecting the N-linked glycosylation pathway. In the first part of the review, we highlight the clinical presentation, general principles of management, and disease-specific therapies for N-linked glycosylation CDG types, organized by organ system. The second part of the review focuses on the therapeutic strategies currently available and under development. We summarize the successful (pre-) clinical application of nutritional therapies, transplantation, activated sugars, gene therapy, and pharmacological chaperones and outline the anticipated expansion of the therapeutic possibilities in CDG. We aim to provide a comprehensive update on the treatable aspects of CDG types involving N-linked glycosylation, with particular emphasis on disease-specific treatment options for the involved organ systems; call for natural history studies; and present current and future therapeutic strategies for CDG.

### Keywords

congenital disorders of glycosylation; CDG; dietary interventions; monosaccharide supplementation; therapy

## INTRODUCTION

Glycosylation is the enzyme-catalyzed process of monosaccharide activation and glycan addition to proteins and lipids, and is essential for correct protein maturation and function. Congenital disorders of glycosylation (CDG) are a group of monogenic disorders

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characterized by impaired glycosylation. The group of CDG includes disorders of protein N-glycosylation, protein O-glycosylation, combined glycosylation defects (multiple pathway involvement), and glycosphingolipid and glycosylphosphatidylinisotol (GPI) anchor synthesis defects. Over 150 CDG types have currently been described, most of which involve defects of N-glycosylation.[1–4] Most CDG types are ultrarare disorders.[3] The current nomenclature includes the “gene name”-CDG, (with the hazard that there is no information about what that gene does, therefore it becomes potentially disconnected from physiological function and the rationale for the therapies).

Diagnosing CDG is often challenging due to the broad clinical presentation affecting multiple organ systems and phenotypic heterogeneity among types. The most common CDG is PMM2-CDG (previous nomenclature: CDG-Ia), with almost 1000 patients reported, and has an estimated prevalence of 1:100,000.[4] Most CDG patients have dysmorphic facial features, abnormal fat distribution, and variable coagulation and endocrine defects. Neurologic, cardiac, gastrointestinal, hepatic, renal, hematologic, immunologic, and skeletal abnormalities are present across the different types of CDG (Fig. 1).[5] There is no comprehensive information on natural history in CDG, and most available data on the clinical spectrum rely on small patient cohorts.[6]

Initial biochemical screening for most N-linked glycosylation disorders is performed by isoelectric focusing or mass spectrometry of serum transferrin. Abnormal transferrin glycosylation patterns can indicate disruption of glycosylation in the cytoplasm and endoplasmic reticulum or in the Golgi apparatus. In CDG type 1 there is a decrease in the synthesis of glycans while in CDG type 2 glycans are incomplete (truncated).[3] A decreased availability of nucleotide sugars can lead to mixed patterns.[7] Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) analysis can provide more information about the type of defect in type II CDG.[4] Abnormal transferrin profiles are an indication for genetic screening with targeted CDG gene panels or exome/genome sequencing to identify pathogenic variants in CDG-associated genes.[2] In many Golgi-related CDG the exact biochemical pathogenesis is not fully understood. In addition, in many CDG, including O-glycosylation disorders, lipid glycosylation disorders, GPI anchor synthesis disorders, and some N-glycosylation disorders, the serum transferrin profile can be normal, complicating biochemical screening for CDG.[1] Early and accurate diagnosis of CDG is crucial for timely implementation of appropriate therapies and improving clinical outcomes. Caveats include small patient cohorts of individual CDG types, making it challenging to provide evidence-based therapeutic recommendations.[4] Many organ systems in CDG are affected due to abnormal glycosylation, raising the possibility for CDG-specific treatments. Unfortunately, there are no “disorder-specific” treatments for hearing loss, ophthalmological, skeletal, renal, cardiac, and muscle involvement in CDG patients. Standard of care treatment should be provided for these systems.

We reviewed the current literature on CDG types involving N-linked glycosylation for which treatment options are possible. We structured our clinical presentation of CDG by affected organ system and present identified phenotypes, their underlying pathophysiology, and the treatment options currently available and in development.

## SEARCH STRATEGY AND SELECTION CRITERIA

We performed a search of PubMed (date of last search June 2019). We used the following search terms, with or without [“CDG” OR “congenital disorders of glycosylation”] and any of the following search terms: neurologic involvement, hearing loss, ophthalmologic involvement, cardiac involvement, gastrointestinal involvement, hepatic involvement, renal involvement, hematologic involvement, endocrine involvement, infections and immunologic involvement, skeletal involvement, lipid abnormalities. We further performed searches for CDG for which information on disease-specific treatment is available: ATP6AP1-CDG, CAD-CDG, CCDC115-CDG, DOLK-CDG, MAGT1-CDG, MPI-CDG, PGM1-CDG, PGM3-CDG, PMM2-CDG SL39A8-CDG, SLC35C1-CDG, SLC35A2-CDG, TMEM165-CDG, and TMEM199-CDG.

### Neurologic involvement

Neurologic involvement is present in most CDG types. The most common symptoms are cerebellar ataxia, central hypotonia, proximal muscle weakness, and spasticity. Peripheral neuropathy is quite common, especially in PMM2-CDG. Stroke-like episodes (SLEs) are life-threatening complications.[3] Both intractable seizures as well as those responsive to anticonvulsant therapy are reported.[6,8] There are only a few CDG types not associated with speech and developmental delay and intellectual disability.[9]

General management focuses on symptoms. For the management of ataxia, physical therapy is most important. Emphasis should be as much on gait training as strengthening of core muscles. Recent reports demonstrated beneficial effects of acetazolamide in PMM2-CDG.[10] In patients with spasticity or dystonia, local injection of botulinum toxin may be useful. Aggressive treatment of increased body temperature (escalating fever), which often exacerbates seizures, myoclonus, and other movement disorders, and may provoke stroke-like episodes in many patients, is essential. A potential thromboembolic etiology should be excluded in the evaluation of a suspected SLE. Arginine therapy hasn’t been shown to reduce the severity or frequency of stroke-like episodes in CDG. Currently, only conservative therapy, such as providing adequate hydration, is recommended. Unilateral weakness due to SLE resolves in less than a week in most CDG patients.[4]

Myoclonus often responds to valproic acid, although this must be used cautiously in patients with liver disease; alternatives include levetiracetam, brivaracetam, and clonazepam. A few patients with intractable epilepsy have been trialed on medical cannabis oil treatment, but no prospective study has been reported yet.[11] Ketogenic diet should be used with caution due to increased risk of hypoglycemia in CDG.[6]

Disease-specific therapeutic approaches in CDG mostly aim at increasing the concentration of activated monosaccharides for glycan synthesis, or their transport to a specific compartment (Table 1). Other approaches focus on trace elements, which are important for the normal function of enzymes participating in glycosylation. Most therapies with dietary monosaccharides do not have an immediate effect on central nervous system function. Most of these therapies have been suggested in case studies, not in prospective trial cohorts.

Oral galactose (1 g/kg/day)[12] and oral manganese therapy (individualized dose) have improved seizure control in SLC39A8-CDG.[13] Oral fucose therapy was found to have positive effects on neurologic development in a few SLC35C1-CDG patients (Table 2).[14–17] Oral galactose improved seizure control in a patient with SLC35A2-CDG.[9,18] Uridine supplementation has shown success in two patients with severe epilepsy in CAD-CDG.[19] An acetylated form of uridine, which is more efficiently taken up, is also used (Xuriden [uridine triacetate]; this is FDA-approved in the United States).

## Gastrointestinal involvement

Failure to thrive is a common feature of many CDG and is probably multifactorial in etiology, including orofacial motor dysfunction secondary to hypotonia, malabsorption, and neurological impairment. The gastrointestinal mucosa is highly glycosylated. Lymph circulation has further been reported to be abnormal in some patients with CDG. Reflux and vomiting are very common in CDG and chronic diarrhea has been reported in many CDG types.[4] A specific feature most commonly found in MPI-CDG, but also present in others such as ALG6-CDG and PMM2-CDG, is protein-losing enteropathy (PLE).

The general approach of treating the gastrointestinal symptoms in CDG include maximal tolerated caloric intake with any type of formula (no special diet required for most CDG patients). In addition to regular albumin infusions, octreotide therapy or a diet rich in midchain fatty acids (MCTs) may be helpful, as in other etiologies of protein-losing enteropathy, in treating PLE. In severe cases feeding assistance by nasogastric tube or percutaneous gastrostomy are advised.[4] However, on longitudinal follow-up this failure to thrive often persists despite treatment.[20] Surprisingly, in one CDG (MAN1B1-CDG) not caloric intervention but caloric restriction is necessary because of progressive truncal obesity.[2]

Treatment with mannose in MPI-CDG was reported in several cases to improve diarrhea and eliminate the need for albumin infusion.[2] A dose of 200 mg/kg 4–6 times/day is suggested to achieve therapeutic serum mannose levels.[2,21,22] In some patients, this therapy causes significant side effects such as hemolysis, increase in HbA1c, and recurrent jaundice.[23] In one case, protein-losing enteropathy improved with heparin infusions.[24]

## Hepatic involvement

The liver is affected in most CDG, which is reflected in the use of transferrin glycoform analysis in diagnosis in most types of CDG (as transferrin is produced by the liver), and elevated transaminases in most young patients. Clinically relevant liver involvement however is only present in 22% of CDG types, although it can be debilitating or even life-threatening with progression to liver cirrhosis or liver failure.[25]

There are two main pathophysiological distinctions in liver involvement: either a developmental abnormality (ductal plate malformation or congenital hepatic fibrosis, as in MPI-CDG) or a clinical picture of elevated liver transaminases and steatosis, as in PMM2-CDG. The spontaneous evolution of the latter can be rather benign with normalization over time, whereas the former is not treatable other than through liver transplantation, as in MPI-CDG.[23] Finally, the most severe presentation of liver disease (acute liver failure) can

arise in the setting of multiorgan failure or severe multisystem disease.[25] Liver involvement is the primary finding in TMEM199-CDG, ATP6AP1-CDG, and CCDC115-CDG, all of which involve the V-type ATPase complex in the Golgi, and are classified as type II CDG.

While there is no specific treatment for liver disease in many CDG, follow-up via a gastroenterologist/hepatologist is mandatory. Standard care for patients with chronic liver disease involves avoidance of hepatotoxic drugs (https://livertox.nlm.nih.gov/php/searchchem.php) and alcohol, vaccination against hepatitis A and B, and in the case of cirrhosis, surveillance for the development of hepatocellular carcinoma.[4] In cases of cholestasis, supplementation of fat-soluble vitamins (mainly vitamins K, D, and E) is necessary and MCT fats can increase caloric uptake. Decreased intake secondary to organomegaly can be alleviated with frequent feeding.[4]

Hypocholesterolemia is a common feature in many CDG but the exact mechanism is still not fully understood.[26] Conversely, in CCDC115-CDG, ATP6VAP1-CDG, and TMEM199-CDG hypercholesterolemia is common.[27] There is no disorder-specific management of lipid abnormalities in CDG.

Specific treatments in liver disease in CDG include mannose therapy in MPI-CDG; however this does not prevent progression to cirrhosis in all patients.[9] In PGM1-CDG, treatment with oral galactose has been shown to improve liver transaminases.[28] In a single case, severe cholestatic liver failure was reversed with long-term galactose therapy (Table 2).[7] Liver transplantation has been successfully performed in several patients, including those with MPI-CDG and CCDC115-CDG (Table 1).[25]

### Hematologic involvement

Abnormal glycosylation of coagulation factors and platelet membrane glycoproteins has been associated with an increased risk of thrombotic and bleeding complications in CDG, especially in PMM2-CDG, MPI-CDG, and ALG1-CDG.[29] Hematologic complications in CDG include arterial and venous thrombosis, mucosal and visceral hemorrhage, and stroke-like episodes of unclear etiology. Cases of ischemic stroke, intracranial hemorrhage, and disseminated intravascular coagulation have been described.[29–31] The coagulation abnormalities in CDG are thought to arise from disequilibrium between procoagulant and anticoagulant factors as well as nonspecific or dysfunctional platelet interactions. Abnormally low levels of factors IX and XI, antithrombin, protein C, and protein S are common.[29,32,33] Deficiencies of other factors, including factors II, V, VII, VIII, and X, as well as prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) and elevated D-dimer can also be seen. Interestingly, coagulation parameters often improve and even normalize over time,[20,30] and there is some evidence that improvement in coagulation parameters predicts a lower risk of clotting and bleeding events in adults.[30] Fever, prolonged immobilization, and tissue damage such as from invasive procedures have been associated with thrombotic events. Decreased antithrombin, protein C, and protein S levels are associated with an increased risk of thrombosis; however, the correlation of thrombotic risk with PT, aPTT, and factor IX and XI levels is less clear.[29]

As a general approach at the time of diagnosis and annually thereafter, monitoring of coagulation parameters, including PT; aPTT; factors I, VIII, IX, and XI; antithrombin; protein C; and protein S, is recommended. Coagulation factors should also be measured before any invasive procedure or during a febrile illness. If PT or aPTT is prolonged, factors II, V, VII, and X should also be measured.

Disease-specific treatment is challenging. There is no consensus as to which anticoagulant medications are most effective in preventing or treating thrombosis in patients with CDG. Primary prophylaxis of thrombosis is not recommended due to the concomitant risk of bleeding, although low-dose aspirin has been suggested for patients with a history of arterial thrombosis.[30] Avoidance of triggering factors such as elective surgeries and oral contraceptives, when feasible, or adequate hydration and early mobilization after invasive procedures have been suggested as risk-modifying strategies.[29] Although many CDG patients are antithrombin-deficient, several studies have reported that hypoglycosylation of antithrombin increases its activity and affinity for heparin,[34,35] and both unfractionated and low–molecular weight heparin have been used effectively in treating thrombosis in CDG.[36] Factor Xa inhibitors are a reasonable alternative to heparin, as rivaroxaban has been used successfully to treat thrombosis in a CDG patient.[37] Vitamin K antagonists (i.e., warfarin) have been used for secondary prophylaxis of venous thrombosis.[36]

Fresh frozen plasma (FFP) has been used, as in other disorders with bleeding diatheses, to prevent bleeding episodes in CDG. This therapy has been shown to improve capillary leakage and edema as well in severe patients, especially during infections (personal communication).

Oral mannose therapy is effective in normalizing coagulation abnormalities in MPI-CDG,[21,38,39] and preventing both bleeding[21] and thrombosis.[39] A case of liver transplantation in MPI-CDG also demonstrated resolution of coagulopathy after transplant.[23] Improvement of coagulation parameters with oral galactose has been observed in PGM1-CDG[28,40] and TMEM165-CDG.[40]

## Endocrine involvement

Patients with CDG suffer from derangements in multiple endocrine pathways, including those involved in growth, thyroid function, glucose metabolism, and sexual development.[41] Growth failure is a common feature of most CDG and results from poor nutrition and/or dysfunction of the growth hormone/insulin-like growth factor 1 cascade. CDG patients are often growth hormone–resistant, as evidenced by low normal to increased serum levels of growth hormone (GH) but decreased levels of insulin-like growth factor 1 (IGF-1). Insulin-like growth factor binding protein 3 (IGFBP-3) levels are frequently decreased due to increased clearance of hypoglycosylated forms.[42] Elevated thyroid-stimulating hormone (TSH) levels can be found in young patients due to receptor glycosylation defects but in in several cases it was reported not to be associated with clinically significant hypothyroidism.[4] Thyroid-binding globulin (TBG) and total T4 levels are often decreased in CDG, although patients have normal levels of thyroid-stimulating hormone (TSH), free T4 (FT4), and T3 and are clinically euthyroid.[4] Hypoglycemia, often associated with hyperinsulinism or adrenal insufficiency (adrenocorticotropic hormone [ACTH] is glycosylated) may present

with lethargy, vomiting, or seizures.[22,43,44] Abnormal pubertal development, amenorrhea, and hypergonadotropic hypogonadism with elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) but low estradiol are also common in females with CDG. Pubertal abnormalities are less common in males, although small testes, elevated FSH, and cryptorchidism have been reported.[4,41]

As a general rule growth parameters should be monitored at every visit. Serum IGF-1 and IGFBP-3 levels should be obtained at the time of diagnosis and repeated if growth failure develops. Recombinant IGF-1 therapy has been used in one patient with PMM2-CDG with excellent growth response.[45] Serum levels of TSH, FT4, and TBG should be measured at diagnosis and annually thereafter. While elevated levels of TSH are common, hypothyroidism in CDG should only be treated with levothyroxine in the presence of decreased FT4. If patients present with hypoglycemia, measurement of serum insulin, cortisol, growth hormone, lactic acid, ammonia, β-hydroxybutyrate, free fatty acids, and urinary ketones is recommended. Frequent meals with complex carbohydrates and continuous or nocturnal tube feeding can be considered.[2] Hyperinsulinemic hypoglycemia is responsive to diazoxide treatment, although some patients have worsening edema, and one patient subsequently required subtotal pancreatectomy due to severe hyponatremia.[46] Patients should be closely followed for signs of pubertal development, and at the onset of puberty, Tanner stage, growth parameters, and bone age should be evaluated. Serum FSH, LH, and estradiol levels in females and testosterone and steroid hormone-binding globulin (SHBG) levels in males should be measured at this time. Hormone replacement therapy with low-dose estradiol or testosterone can be considered for patients with delayed puberty and have not been associated with an increased risk of thrombosis.

With respect to disease-specific therapies oral mannose therapy in MPI-CDG results in improvement in growth velocity and hypoglycemia.[19,22,47] Galactose supplementation improves hypogonadotropic hypogonadism and hypoglycemia in PGM1-CDG,[28,48] and levels of IGF-1 and IGFBP-3 in TMEM165-CDG.[40]

## Infections and immunologic involvement

Glycosylation is required for normal function of cell-surface receptors, antibodies, and other critical components of the innate and adaptive immune systems.[49] Immune involvement is a prominent feature of several CDG, notably ALG12-CDG, MAGT1-CDG, MOGS-CDG, PGM3-CDG, ATP6AP1-CDG/ATP6AP2-CDG, and SLC35C1-CDG.[50] The typical presentation is with immune deficiency, including frequent or severe infections (bacterial, viral, fungal) and inadequate antibody response to vaccination.[51] Sinopulmonary, gastrointestinal, and skin infections are common. In addition, PGM3-CDG often presents with a hyper-IgE phenotype characterized by atopy and autoimmunity.[52–55] Abnormal leukocyte counts (neutrophilia or neutropenia, lymphopenia) and low immunoglobulin levels (primarily IgA and IgG) are the most common laboratory abnormalities. Hypogammaglobulinemia has been attributed to a combination of decreased production due to B-cell dysfunction, faster clearance due to hypoglycosylation, or loss due to nephrotic syndrome or protein-losing enteropathy.[49,50] Infections in the abovementioned CDG types are most severe in early childhood and improve over time.

The general recommendation is that if there is a history of recurrent or severe infections, leukocyte count with differential (including neutrophils, B- and T-lymphocytes, and natural killer cells) and serum immunoglobulin levels (including IgA, IgG, and IgM) should be measured at the time of diagnosis and repeated during episodes of acute infection.[4] In the absence of contraindications, age-appropriate vaccination is recommended,[56] and antibody titers should be measured after vaccination to evaluate for response. Infections should be treated with appropriate antibiotics and patients should be monitored carefully during therapy due to the increased risk of complications such as sepsis. Intravenous immunoglobulin administration has been shown to improve recurrent infections. Prophylactic or suppressive antibiotics can also be considered.[4]

Disease-specific therapy is available for SLC35C1-CDG, where oral fucose can improve recurrent infections and in a few cases normalized neutrophil counts.[14–17] However, one patient subsequently developed autoimmune neutropenia.[15] Oral magnesium supplementation in MAGT1-CDG can improve the persistent Epstein–Barr viremia characteristic of this disorder and may reduce the risk of EBV-associated lymphoid malignancy.[57] One patient with SLC35A1-CDG (Golgi sialic transporter defect) underwent bone marrow transplant but subsequently died from complications of the procedure, including graft-versus-host disease and pulmonary hemorrhage.[58] Severe combined immunodeficiency in PGM3-CDG has been successfully treated with hematopoietic stem cell transplant.[49,54]

## CURRENT AND FUTURE TREATMENT OPTIONS

Most of the currently available treatment options in CDG are symptomatic, and curative therapies are a significant unmet need. A few emerging therapy options exist with promising preliminary results, which are listed below. Several new therapeutic approaches are under preclinical investigation, of which activated sugars, pharmacological chaperones, and gene therapy hold greatest promise for future application.

### Nutritional therapies

Oral supplementation of high doses of mannose (Man) in MPI-CDG represents the oldest successful CDG treatment.[21,39,59] Currently, dietary supplementation is still one of the most widely applied therapies for CDG (Table 1). Dietary supplementation benefits from relatively high safety, low cost of compounds, and ease of supplementation. Supplementation compounds could theoretically also include activated sugars, nucleotide sugars, in addition to monosaccharides and trace elements.

The therapeutic strategy in sugar supplementation is to provide exogenous monosaccharides to circumvent the disruption of glycosylation through recruitment of complementary mechanisms or upregulation of affected pathways (Fig. 2).

In MPI-CDG, supplementation of Man provides increased substrate for hexokinase, which phosphorylates the exogenous Man to mannose-6-phosphate. This bypasses the enzymatic defect in MPI-CDG, which under normal conditions converts fructose-6-phosphate to mannose-6-phosphate. Man supplementation in MPI-CDG restores endocrine function

and coagulation and alleviates enteropathy, but does not always rescue progressive hepatic involvement.[38] In addition, during high dose of Man intake there are potential gastrointestinal and hematologic side effects.[23,38]

SLC35C1-CDG is characterized by disrupted import of GDP-fucose into the Golgi due to decreased SLC35C1 enzymatic activity. Fucose supplementation in SLC35C1-CDG is able to facilitate fucosylation in the Golgi. A potential mechanism could act though import of GDP-fucose into the Golgi through upregulation of the GDP-fucose transporter with diminished but not absent activity by increased exogenous fucose availability. Fucose supplementation in SLC35C1-CDG decreased infection rates, improved expression of E- and P-selectin ligands, and restored neutrophil numbers in three of five patients.[14–16] It improved psychomotor development in two additional milder cases, carrying the *SLC35A1* p.F168del variant, associated with minimal immune deficiency and delayed growth and development (Table 2).[17] Fucose therapy in SLC35C1-CDG should be monitored carefully due to the risk of autoimmune and hemolytic reactions.[15]

Galactose (Gal) supplementation shows beneficial effects in two pilot studies in PGM1-CDG, and promising results in SLC35A2-CDG, SLC39A8-CDG, and TMEM165-CDG with clinical effect in single cases or small case studies (Table 2).[9] Gal supplementation has been investigated extensively in treatment of PGM1-CDG.[7,28,60] PGM1-CDG is characterized by disrupted interconversion of glucose-1-P to glucose-6-P. Gal supplementation has been shown to rewire sugar metabolism in vitro, restoring levels of the activated sugars UDP-glucose and UDP-galactose and increasing incorporation of exogenous Gal into newly formed N-glycans. Gal supplementation in vitro restored endoplasmic reticulum (ER) glycan synthesis and galactosylation.[5] Clinically, patients show improved glycosylation, endocrine function, and coagulation without adverse effects. Cosupplement with uridine with Gal is further being explored for CAD-CDG and SLC35A2-CDG.[2]

## Transplantation

Organ and stem cell transplantation have been applied as a treatment option in cases of severe and progressive cardiac and hepatic involvement.

Successful liver transplantation has been performed in MPI-CDG patients supplemented with Man.[23] Liver transplant has been performed with varying success rates in CCDC115-CDG and ATP6AP1-CDG.[61,62]

Heart transplantation could be considered as a treatment option in CDG with cardiac involvement. Successful heart transplantation has been performed for several DOLK-CDG patients.[63,64]

Hematopoietic stem cell transplantation has been successfully performed as treatment for CDG presenting with immunodeficiency. Engraftment of cord blood and bone marrow stem cells in three PGM3-CDG patients showed alleviation of immune involvement.[54]

## Enzyme therapy

Direct supplementation of the deficient enzyme has been a successful therapeutic approach in another group of inborn errors of metabolism with multisystemic involvement, the lysosomal storage disorders. Although nonlysosomal enzyme therapy is theoretically possible in PMM2-CDG,[65] several difficulties limit the application of enzyme replacement as a feasible treatment in CDG. Of these, cell compartmental targeting, low levels of replaced enzyme, cellular uptake of the supplemented enzyme, and delivery across the blood–brain barrier remain most problematic. Even if an enzyme crosses the blood–brain barrier, and gets into the right cells, it would only affect current glycosylation-dependent cell functions and may or may not affect development.

## Pharmacological chaperones

Pharmacological chaperones (PCs) are small molecules that bind directly to the mutated protein. PCs enhance protein conformation through sequestering proteins toward ER and Golgi compartments for correct protein folding and glycosylation. PCs are effective in the rescue of enzymatic function in proteins harboring pathogenic missense variants disrupting protein folding and conformation. Since most patients are compound heterozygotes, it is difficult to predict individual outcome. Frameshift and premature stop codon variants resulting in a complete loss of mutant protein translation do not represent targets for PCs. PCs show promise as therapy in PMM2-CDG. In PMM2, up to 80% of patients harbor a pathogenic missense variant, most commonly the p.R141H variant.[66] Pathogenicity assessment of several *PMM2* missense variants showed reduced protein stability as the causative mechanism for loss of function.[67] High-throughput screening of missense loss-of-function variants in *PMM2* identified several chaperone candidates that improve PMM2 stability.[68] Recently, a clinical trial on oral acetazolamide therapy in PMM2-CDG patients presenting with neurologic involvement showed improvement of clinical severity, motor cerebellar involvement, and coagulation.[10] Transfer of the therapeutic agent through the blood–brain barrier is essential for treatment of neurologic involvement in CDG. PCs have been shown to travel across the blood–brain barrier and hold promise for alleviating central nervous system involvement, including Gaucher and Fabry disease.[69] However, there is no convincing evidence the central nervous system/development issues are alleviated.

Another class of small chaperone molecules, proteostasis regulators (PRs), enhance enzymatic activity of enzymes by regulating proteostasis to support proper protein folding and prevention of protein aggregation.[70]

## Other approaches

Acetazolamide is a carbonic anhydrase that lowers plasma pH and increases intracellular $Ca^{2+}$ availability. Acetazolamide shows efficacy in treating SLEs in *CACNA1A* familial hemiplegic migraine.[10,71] Remarkably, in PMM2 patients, coagulation parameters show improvement in addition to neurologic involvement. Enzymatic activity of PMM2 is dependent on $Ca^{2+}$ binding. Whether the observed coagulation improvement is related to rescue of PMM2 activity, putatively through increased PMM2-$Ca^{2+}$ binding, remains elusive as PMM2 enzyme activity assays were not performed.

### Activated sugar compounds

Most preclinical studies involve different molecular forms and different delivery forms of mannose-1-phosphate in PMM2-CDG. Mannose-1-phosphate is a very unstable molecule. Liposomal targeting could be an option for efficient liver targeting of the active compound; however, it is technically difficult to target Man-1-P to liposomes. Another alternative is to be used encapsuled in a larger complex molecule (in a molecular “protective coat”), but it might be too large for efficient cellular uptake. Future trials should focus on molecular stability and targeting the compounds to the cytoplasmic side of the endoplasmic reticulum. At this point none of these compounds are yet in clinical trials.

### Gene therapy

Gene therapy approaches exploit the monogenic nature of CDG by aiming to restore the wild-type sequence of the mutated gene through transgene introduction. Adeno-associated virus (AAV) vectors represent a major mechanism for in vivo gene therapy. AAVs are thought to be a relatively safe and efficient technology applicable to a wide range of target tissues, although AAV immune responses are observed in human.[72] AAV therapy in CDG has been limited to GNE-CDG in mice[73] and human primary muscle cells,[74] where AAV therapy resulted in coexpression of wild-type and mutated GNE transcripts.

Nonviral transgene delivery methods include zinc-finger nucleases, TALENs, and CRISPR/Cas9 technology. Although these methods have potential for highly efficient gene therapy treatment, no clinical trials have been performed in CDG yet. Promising preclinical results have been obtained for zinc-finger nucleases, where restoration of deficient enzymes in lysosomal storage disorders was shown in mice.[75] The application of targeted genome editing in CDG is expected to increase in the near future.

Antisense therapy is aimed at restoration of transcript splicing when disrupted by pathogenic splice variants. Proof-of-concept antisense therapy has been performed in vitro in PMM2-CDG patient-derived cells. Morpholino oligonucleotides delivered in vitro rescued aberrant splicing in PMM2-CDG patient fibroblasts.[76] Antisense therapy shows promise in TMEM165-CDG, where a deep intronic insertion resulted in transcription of a pseudo-exon. TMEM165 antisense morpholino oligonucleotide therapy resulted in skipping of the pseudo-exon and restored expression of the normal protein in patient fibroblasts.[77]

## CONCLUSIONS

We reviewed current literature on therapeutic strategies for disorders involving N-linked glycosylation. Here we suggest CDG-specific therapeutic strategies for treatment of neurologic involvement, gastrointestinal involvement, hepatic involvement, hematologic involvement, endocrine involvement, infections and immune involvement.

Unfortunately there are no systematic data on the natural course of this growing group of orphan disorders, to better understand the biochemical pathomechanisms and learn natural outcome, necessitating natural history studies. Most of our therapeutic experience is based on individual cases, not on clinical trials, which makes it difficult to give evidence-based

recommendations, except for MPI-CDG and PGM1-CDG. Small cohorts make future trials even more challenging.

Effective therapies are currently limited to dietary interventions and organ transplantation. Fortunately, preclinical investigations indicate great therapeutic potential for activated sugar compounds, pharmacological chaperones, and gene therapy. Based on the biochemical background it is expected that these treatment options will become available for therapy in the coming years and expand our therapeutic approach in disorders involving N-linked glycosylation.

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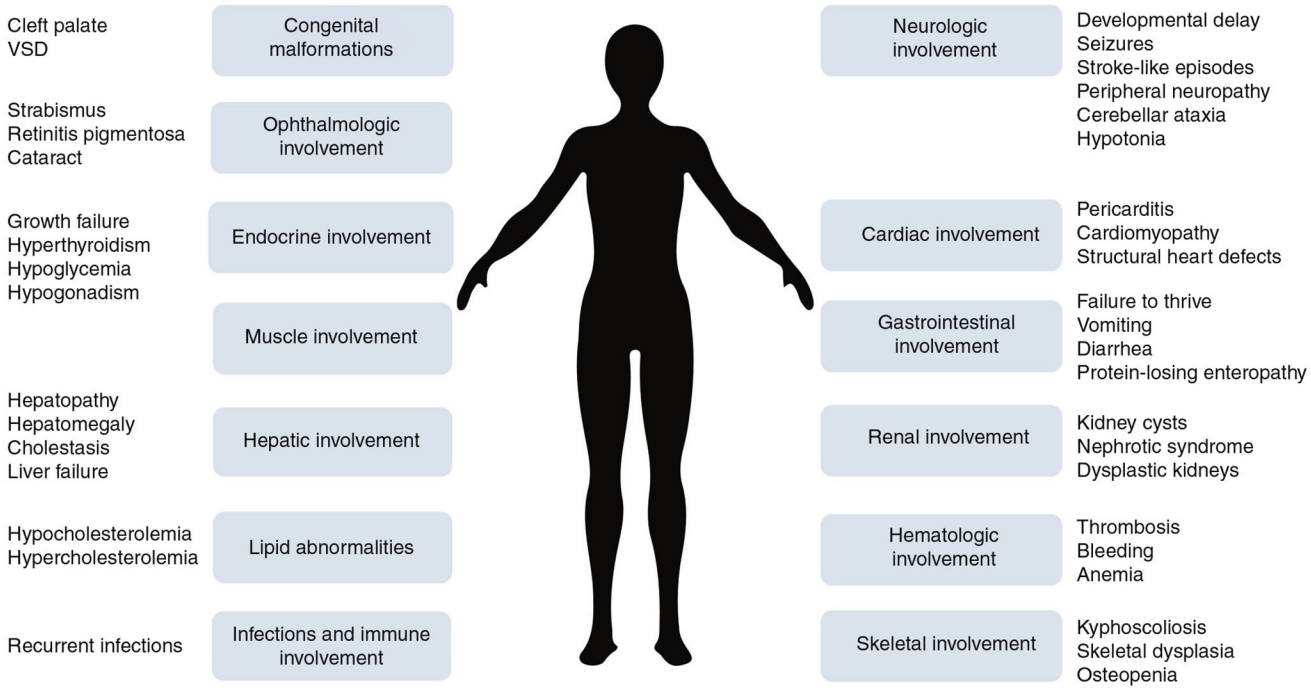


**Fig. 1. Overview of involved organ systems in disorders of N-linked glycosylation for which therapies are available.**

Affected systems are depicted with common involvement in congenital disorders of glycosylation (CDG). *VSD* ventricular septal defect.

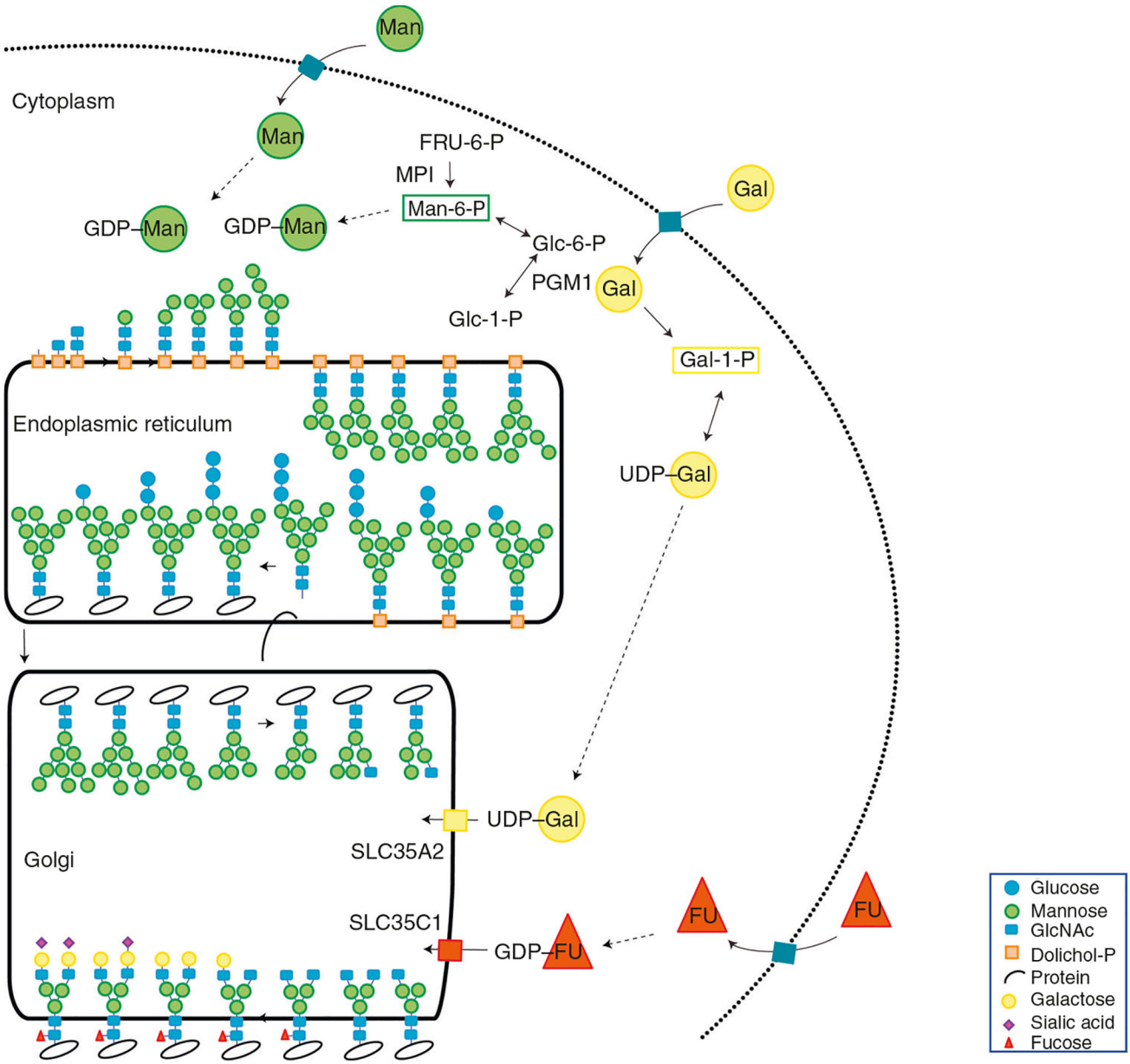


**Fig. 2. Therapeutic mechanisms of monosaccharide supplementation in N-linked glycosylation.**

Man supplementation in MPI-CDG bypasses disrupted MPI enzyme activity by providing exogenous Man for synthesis of mannose-6-phosphate, which is ultimately converted to GDP-Man and incorporated into the growing N-glycans on the endoplasmic reticulum (ER) membrane. Gal supplementation in PGM1-CDG restores levels of activated sugar UDP-GLU and UDP-Gal for incorporation into N-glycans in the Golgi, effectively redirecting cellular sugar metabolism to PGM1-independent pathways. Fucose supplementation in SLC35C1-CDG increases fucose availability in the Golgi (54).

**Table 1**

Successful treatment strategies in N-linked glycosylation CDG

| Therapy | Compound | CDG subtype | Main findings | Reference |
|---|---|---|---|---|
| Monosaccharide supplementation | Mannose | MPI-CDG | Restored endocrine function, coagulation, and alleviated enteropathy, but does not rescue progressive hepatic involvement | 19,21,22,39,59 |
| | Galactose | PGM1-CDG | Improved endocrine function, liver transaminases, and coagulation | 7,28,60 |
| | | SLC35A2-CDG | Restored glycosylation, improved seizure control | 18 |
| | | SLC39A8-CDG | Restored glycosylation, improved seizure control | 12 |
| | | TMEM165-CDG | Restored glycosylation and coagulation | 40 |
| | Fucose | SLC35C1-CDG | Decreased infection rates, increased psychomotor capabilities and restoration of E- and P-selectin ligands and neutrophil numbers | 14–17 |
| Dietary intervention | Uridine | SLC39A8-CDG | Improved seizure control | 13 |
| | | CAD-CDG | Improved seizure control | 19 |
| | Manganese | SLC39A8-CDG | Improved seizure control | 13 |
| | Ketogenic diet | PIGA-CDG | Improved seizure control | 78 |
| Transplantation | | | | |
| | Heart | DOLK-CDG | Rescued cardiomyopathy | 63,64 |
| | Liver | MPI-CDG | Rescued exercise tolerance, pulmonary functions, and metabolic parameters | 23 |
| | | CCDC115-CDG | Restored aminotransferase and glycosylation | 62 |
| | Hematopoietic stem cells | PGM3-CDG | Reduced immune involvement | 54 |
| Pharmacological chaperones | | | | |
| | Multiple chaperone compounds | PMM2-CDG | Improved PMM2 protein stability | 68 |
| Other | | | | |
| | Acetazolamide | PMM2-CDG | Improved clinical severity, motor cerebellar involvement, and coagulation | 10 |
| Gene therapy | | | | |
| | Adeno-associated virus (AAV) | GNE-CDG in vitro muscle cells | | |
| In vitro muscle cells | Wild-type and altered GNE transcript due to pathogenic variant coexpression | 74 | | |
| | Morpholino oligonucleotides | PMM2-CDG in vitro fibroblasts | Rescue of aberrant transcript splicing | 76 |
| | | TMEM165-CDG in vitro fibroblasts | Restored expression of wild-type protein | 77 |

Successful application of monosaccharide supplementation, dietary intervention, transplantation, molecular chaperones, and gene therapy has been described for several CDG. *CDG* congenital disorders of glycosylation.

**Table 2**

Nutritional therapies and the therapeutic success rate according to case studies and pilot studies

| Disorder | Biochemical background | Estimated number (reported patients) | Therapy | Reported patients on therapy | Clinical outcome | Reference for successful cases |
|---|---|---|---|---|---|---|
| MPI-CDG (MIM 602579) | Interconversion of fructose-6-P (Fru-6-P) and mannose-6-P (Man-6-P)CDG type 1 | 35 | Mannose 200 mg/kg/dose oral 4–6 times a day | 12 | 12/12 Positive effect on multisystem disease (2 patients had side effects; hemolysis) | [19,21,22,39,59] |
| PMM2-CDG (MIM 212065) | Converts Man-6-P to mannose-1-phosphate (Man-l-P) CDG type 1 | 980 | Mannose 200 mg/kg/dose oral 4 times a day | 3 | No positive effect has been confirmed in vivo | [79–81] |
| PGM1-CDG (MIM 614921) | Conversion of glucose-1-phosphate (Glc-1-P) to glucose-6-phosphate (Glc-6-P) CDG type 1/2 | 50 | D-Galactose 1 g/kg/day oral | 20 | 19/20 Positive effect on multisystem disease (17 patients were prospectively trialed in clinical pilot study) | [7,28,60] |
| SLC35C1-CDG (MIM 266265) | GDP-fucose transmembrane transporter to Golgi CDG type 2 | 10 | Fucose oral in variable doses from 50 mg/kg to 200 mg/kg 4 times a day | 8 | 5/8 Positive effect on immune disease (2 patients had only developmental improvement) | [14–17] |
| SLC35A2-CDG (MIM 300896) | Golgi UDP-Gal transport CDG type 2 | 40 | Galactose 1 g/kg/day, oral | 1 | 1/1 Improvement of seizure control | [18] |
| TMEM165-CDG (MIM 614727) | Golgi function regulator CDG type 2 | 3 | Galactose 1 g/kg/day oral | 2 | 2/2 Improvement of liver function and endocrine function | [40] |
| SLC39A8-CDG (MIM 616721) | Golgi manganese transporter CDG type 2 | 20 | Galactose 1 g/kg/day, manganese individualized dose | 2 | 2/2 Intractable seizures improved significantly | [12,13] |
| CAD-CDG (MIM 616457) | Catalyzes the first steps of de novo pyrimidine biosynthesis for nucleotide sugars | 5 | Uridine 100 mg/kg per day oral 4 times a day | 2 | 2/2 Positive effect: patients became rapidly seizure-free | [19] |

*CDG* congenital disorders of glycosylation.