REVIEW

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# Endocrine Implications of Congenital Disorders of Glycosylation

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## ABSTRACT

Glycosylation, attachment of monosaccharides or glycans to specific residues of proteins and lipids, is the most common post-translational modification. Defects among glycoprotein synthesis or modification pathways result in a genetically and clinically heterogenous group of metabolic disorders, congenital disorders of glycosylation (CDGs) with an estimated prevalence of 1/10,000. CDGs have multisystem involvement in which significant neurological dysfunction is frequent, with variable impairment of other organ functions. Most of the proteins responsible for endocrine homeostasis are essentially glycoproteins so disorders of glycosylation have an impact on hormone secretory pathways, changing hormone and carrier protein stability, circulatory half-live and abundance, alternating receptor configuration, activation, hormone-substrate affinity, and resetting endocrine control and feedback loops. Endocrine implications of CDGs are extensive and are described in up to 55% of all patients with CDGs during the natural course of the disease. This frequency is increased up to 85% in some CDG subgroups. Impacts on growth and growth factors, thyroid hormones, hypothalamo-pituitary-adrenal axis, hypothalamo-pituitary-gonadal axis, glucose metabolism, bone health and prolactin have been reported, yet clinical studies are scarce, with data mostly derived from case series. The aim of this review is to describe the current understanding of the endocrine implications of CDGs, focusing on both preclinical and clinical studies, highlighting the broad spectrum of findings. Clinical and laboratory findings of CDGs and the effect of current treatment strategies on endocrine function will be briefly discussed.

**Keywords:** Congenital disorders of glycosylation, endocrine, growth, bone, thyroid, adrenal, hypogonadism

## Introduction

Glycosylation is the covalent attachment of monosaccharides or glycans (polysaccharides) to selected residues of target proteins and lipids, occurring in diverse subcellular locations but mostly within the endoplasmic reticulum and Golgi apparatus (1). Glycosylation is the most common post-translational modification of proteins. Its biological role is essential for normal protein maturation and function, ensuring maintenance of protein solubility, proper protein folding and conformation, which in turn maintains tissue structure, integrity and porosity (2,3). In addition, glycosylation of proteins controls leukocyte, extracellular and intracellular trafficking, protease resistance, cell-substrate and cell-cell interactions, and growth regulation (4). Therefore, glycosylation is central to normal development, growth, and functioning of the organism.

Defects among glycoprotein synthesis or modification pathways result in a genetically and clinically heterogenous group of metabolic disorders, known as congenital disorders of glycosylation (CDGs)

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(5). After the initial report in 1980, the clinical and biochemical features as well as the natural course of CDGs were identified in 1991. Initially, solely associated with phosphomannomutase deficiency, this was called "carbohydrate deficient syndrome" in 1997 (6). Advances in biochemical testing and exome sequencing enabled discovery of new forms and today, more than 130 separate CDGs have been described (7,8). Most of these monogenic diseases are autosomal recessive (AR) in inheritance, however autosomal dominant (AD) and X-linked forms have also been described (9).

CDGs exhibit multisystem involvement, usually with significant neurologic dysfunction in addition to variable impairment of other organ functions. There have been reports of cardiovascular, gastroenterological, renal, hematological, immunological, ophthalmological, and lipid metabolism impairments, as well as endocrinopathy. Since proteins involved in endocrine homeostasis are essentially glycoproteins, reports of endocrine symptoms are common. Alterations in glycosylation have an impact on hormone secretory pathways, modulating circulatory half-lives, changed stability, carrier protein availability and binding, alternating receptor configuration, binding, and activation, dysregulation of autocrine and paracrine actions, and resetting of endocrine control and feedback loops (10). Endocrine findings make up 5-7% of symptoms at presentation with hypoglycemia being the most common, reported in 7% of CDGs. Endocrine changes are diverse and are described in up to 55% of all patients with CDGs (n=280) during the natural course of the disease. This frequency is increased up to 85% in some CDG subgroups. In a recent natural history study, findings regarding virtually every endocrine axis have been described. Alterations in thyroid and adrenal function, growth, sexual development and bone and glucose metabolism have been reported (4).

In this review we will briefly address clinical and laboratory findings of CDGs, then focus on endocrine system involvement, highlighting the broad spectrum of findings. In addition, the effect of current treatment strategies on endocrine function will be discussed.

## Epidemiology

The incidence and prevalence of all types of CDG is not well established, since some forms are quite rare. Globally, reports of CDGs from practically every ethnic group have been made and both sexes are equally affected (9). The estimated prevalence in European and African-American populations is 1/10,000 (11,12,13). The prevalence of the most common CDG, PMM2-CDG ranges from 1/20,000 in Dutch populations to 1/77,000 in Estonia based on isolated reports (9). However, to date, fewer than 100 cases have been reported for most CDG types (9).

## Biochemical Classification, and Nomenclature

Historically, CDGs were classified by patterns of transferrin isoform analysis. Currently CDGs are classified into four groups: (I) *N*-linked glycosylation; (II) O-linked glycosylation; (III) combined N- and O-linked/multiple glycosylation; and (IV) lipid and glycosylphosphatidylinositol anchor biosynthesis defects (9).

CDG nomenclature was revised in 2008 to reflect molecular etiology considering the developments in molecular diagnostics. Currently, CDG nomenclature is denoted by the name of the affected gene, followed by-CDG (e.g. *PMM2-CDG*) (14).

## Inheritance

The majority of CDGs are AR, while a small number of CDGs are AD, including GANAB-CDG, PRKCSH-CDG, EXT1/EXT2-CDG, POFUT1-CDG, and POGLUT1-CDG. A few are known to be X-linked and these are ALG13-CDG, SSR4-CDG, PIGA-CDG, SLC35A2-CDG, and ATP6AP1-CDG. Most dominant and some X-linked forms of CDG are due to *de novo* mutations (9). Genotype-phenotype correlations have been proposed, however, there is significant phenotypic variability, even within the same genotype (15).

## Clinical Findings

Glycosylation is critical in many metabolic pathways, thus, there is considerable clinical heterogeneity in symptoms and findings (4). Age of onset and disease severity is diverse. Neonatal lethal forms, as well as nearly asymptomatic adults have been reported. The most frequent presentation is multi-systemic involvement within the first few years of life. Almost any organ system may be affected, the nervous system is the most frequent system involved (76%) (16,17). Mild to severe psychomotor retardation, hypotonia, cognitive difficulties, epileptic seizures, ataxia, polyneuropathy, and stroke-like events have been reported. Hypoglycemia, and various liver, eye, skin, gastrointestinal, immunological, skeletal, and coagulation disorders, are commonly noted. Nearly all patients experience feeding difficulties and failure to thrive (9,17,18,19).

The most common form, PMM2-CDG, causes neurologic symptoms with intellectual disability affecting 96% of patients, cerebellar ataxia and atrophy in 96%, hypotonia in 92% and peripheral neuropathy in 53%. PMM2-CDG has also been reported to involve cardiac (pericardial effusion in72% and cardiomyopathy in 25%) and gastrointestinal systems, with failure to thrive in 67%, hepatomegaly in between 18-100% of patients and hepatopathy again ranging widely from 12.5 to 100%. Thoracic deformities (84%) and kyphoscoliosis (53%), typical dysmorphia [inverted nipples (53%) and lipodystrophy (47%)], coagulopathy and recurrent infections (39%) have also been reported. Adults show stable neurologic findings, but kyphoscoliosis and osteoporosis are progressive (20,21,22,23).

Some CDGs affect only a single organ system. These include the retina in DHDDS-CDG; neuromuscular junction in ALG2-CDG, ALG14-CDG, CFPT1-CDG; brain in ST3GAL3-CDG, TUSC3-CDG; skin

or skeletal muscle in POGLUT1-CDG, POFUT1-CDG; cartilage in EXT1/EXT2-CDG; liver in TMEM199-CDG; and red blood cells in SEC23B-CDG (9). Clinical manifestations of CDGs are summarized in Table 1, in addition to endocrine manifestations.

Since many CDG subtypes are rare, the complete phenotype is still unclear. Therefore, in cases of multi-systemic disease, CDGs should be considered, particularly when there is developmental delay of unclear etiology. With a greater understanding of this subset of complex disorders, CDGs have become more frequently recognized in people with unexplained symptoms involving more than one system.

## Diagnosis

Serum carbohydrate deficient transferrin analysis is the first-line screening test in patients suspected of CDG (9). This diagnostic test is performed by isoelectric focusing or capillary electrophoresis, gas chromatography/mass spectrometry, capillary electrophoresis/electrospray ionization/mass spectrometry or matrix-assisted laser desorption ionization/mass spectrometry to determine the presence and number of incomplete sialylated *N*-linked oligosaccharide residues linked to serum transferrin (24). Second-line tests include dolichol-linked glycan analysis and genetic testing, either by single gene, *CDG* gene panel or whole exome/whole genome sequencing.

Novel approaches studying whole plasma/serum N-glycome by various mass spectrophotometric techniques may identify defects on glycoproteins other than transferrin, which is especially useful in some CDGs characterized by normal transferrin profiles. Moreover, metabolomics and metallomics offer exciting prospects in both clinical practice (biomarkers for precision diagnostics, disease follow-up, treatment management) and in research (better understanding of the role of actors in glycosylation, application to the development of novel pharmacological agents) areas (25). Early and specific diagnosis of CDG subtype is imperative as there is a possibility of specific pharmacological treatment in some forms (8,9,26).

## Endocrine Implications

In the initial report, most striking features involved the endocrine system. In 1980, Jaeken et al. (7) described identical twin-sisters with familial psychomotor retardation and endocrine findings proposing that these findings may be a part of a new syndrome. Born at 36 weeks with normal birthweight, the twins presented at two years of age with marked psychomotor retardation and a bone-age of one year. Physical examination and anthropometric measures were normal. Repeated investigations revealed markedly fluctuating serum prolactin (PRL), follicle stimulating hormone (FSH) and growth hormone (GH) levels, partial thyroxine binding globulin (TBG) deficiency, increased serum arylsulphatase A and increased cerebrospinal fluid protein, which were also present in the father (7). Since this initial report, findings in patients with CDGs have reported changes in virtually every endocrine axis. These CDG-associated alterations in endocrine systems are discussed in detail below.

### Implications of CDG for Growth and Growth Factors

Growth rate of the initially described twin sisters were normal but later studies demonstrated growth failure in different CDG types due to a variety of reasons. Babovic-Vuksanovic et al. (27) reported a 30-month-old girl who presented with recurrent severe and persistent hypoglycemia, and who developed feeding difficulties, protein losing enteropathy and short stature (3$^{rd}$ percentile). She was diagnosed with MPI-CDG. Following specific treatment with mannose for six months, she exhibited catch-up growth (43$^{rd}$ percentile) (4,27). A similar patient with MPI-CDG whose anthropometric measures were at the 2$^{nd}$ percentile on admission, was reported by Hendriks et al. (28). Catch-up growth was attained after mannose treatment (25$^{th}$ percentile) (28). In a case reported by Miller et al. (29), a child with PMM2-CDG had severe growth failure, insulin like growth factor-1 (IGF-1) levels were low, and response to IGF-1 generation test was absent, suggestive of GH resistance. Catch-up growth was attained following treatment with recombinant human IGF-1 (29). Alsharhan et al. (5) reported two patients with ALG3-CDG diagnosed with panhypopituitarism [hypothyroidism, GH deficiency, and adrenal insufficiency (AI)]. Response to GH treatment has not been published yet.

Jaeken (30) summarized the natural course of growth in 29 patients with PMM2-CDG. In their study, birth weight, height, and growth rate in the first years of life were normal. Growth rate declined between the second and third years and a successive decline was noted in the following years. After adolescence, disproportionate short stature was observed in all cases, the majority of which were associated with marked skeletal deformities (kyphosis, kyphoscoliosis and vertebral fractures), leg length was normal when assessed (30). Similarly, the largest longitudinal study of children with PMM2-CDG concluded that anthropometric measures were within normal range at birth. Linear growth was restricted in the first six to nine months of life [-2.4 standard deviation score (SDS)]. Although a slight improvement was observed at the end of the second year (mean height -1.8 SDS), this improvement was not sustained and catch-up growth was not observed until 10 years of age. It was suggested that feeding difficulties could both contribute to and serve as the primary cause of severe growth failure (31).

The main determinant of growth early in life is quality and quantity of nutrition while this becomes endocrine regulation after the first two years (32). The GH/IGF cascade being the predominant factor, thyroid, adrenal hormones, and sex steroids regulate growth, differentiation, and metabolism. Circulating

IGFs (IGF-1 and IGF-2) which are GH-dependent, exert pleiotropic effects through activation of IGF receptors (IGF-1R and IGF-2R) and the insulin receptor (IR) signaling cascade (33). It is known that 10-15% of IGFs form binary complexes with IGF-binding proteins (IGFBPs: IGFBP-1, IGFBP-2, IGFBP-4, IGFBP-6) while 80-90% form ternary complexes with IGFBPs (IGFBP-3, IGFBP-5) and acid-labile subunit (ALS) in the circulation. Formation of ternary complex is essential for stability and delivery of IGFs to the target tissues (34,35,36,37). Although IGFs, IGFBP-1 and IGFBP-2 are non-glycosylated, the components of the ternary complex are glycosylated with IGFBP-3 and ALS being N-glycosylated, and IGFBP-5 being O-glycosylated). IGFBP-4 and IGFBP-6 have also been shown to be glycosylated.

Previous *in vitro* studies presented the significance of optimum glycosylation on stability and function of the ternary complex. The number of N-glycosylation sites in ALS was proven to enable IGF1/IGFBP-3/ALS ternary complex formation (38,39,40). Enzymatic hypoglycosylation of ALS in mouse models reduced the affinity of ALS for IGFBP-3/IGF complexes by 50-100% depending on its extent (41). Despite *N*-linked glycans on IGFBP-3 being non-essential for ALS or IGF binding, it was postulated that glycosylation may modulate other biological activities of IGFBP-3, such as extracellular matrix binding (38). Indeed, non-glycosylated IGFBP-3 had a shorter half-life than glycosylated IGFBP-3 when administered to rats (41). In a study conducted on peripheral blood lymphocytes from 12 patients with CDG (patients were grouped according to previous nomenclature), compared to healthy controls, IGF-I levels were normal in CDG type-I and significantly reduced in CDG-II. IGF-1R was significantly reduced in lymphocytes and markedly reduced in carbohydrate content. Selective impairment in IGF-1-induced synthesis of DNA was reported. All patients displayed impaired mitogenic response. Although the study was limited to changes observed in lymphocytes, it was proposed by the authors that the results may be inferred to all tissues (42).

These *in vitro* findings were supported by *in vivo* studies. In a study of 26 patients (12 female and 14 male; 1-20 years of age) with CDG type 1 (7 longitudinally, 19 cross-sectionally) by de Zegher and Jaeken (10) it was reported that basal serum GH concentrations were normally low (GH: <10 mcg/L) in the majority of the boys (13/14) and 13.5 mcg/L in a 2 month-old boy, while basal serum GH concentrations were high in most of the girls (8/12) and extremely high in three girls (basal serum GH of one-month-old, two-month-old and 2-year-old girls were 192, 120 and 144 mcg/L, respectively). Longitudinal assessment of basal serum GH concentrations of three girl with high basal serum GH were documented to be <20 mcg/L within the following six months. Upon glucagon stimulation, biphasic GH hyper-responsiveness was observed in the initially described twin sisters. The same study reported that IGF-1 levels were low during infancy and low-normal during childhood and adolescence (10). Miller et al. (41) compared 12 patients with PMM2-CDG with age matched healthy controls in terms of the GH/IGF-1 axis. The study found that children with PMM2-CDG displayed significantly decreased (~50%) levels of both glycosylated (ALS and *IGFBP3*; 50%) and nonglycosylated (IGF-1 and IGF-2) components of ternary complex compared to controls (41). Reduced ALS glycosylation was shown to result in a neutral shift in the isoelectric point leading to a reduction in the affinity of ALS for IGFBP-3-IGF binary complex. Ternary complex formation was subsequently decreased. In this study, adequate nutrition, and oral mannose treatment in a child with MPI-CDG was shown to partially correct hypoglycosylation of ALS and IGFBP-3, enabling catch-up growth (41).

Growth failure is common in the majority of CDGs. It is likely that in addition to changes in GH/IGF-1 axis, feeding difficulties and nutritional factors as well as concomitant endocrine manifestations (hypothyroidism, AI, hypogonadism) and skeletal features lead to growth failure (Table 1). Management of these accompanying factors will help restore growth rate. Further studies are necessary to determine the extent to which protein hypoglycosylation negatively impacts function and stability of GH/IGF-1 axis, as well as to demonstrate natural growth and efficacy of GH treatment in children with CDG.

## Implications of CDGs for Thyroid Hormones

Normal thyroid hormone biosynthesis starts with iodide uptake from circulation across the basolateral membrane of thyrocyte by the sodium-iodide symporter, which coordinates electrogenic symport of two sodium ions for one iodide ion down an electrochemical gradient generated by the Na+/K+ ATPase. Specific transporters (pendrin and anoctamin-1) then mediate iodide efflux into the follicular lumen. Synthesized by thyrocytes, thyroglobulin is the protein skeleton for thyroid hormone biosynthesis. Iodide is oxidized when hydrogen peroxide is present and incorporated into tyrosyl residues on the surface of thyroglobulin to form monoiodotyrosyl (MIT) and diiodottyrosyl (DIT) (organification). MIT and DIT couple to form thyroid hormones (T4 and triiodothyronine). Thyroid peroxidase (TPO) catalyzes hydrogen peroxide-dependent oxidation, organification and coupling of iodine. DUOX2 (a NADPH-oxidase) and its accessory protein, DUOXA2, are the predominant sources of hydrogen peroxide (43). Thyroglobulin is endocytosed back into thyroid follicular cell then cleaved and thyroid hormones are secreted into circulation. Thyroid hormone biosynthesis is regulated by thyrotropin [thyroid-stimulating hormone (TSH); secreted from the anterior pituitary] and thyroid hormones are carried by TBG albumin and transthyretin in the circulation.

Most of these proteins involved in thyroid hormone biosynthesis, regulation and secretion are essentially glycoproteins, and

glycosylation defects cause significant alterations to thyroid function and/or homeostasis. TBG hypoglycosylation has been shown to reduce the half-life by 15% (20). One of the initially described findings frequently reported in patients with CDG is low levels of TBG (75%) (44,45). Despite a decrease in total thyroid hormone levels, free hormone levels and TSH are reported to be normal (4,46). Although free hormone levels might be low via indirect measurement techniques from time to time, results with direct measurement techniques were normal (43). The most frequently described scenario is euthyroid with low TBG, however, as summarized above, proteins taking part in thyroid hormone biosynthesis, regulation and secretion are glycoproteins, and disorders of glycosylation may result in alterations in thyroid function as well (47). Furthermore, TBG, TPO, pendrin, DUOX2, and DUOXA2, which are essential for thyroid hormone biosynthesis, all achieve proper folding to three-dimensional functional conformation after post-translational modifications consisting of glycosylation (48,49,50,51,52,53,54). TSH was shown to have reduced bioactivity and receptor affinity due to lack of glycosylation (55,56,57). Given this high degree of glycosylation, CDGs may lead to several alterations in thyroid hormone levels, for example low total T4 and TBG with increased TSH which may raise suspicion of hypothyroidism, low free T4 (FT4) that is biochemical hypothyroidism but without clinical hypothyroidism (euthyroid). Clinical assessment of hypothyroidism may be difficult since developmental delay and neurologic findings are also common features of CDGs. However, for optimal development and metabolism, clinical hypothyroidism must be corrected (45).

Clinical hypothyroidism is rare in patients with CDG, however, abnormal thyroid function tests, like decreased TBG are frequently reported, especially in PMM2-CDG (4,46,58). Elevated TSH has been reported, especially during infancy (10,59). A study evaluating thyroid function in 18 patients with PMM2-CDG revealed positive neonatal screening test results in 10, elevated TSH levels in nine, and low FT4 in two. During follow-up, TSH elevation was transient in 3/9 and treatment was not started. Six patients were started on thyroid hormone replacement therapy (HRT) due to multi-organ failure in first few months of life (3/6), persistently elevated TSH during neonatal period (1/6) and elevated TSH accompanied by clinical signs of hypothyroidism such as low calorimetric measurements (decreased resting energy expenditure), low body temperature, constipation, and myxedema (2/6). Apart from the latter two patients with clinical findings of hypothyroidism, the reason for treatment was TSH elevation (60). A review of seven patients with PMM2-CDG, MPI-CDG, or ALG6-CDG reported low levels of serum TBG and T4 concentrations, but normal FT4 and TSH levels. Most of the reported ALG6-CDG patients were euthyroid (46,60). Two patients with MPI-CDG had TBG deficiency with normal TSH and FT4 (61). Alsharhan et al. (5) reported 10 patients with ALG3-CDG, four of which had central hypothyroidism and three required thyroid HRT. Other CDG subtypes with abnormal thyroid assessments include ALG1-CDG and ALG8-CDG (62).

In conclusion, hypoglycolysation of proteins essential for normal thyroid hormone biosynthesis may result in alterations of thyroid hormone and TSH levels. Thyroid function tests of individuals with CDG may be difficult to assess since clinical symptoms of hypothyroidism may be masked or mimicked by other, more severe CDG symptoms, and the diagnosis of hypothyroidism may be complicated (60). In critical circumstances (hypoalbuminemia, sepsis, protein-losing enteropathy, etc.), re-measurements of TSH and FT4 are recommended, and only patients with clinical signs of hypothyroidism should receive thyroid hormone replacement treatment after ruling out euthyroid sick syndrome (5). Long term follow-up for thyroid hormones is not established yet for CDG, but individuals with PMM2-CDG should have their thyroid hormone levels checked every six months, for the first two years of life, and once a year after that, to monitor for hypothyroidism (5). Considering the changes in thyroid hormone biosynthesis, it may be reasonable to generalize this suggestion to all CDGs (Table 2).

## Implications of CDGs for Hypothalamo-Pituitary-Adrenal Axis

The hypothalamo-pituitary-adrenal axis (HPA) has a central role in regulating response to internal and external stressors. The hypothalamic parvocellular nucleus collects and integrates neuronal and humoral inputs to synthesize and secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal system (63). Activation of CRH-receptor 1 via CRH and AVP, initiates synthesis of adrenocorticotropic hormone (ACTH) from proopiomelanocortin. This step is catalyzed by prohormone convertase 1/3 enzyme and ACTH is then released from the anterior pituitary into the circulation (64,65). Upon reaching the adrenal cortex, ACTH binds to melanocortin 2 receptor (MC2R) which in turn stimulates synthesis and release of cortisol (66,67). Cortisol is mainly carried bound to proteins, such as albumin and corticosteroid binding globulin (CBG) in the circulation, and CBG regulates cortisol bioavailability (68). Proteins of the HPA such as CRHR1, MC2R, prohormone convertase 1/3, and CBG are N-glycosylated glycoproteins (69,70). The number and presence of *N*-linked glycosylation sites in the CRHR family were shown to have an important role in ligand binding and signal transduction. Disordered glycosylation could therefore lead to decreased ACTH and cortisol production (71). Furthermore, hypoglycosylation may decrease the steroid-binding capacity of CBG, diminishing total cortisol levels, and resulting in low to normal free cortisol.

The largest series evaluating the effect of CDGs on the HPA stemmed from an international natural course study with

contributions from many centers, observing 139 patients with PMM2-CDG longitudinally for four years with 6-monthly assessments (71). Čechová et al. (71) evaluated adrenal functions of 43 patients (20 girls) with available ACTH and cortisol data. Since cortisol was <5 mcg/dL without an increase in ACTH in 11 patients, central AI was suspected. Two patients were diagnosed with central AI and hydrocortisone was started. One of them was diagnosed during evaluation for hypoglycemia and accompanying GH deficiency as well as central hypothyroidism. Three of the remaining nine patients had normal peak cortisol response to low dose ACTH stimulation test. Despite slightly low response in one patient, hydrocortisone was not started. Low dose ACTH stimulation test was planned in five patients. Primary AI was not suspected in any of the patients (71). Another study described normal serum cortisol levels with diminished serum CBG in a patient with PMM2-CDG. These findings were attributed to loss of CBG due to protein-losing enteropathy (10). Other forms of CDG with reported AI are ALG6-CDG and ALG3-CDG.

In conclusion, glycosylation defects of proteins responsible for regulation of the HPA axis as well as hypoproteinemia due to protein losing enteropathy may lead to AI in patients with CDG. Annual evaluation of morning cortisol and ACTH were recommended in patients with PMM2-CDG. If abnormal, low dose ACTH stimulation test can be performed to evaluate the HPA axis (71) (Table 2).

### Effects of CDG on the Hypothalamo-Pituitary-Gonadal Axis

Hypothalamic gonadotrophin-releasing hormone (GnRH) is the central regulator of synthesis and release of the pituitary gonadotrophins, luteinizing hormone (LH) and FSH which are essential for normal sexual development, maturation, and reproductive function (72). GnRH is synthesized in hypothalamic neurons and is secreted into the hypophyseal portal circulation to act primarily on the anterior pituitary by binding to the GnRH receptor (GnRHR) (73). Variations of GnRH pulsatility (pulse frequency) and amplitude have separate effects on FSH and LH (74). LH and FSH are secreted into peripheral circulation, acting on ovaries or testes to regulate folliculogenesis, ovulation, spermatogenesis, and steroidogenesis. FSH and LH are glycoprotein hormones with similarities in their chemical structures. Variation in glycosylation and glycan composition may lead to considerable heterogeneity in terms of half-life and bioactivity (75). Reduced FSH bioactivity and bioavailability was associated with delayed puberty (10,76). FSH and LH receptors (FSHR and LHR) are also glycosylated proteins. FSHR has more glycosylation sites than LHR and therefore it is presumed that FSHR function is more likely to be affected by impaired glycosylation and may result in hypergonadotropic hypogonadism (77). GnRHR is also a glycosylated protein, whether its glycosylation status has an influence on the pathophysiology of hypogonadism remains to be elucidated.

Impaired glycosylation of LH and FSH in patients with PMM2-CDG results in a variety of changes in the hypothalamo-pituitary-gonad axis. In the initial report of the twin sisters with CDG, fluctuating basal serum gonadotropin levels were described with respect to age. FSH was particularly elevated during infancy (normal, <5 IU/mL) and adolescence (normal, <20 IU/mL) while LH was consistently increased during adolescence (normal, <20 IU/mL). Following GnRH administration, at 2 and 13 years of age, a homogeneous hyper response of FSH and LH (serum levels at 13 years higher than that at 2 years) were noted. When secretory patterns were evaluated by deconvolution analysis of serum profiles during these tests, the serum half-life of LH was extremely long, and FSH bursts were delayed and prolonged. A woman with MPI-CDG and one with ALG6-CDG had normal levels of LH, FSH, and estradiol (61,77,78,79,80).

The effect of CDGs on puberty is variable. Delayed puberty, pubertal arrest, amenorrhea, hypergonadotropic and hypogonadotropic hypogonadism, as well as normal puberty and menstruation have been described (10,20,81). Patients with PMM2-CDG generally had hypergonadotropic hypogonadism (7/8) (30). Pérez-Dueñas et al. (82) followed two patients with PMM2-CDG until adulthood. One had hypergonadotropic hypogonadism while the other (milder phenotype) had a normal menstrual cycle (82). In other reports, 6/6 females with CDG syndrome type I had hypergonadotropic hypogonadism and the ovaries were not detected in 3/6 (76). Hypogonadotropic hypogonadism was described in four adolescent girls (10). Three woman with MPI-CDG developed normal puberty and delivered three healthy children after uncomplicated pregnancies (61,78,79,80). A patient with ALG6-CDG had regular menses with normal hormonal profile (77).

In contrast to females with CDG, males mostly expressed age appropriate secondary sex characteristics and underwent normal pubertal development (76). Some reports have described boys with normal puberty and virilization, but small testes, and low-normal testosterone values (10,76). A study described 2/3 male patients who passed 16 years of age and had normal puberty and secondary sex characteristics (30).

HRT in patients with hypogonadism is critical for initiation and progression of puberty, achieving appropriate body composition, optimum bone health, and increased health related quality of life. However, congenitally deficient or dysfunctional major natural anticoagulants (antithrombin III, protein S, and protein C) in CDGs are associated with life-threatening coagulopathies early in life. Though not always evident at birth, Eklund et al. (83) suggested that it would be prudent to consider CDGs in the category of thrombophilia wherein administrating HRT should be approached with caution. Guidelines for optimum HRT in CDG have not been established. Eklund et al. (83)

selected transdermal estrogen replacement in four patients with hypergonadotropic hypogonadism and PMM2-CDG to mimic physiology. All of them experienced deep vein thrombosis, even though one was on prophylactic anticoagulant therapy (20,83). It was suggested by the study that further research is necessary to determine the best combination of estrogen and anticoagulants, timing of treatment, and duration of primary prophylaxis (83).

### Effects of CDG on Glucose Metabolism

Hypoglycemia was initially described in three patients with MPI-CDG. Hyperinsulinism that responded well to diazoxide was documented (9). Though infrequent, hypoglycemia has been described in other types of CDG. PMM2-CDG is the most common CDG to manifest with hypoglycemia. Vurallı et al. (84) reviewed these cases. Hypoglycemia was reported in 37 (3.4%) of the total of 1,060 patients published. While most of the cases presented with a wide spectrum of multisystem involvement, 24% was admitted solely due to symptoms of hypoglycemia, occurring in the first year or in the early months of life (84). In an MPI-CDG case series, hypoglycemia was present in majority of the patients and classified as a potential presenting sign, however it was rarely isolated. Hypoglycemia mainly manifested during infancy (first hypoglycemia observed from perinatal period to three years of age) with a mean age of 6.8 months (61).

The mechanism by which hypoglycosylation may cause hyperinsulinism in patients with CDG is yet to be explained. Since hyperinsulinemic hypoglycemia (HH) in patients with CDG usually responds well to diazoxide, hyperinsulinemia was suggested to have resulted because of disorders of glycosylation in the ATP-sensitive potassium (KATP) channel of the pancreatic beta cells (84). Physiologically, glucose metabolism alters intracellular the ADP/ATP ratio resulting in insulin secretion. ATP-channel binding induces channel closure, depolarization of the membrane, and activation of voltage-dependent calcium channels, leading to calcium influx, and exocytosis of insulin granules (85). So, KATP channels couple glucose metabolism to membrane electrical activity and insulin release. KATP channels containing four ion channels (Kir6.2) and four regulatory SUR1 receptors control glucose-stimulated release of insulin. Proper glycosylation of SUR1 is required for expression of KATP channels. Change in glycosylation of SUR1 in CDG is presumed to precipitate HH (4,86). Furthermore, insulin exerts its effects upon binding to the IR. The IR consists of two extracellular subunits and two transmembrane subunits which are both glycoproteins. Whether glycosylation (or hypoglycosylation) of IR has a role in HH pathogenesis still needs to be delineated (87).

Out of the 25 cases with hypoglycemia described by Vurallı et al. (84), (36%) were due to HH (9). Though patients responded well to diazoxide, one with permanent HH required pancreatectomy due to treatment side effects (20,84). While patients with transient HH were alive, 4/9 of the cases with permanent HH died (84). The most common cause of hypoglycemia was HH in MPI-CDG (61). Two cases with HH due to MPI-CDG were treated initially with a combination of frequent meals and diazoxide. However, after mannose was started, rapid tapering of diazoxide without recurrent hypoglycemia was possible (27,88). Rapid resolution of hypoglycemia following mannose administration in patients with MPI-CDG supports the notion that glycosylation is required for maintenance of normoglycemia. Other forms of CDG associated with HH are PGM1-CDG and ALG3-CDG (4,89,90). As HH was documented in several patients, one could also speculate that glycosylation is important in the regulation of insulin secretion, possibly via the SUR1 receptor. However, HH was not detected in three of the reported patients with hypoglycemia in another study (91). It should be kept in mind that poor feeding, feeding intolerance, vomiting, diarrhea, and hepatic dysfunction may also contribute to hypoglycemia. Optimization of feeding is advised for better glycemic control (84).

### Skeletal Features and Effects of CDG on Bone Mineral Density

Skeletal abnormalities (kypho/scoliosis, severe spinal cord deformities and vertebral compression fractures), joint laxity or contractures and osteopenia are common in PMM2-CDG (15,92). Usually diagnosed during childhood, these findings effect health related quality of life (20). Fractures are common and appear to heal normally. Fibrillar collagen type I and II, which are initially synthesized as procollagens, are present in tendon, skin, epiphyseal growth plate and hyaline cartilage, making up the extracellular matrix of bone. Post-translational modification of procollagen I and procollagen II results in mature collagen I and II, characterized by a triple helical domain with fibrillar properties. This modification is achieved by N-glycosylation of C-terminal procollagen and subsequent cleavage of the N- and C-terminal propeptide domains. Since mutations of genes encoding type I and II collagen are known to cause skeletal dysplasia, it may be speculated that abnormal N-glycosylation at this step may result in a skeletal phenotype in some CDGs. However, skeletal features of CDGs are variable. This variability has been explained by the hypothesis that skeletal phenotype is a combined result of glycosylation defect and individual polymorphisms in genes responsible for bone and skeletal development (93).

In addition to that, dentin and extracellular matrix of bone contains non-collagenous proteins (osteopontin, bone sialoprotein, dentin matrix protein 1, dentin sialophosphoprotein, and matrix extracellular phosphoglycoprotein) which have a role in inhibition of bone mineralization and regulation of osteoblast activity. Defects in glycosylation will affect function of these glycoproteins, disrupting bone mineralization. Osteopenia as well as exostoses described in some forms of CDG may potentially be a result of the imbalance between bone formation and

resorption because of altered glycosylation of extracellular matrix proteins responsible for remodeling (92). Heparan sulphate, a glycosaminoglycan usually found on cell surface and extracellular matrix, and fibrillin, an extracellular matrix glycoprotein, play an integral role in the structural integrity of various tissues with roles in ligand binding, cell adhesion and cell singling (94,95). Whether hypoglycolysation of glycosaminoglycans and extracellular matrix glycoproteins play a role in the skeletal dysplasia phenotype is a subject worth investigating since the skeletal phenotype of CDGs and mucopolysaccaridoses are different from each other. It is known that bone phenotype in CDGs is multifactorial. Contributing factors are feeding difficulties, malabsorption, hepatic dysfunction, restrictions in movement as well as hypogonadism and short stature (15,93,96).

Skeletal dysplasia and associated short stature are well characterized in CDGs, including ALG12-CDG, ALG3-CDG, ALG9-CDG, ALG6-CDG, PGM3-CDG, COG7- CDG, COG1-CDG and COG8-CDG and TMEM165-CDG (Table 1) (97,98,99). Short stature, generalized osteopenia/osteoporosis and epi- and meta-physeal dysplasia were reported in patients with TMEM165-CDG (100,101,102). Osteopenia/osteoporosis in CDG was mostly reported in PMM2-CDG, TMEM165-CDG, B4GALT7-CDG and B3GAT3-CDG (15,99,103).

As portrayed, glycosylation is essential for proteins involved in the development of cartilage and bone, as well as in skeletal patterning pathways. CDGs should be considered in the differential diagnosis of skeletal dysplasias and defects in cartilage development, especially if systemic involvement is present (15). Furthermore, evaluation of bone health is generally overlooked in CDGs. Annual evaluation of conventional lateral lumbar radiography is advised in patients with normal levels of serum calcium, phosphate, and magnesium. If fractures are observed, measurement of bone mineral density via dual energy X-ray absorptiometry should be considered. Restoration of accompanying complications associated with CDG, like malnutrition, hypovitaminosis D, enteropathy, hypogonadism, coagulopathy, and hepatic dysfunction is crucial for bone health, and physical therapy will also improve bone mineralization. Patients with scoliosis should have regular orthopedic assessment and intervention, and assessment for atlantoaxial instability is also required. PGM1-CDG and TMEM165-CDG, characterized by under glycosylation of B-glycans were shown to improve glycosylation status following galactose supplementation (104,105). Mannose in MPI-CDG is known to restore other endocrine system functions as well as enteropathy (27,78). However, it is not yet clear whether these disease specific treatments have an impact on skeletal phenotype. Long-term prospective observational studies are needed to evaluate bone health in CDGs and to inquire whether disease specific treatment as well as supportive management has an influence on findings.

## Effects of CDG on Prolactin Level and Function

Change in PRL level was one of the initially described endocrine manifestations of CDG (7). PRL is a protein hormone (106). Numerous variants of PRL have been identified, many of which result from post-translational modification (phosphorylation, glycosylation, sulfation and deamidation) of mature PRL protein (107). The PRL receptor is a class 1 receptor composed of three major domains (extracellular, transmembrane, and intracellular). The extracellular domain is known to be glycosylated. However, neither variants in the structure nor variation of the polysaccharides associated with the PRL receptor have been identified (108). Glycosylation defects are expected to alter serum PRL levels and PRL signaling because of the posttranslational modifications described in both PRL and its receptor. However, currently this area of endocrine manifestation remains largely unexplored.

**Table 1. Summary of CDG with reported endocrine manifestations**

| CDG (OMIM) | Localization | Affected protein | Inheritance | Clinical manifestations | Endocrine manifestations and skeletal features | Reference |
|---|---|---|---|---|---|---|
| **Disorders of *N*-linked glycosylation** | | | | | | |
| **PMM2-CDG (212065)** | | Phosphomannomutase 2 | AR | -Failure to thrive, feeding difficulties<br>-DD (normal in 10%, borderline in 2%; mild in 27%, moderate in 28%, severe in 30% and profound in 3%), microcephaly, seizures, hypotonia, ataxia, hyporeflexia, stroke like episodes<br>-Strabismus, nystagmus, retinitis pigmentosa, optic hypoplasia, peripheral neuropathy, cerebellar atrophy/hypoplasia, olivopontocerebellar atrophy<br>-Flat nasal bridge, large ears, thin upper lip, long philtrum, high arched palate, prominent jaw, retrognathia (in infancy), almond shaped eyes<br>-Pericardial effusion, hypertrophic cardiomyopathy, cardiac failure, tamponade, conotruncal malformations<br>-Inverted nipple, lipodystrophy, fat pads, p'eud orange,<br>-Hepatomegaly, cirrhosis, liver steatosis, vomiting, protein losing enteropathy, diarrhea, GERD<br>-Hydrops fetalis, non-immune, hydropic placenta, mirror syndrome<br>-Edema and hypoalbuminemia, low cholesterol<br>-Coagulopathy and thrombosis (factor II, V, VII, VIII, IX, X, XI, antithrombin III, protein C, protein S deficiency)<br>-Recurrent infections, hypogammaglobulinemia, lack of response to vaccination<br>-Hyperechoic kidneys, hydronephrosis, cysts, proteinuria, proximal tubulopathy<br>-Disproportionate short stature, kyphoscoliosis, skeletal dysplasia (skeletal appearance were consistent with spondyloepiphyseal dysplasia congenita or Kniest dysplasia | -Panhypopituitarism<br>-Hypothyroidism, decreased TBG,<br>-Growth hormone resistance<br>-Female: Delayed puberty, pubertal arrest, amenorrhea, hypergonadotropic and hypogonadotropic hypogonadism (normal puberty and menstruation have been described)<br>-Male: Normal puberty and virilization but small testes, and low-normal testosterone, hypogonadism<br>-Hyperprolactinemia<br>-Hyperinsulinemic hypoglycemia<br>-Adrenal insufficiency (in some patients)<br>-Osteopenia, osteoporosis | (4,9,30,71,84,92,109) |

**Table 1. Continued**

| CDG (OMIM) | Localization | Affected protein | Inheritance | Clinical manifestations | Endocrine manifestations and skeletal features | Reference |
|---|---|---|---|---|---|---|
| **Disorders of N-linked glycosylation** | | | | | | |
| **MPI-CDG (602579)** | 15q24.1-q24.2 | Mannosephosphate Isomerase | AR | -Failure to thrive<br>-Vomiting, diarrhea, villous atrophy, lymphangiectasia, protein-losing enteropathy<br>-Hepatomegaly, hepatic fibrosis, cirrhosis, hepatic failure<br>-Hypotonia<br>-Anti-thrombin III, Protein C, Protein S deficiency, thrombosis, factor XI deficiency<br>-Short stature | -Hyperinsulinemic hypoglycemia<br>Treatment beyond symptomatic: Mannose 150 to 170 mg/kg/dose four to five times a day, po | (9,27,110,111) |
| **ALG6-CDG (603147)** | 1p31.3 | Alpha-1,3-glucosyltransferase | AR | -Failure to thrive<br>-Large open fontanel, low-set ears, hypertelorism, macroglossia, brachydactyly distal phalangeal hypoplasia, scoliosis<br>-Axial hypotonia, psychomotor retardation, areflexia, seizures, ataxia, strabismus<br>-Decreased serum cholesterol, factor XI, antithrombin III and protein C | -Hypoglycemia<br>-Hypothyroidism<br>-Low corticosteroid binding globulin, normal cortisol | (9,15,112,113,114) |
| **ALG3-CDG (608750)** | 3q27.1 | Alpha-1,3-mannosyltransferase | ?? | -DD (mostly severe hence variable)<br>-Failure to thrive<br>-Strabismus and optic atrophy<br>-Dilated aortic root<br>-Craniofacial abnormalities (epicanthal folds, down slanting palpebral fissures, broad/flat nasal bridge, high palate, micrognathia, and dysplastic ears)<br>-Skeletal dysplasia (arthrogryposis, scoliosis, club feet, hip dysplasia, camptodactyly, contractures, overlapping digits, and talipes, rhizomelic short stature, wide metaphysis, hypoplastic cervical vertebrae, narrow thorax, rounded iliac wings. chondrodysplasia punctata)<br>-Feeding problems<br>-Hypoalbuminemia, elevated transaminases, decreased factor XI, antithrombin III<br>-Hypolipidemia | -Panhypopituitarism (central hypothyroidism, central adrenal insufficiency, growth hormone deficiency)<br>-Hypoglycemia<br>-Osteopenia and recurrent fractures | (5,15,114) |

**Table 1. Continued**

| CDG (OMIM) | Localization | Affected protein | Inheritance | Clinical manifestations | Endocrine manifestations and skeletal features | Reference |
|---|---|---|---|---|---|---|
| **Disorders of *N*-linked glycosylation** | | | | | | |
| **ALG9-CDG (608776)** | 11q23.1 | Alpha-1,2-Mannosyltransferase | AR | -Failure to thrive<br>-Microcephaly, frontal bossing, long philtrum, low-set ears, hypertelorism, esotropia<br>-Inverted nipples- DD, epileptic encephalopathy, seizures, intractable, hyperreflexia<br>-Cortical and cerebellar atrophy, delayed myelination<br>-Congenital heart defects, pericardial effusion | **Short stature**<br>-Severe skeletal dysplasia (decreased ossification of the frontoparietal bones, thickening of the occipital bones, deficient ossification of cervical vertebral bodies and pubic bones, round pelvis, and short tubular bones with metaphyseal flaring).<br>-Mild skeletal dysplasia have been reported (delayed bone age, mesomelic brachymelia with thickening of frontal and occipital bone, mild kyphosis of thoracolumbar spine, bilateral hip dislocation, round pelvis, brachycephaly, and shortening of greater sciatic notch.) | (15,98,115) |
| **ALG12-CDG (607143)** | 22q13.33 | Alpha-1,6-Mannosyltransferase | ?? | -Microcephaly, hypotonia, psychomotor retardation<br>-Midface hypoplasia, broad nose, thin upper lip thick ears, sensorineural deafness<br>-Retinal decollement<br>-Patent foramen ovale, patent ductus arteriosus<br>-Hypogammaglobulinemia<br>-Severe skeletal dysplasia (interphalangeal dislocations, scoliosis, talipes equinovarus, rhizomelic limb shortening, short metacarpals, horizontal acetabular roof)<br>-Short ribs with flared metaphysis, scoliosis<br>-Short stature | -Hypoglycemia | (116) |
| **PGM1-CDG (614921)** | 1p31.3 | Phosphoglucomutase 1 | AR | -Facial dysmorphism (hypertelorism, short neck, retrognathia, smooth philtrum and low set ears) bifid uvula/palate,<br>-Hepatopathy, malignant hyperthermia<br>-Imperforate anus<br>-Rhabdomyolysis, exercise intolerance, axial hypotonia, dilated cardiomyopathy<br>-Anti-thrombin III, Protein C, Protein S deficiency | -Hypoglycemia (ketotic or hyperinsulinemic)<br>-GH deficiency, decreased IGF-1 and IGFBP-3 levels<br>-High TSH, decreased TBG<br>-Adrenal insufficiency<br>-Hypogonadotropic hypogonadism<br>Treatment beyond symptomatic: D-galactose 0.5 to 2.5 g/kg/day, five to six times a day, po (max: 50 g) | (117,118,119) |

**Table 1. Continued**

| CDG (OMIM) | Localization | Affected protein | Inheritance | Clinical manifestations | Endocrine manifestations and skeletal features | Reference |
|---|---|---|---|---|---|---|
| **Disorders of N-linked glycosylation** | | | | | | |
| **TMEM165 (614727)** | 4q12 | Transmembrane protein 165 | AR | -DD, seizures, hypotonia<br>-Microcephaly<br>-Short stature<br>-Skeletal dysplasia<br>- Epi-metaphyseal dysplasia and joint destruction diagnosed as Desbuquois syndrome; pectus carinatum, kyphosis and scoliosis, short distal phalanges, genu varus, joint hyperlaxity, epi- and metaphyseal dysplasia with broad metaphysis | Generalized osteoporosis<br>Treatment beyond symptomatic: Galactose 1 g/kg/day po | (15,99) |
| **MAN2B2-CDG (NA)** | 4p16.1 | Mannosidase alpha class 2B member 2 | AR | -DD<br>-Chronic diarrhea<br>-Coagulopathy and multiple thrombotic strokes, pancytopenia<br>-Immunodeficiency, small-vessel vasculitis | Short stature<br>Treatment beyond symptomatic: HScT | (120) |
| **O-linked glycosylation** | | | | | | |
| **EXT1(133700) /EXT2-CDG (133701)** | 8q24.11/11p11.2 | Exostosin Glycosyltransferase 1/ Exostosin Glycosyltransferase 2 | AD | -DD, muscular dystrophy, hypotonia, polymicrogyria, lissencephaly<br>-Loose skin, reticulate pattern of hyperpigmentation, hypermobility<br>-Elevated CK, dysmorphic features | Skeletal dysplasia, multiple exostoses | (121) |
| **B3GLCT-CDG (261540/ 610308)** | 13q12.3 | Beta 3-glucosyltransferase | AR | Embryonic development of the eye is defective (corneal clouding and variable iridolenticulocorneal adhesions)<br>-Cupid bow shape of the upper lip, cleft lip, cleft palate<br>-Kyphoscoliosis, foot deformity, radioulnar synostosis | -Prenatal growth retardation, postnatal disproportionate short stature<br>-Osteopenia | (15,122,123) |
| **GALNT3-CDG (211900)** | 2q24.3 | Polypeptide N-acetyl galactosaminyl transferase 3 | AR | -Retinal angioid streaks, conjunctival irritation, eyelid calcifications | -Hyperphosphatemia associated with periosteal reaction and cortical hyperostosis (recurrent episodes of swelling, pain, and tenderness)<br>-Elevated renotubular phosphate reabsorption<br>-Increased serum FGF23<br>-Normal serum calcium<br>-Normal serum parathyroid hormone | (124,125,126) |

**Table 1. Continued**

| CDG (OMIM) | Localization | Affected protein | Inheritance | Clinical manifestations | Endocrine manifestations and skeletal features | Reference |
|---|---|---|---|---|---|---|
| **O-linked glycosylation** | | | | | | |
| **SLC35C1-CDG (605881)** | 11p11.2 | Solute carrier family 35 member C1 | | -Severe mental retardation, cortical atrophy, seizures, hypotonia, microcephaly<br>-Markedly reduced neutrophil motility, reduced neutrophil adherence | -Short stature<br>Treatment beyond symptomatic: Fucose, po | (127) |
| **CSGALNACT1-CDG (618870)** | 8p21.3 | Chondroitin sulfate N-acetylgalactosaminyl transferase 1 | AR | | -Skeletal dysplasia<br>-Micromelia, disproportionate short stature | (128,129) |
| **EXT3-CDG (617425)** | 8p21.1 | Exostosin like-glycosyltransferase 3 | AR | -Neuro/immuno/skeletal (DD, seizures, SCID) | Various skeletal dysplasia (platyspondyly, severe, cervical spine malformation, cervical instability, progressive kyphoscoliosis, brachydactyly, delayed carpal ossification, epi-, metaphyseal dysplasia | (17) |
| **Disorders of mixed glycosylation** | | | | | | |
| **OGT-CDG (300997)** | Xq13.1 | O-GlcNAc transferase subunit p110 | XLR | -Neuro/growth/ophthalmo (intellectual delay, hypotonia, eye abnormalities, hearing impairment, behavioural problems, dysmorphism) | Short stature | (130) |
| **GPI anchor disorder** | | | | | | |
| **PIGA-CDG (311770)** | Xp22.2 | Phosphatidylinositol Glycan Anchor Biosynthesis Class A | XLR | -Micrognathia, malar flattening, coarse facies, polyhydramnios and hydrops fetalis<br>-Microcephaly, epileptic encephalopathy (hypsarrhythmia, burst-suppression pattern seen on EEG, irregular spike and slow waves, myoclonic seizures), severe DD, axial hypotonia, hyperreflexia, cerebellar hypoplasia, corpus callosum hypoplasia, cortical atrophy, spongy gliosis, delayed myelination | - Increased birth length (in some patients) and birth weight (in some patients)<br>- Overgrowth | (131) |
| **Disorders of multiple glycosylation pathways: disorders of Golgi pH and ion homeostasis** | | | | | | |
| **SLC10A7-CDG (618363)** | 4q31.22 | Solute carrier family 10 member 7 | AR | -Round face, micrognathia, micro retrognathia, mandibular hypoplasia, cleft palate<br>-Mild DD<br>-Hearing and visual impairment<br>-Amelogenesis imperfecta | -Disproportionate short stature, prenatal and postnatal (< -3 SD)<br>-Obesity (in some patients)<br>-Skeletal dysplasia (advanced bone age, proximal femur "Swedish key", short metacarpals and phalanges, irregular vertebra corpus, wide metaphysis, coxa valga<br>-Osteoporosis | (132,133) |

**Table 1. Continued**

| CDG (OMIM) | Localization | Affected protein | Inheritance | Clinical manifestations | Endocrine manifestations and skeletal features | Reference |
|---|---|---|---|---|---|---|
| **Disorders of multiple glycosylation pathways: disorders of Golgi pH and ion homeostasis** | | | | | | |
| **PGM3-CDG (615816)** | 6q14.1 | Phosphoglucomutase 3 | AR | Hyper IgE syndrome (elevated serum IgE, recurrent skin and pulmonary infections, abscesses, eczema, and bronchiectasis) | -Severe skeletal dysplasia (radiographic pattern of Desbuquois dysplasia) | (97) |
| **COG7-CDG (608779)** | 16p12.2 | Component of oligomeric Golgi complex 7 | AR | -Progressive microcephaly<br>-Dysmorphic facial features (narrow, flat forehead, micrognathia, retrognathia, low-set ears, dysplastic ears)<br>-Global DD, cerebral and cerebellar atrophy, hypoplasia of corpus callosum, delayed myelination | -Intrauterine growth retardation, failure to thrive, short stature<br>-Variable skeletal anomalies (Adducted thumbs, overlapping, long fingers, Simian crease, contractures of the PIP and DIP joints with ulnar deviation of the hands) | (15,134) |
| **COG1-CDG (611209)** | 17q25.1 | Component of oligomeric Golgi complex 1 | AR | -Progressive microcephaly<br>-Dysmorphic facial features (midface hypoplasia, micrognathia, low-set ears, microtia, hypertelorism, thin upper lip, high arched palate, hearing loss)<br>-Global DD<br>-Cerebral and cerebellar atrophy<br>-Anemia, thrombocytopenia<br>-Recurrent infections | -Rhizomelic short stature<br>-Rib fusions, rib abnormalities, vertebral abnormalities | (15,135) |
| **COG8-CDG (611182)** | 16q22.1 | Component of oligomeric Golgi complex 8 | NA | -Microcephaly<br>-Hypotonia, seizures,<br>-Cortical atrophy | -Small hands and feet, hypoplasia of the first phalanx of some fingers and toes, sandal gap, clinodactyly | (136,137) |

AR: autosomal recessive, AD: autosomal dominant, CDG: congenital disorders of glycosylation, CK: creatine kinase, DD: developmental delay, SCID: severe combined immunodeficiency, EEG: electroencephalogram, DIP: distal interphalangeal, GERD: gastro-esophageal reflux, HH: hyperinsulinemic hypoglycemia, HScT: hematopoietic stem cell transplantation, NA: not available, OMIM: Online Mendelian Inheritance in Man, PIP: proximal interphalangeal, TBG: thyroxine binding globulin, XLR: X-linked recessive, g: gram, po: per oral

**Table 2. Recommended endocrine evaluation for patients with CDG**

| | On admission | First two years of life (six-month intervals) | After first two years (annually) |
|---|---|---|---|
| Height measurement | + | + | + |
| Glucose* | + | + | If needed |
| Calcium, phosphate, magnesium and vitamin D measurement | + | + | + |
| TSH, FT4 | + | + | + |
| ACTH, cortisol** | + | Annually | + |
| FSH, LH, estradiol or testosterone | + | - | If needed |
| Lateral lumbar radiography | + | - | + |

*If hypoglycemia is detected blood glucose should be measured biochemically with insulin, ACTH, cortisol, growth hormone, bicarbonate, lactate, acylcarnitine analysis, urine ketone analysis.
**If low, perform low dose ACTH stimulation test.
CDG: congenital disorders of glycosylation, TSH: thyroid-stimulating hormone, FT4: free T4, ACTH: adrenocorticotropic hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone

In a case series of PMM2-CDG, basal serum PRL concentrations were reported to be normally elevated in three studied newborns and normally low (<I5 pg/L) in 22/26 patients examined after the neonatal period. Slightly elevated basal PRL levels were observed in four femaless (the initially described twin sisters (778-5652 U/mL, normal range <800) and two girls aged 2 years old (659 and 829 U/mL) (7,10). In the initially described twin sisters, prolactin decreased gradually over the course of 15 years and was sensitive to release-inhibitory action of L-dopa when they were 3 years old (10).

## Conclusion and Future Prospects

Glycoproteins are essential for endocrine homeostasis where alterations in glycosylation change hormone and carrier protein stability, circulatory half-life and abundance, receptor configuration, activation, hormone-substrate affinity and reset endocrine control and feedback loops. Therefore, every endocrine axis may be affected in CDGs. It is known that CDG should be considered in patients with multisystemic disease, especially in cases with neurologic findings of nonspecific developmental delay with unclear etiology. CDGs should also be considered in the differential diagnosis of patients with endocrine manifestations of unclear etiology and multisystem involvement.

Clinical findings of CDG regarding endocrine system may be masked or mimicked by other, more severe CDG symptoms and endocrine problems may be overlooked. Evaluation of laboratory results in individuals with CDG may be difficult to interpret as structurally and functionally altered glycosylated proteins precede changed serum hormone levels. Given this, regular evaluation of endocrine manifestations is advised (Table 2). *In vitro* and clinical studies focusing on defects of glycosylation and its effects are emerging, hence there are some limitations in the existing literature that should be acknowledged. As seen, large-scale clinical studies focusing on implications of disorders of glycosylation on endocrine systems are scarce and data are mostly derived from case series. Studies focusing on alterations of glycosylation patterns and three dimensional structure of specific hormones may help clarify pathophysiology of hypogonadism, AI and defects of bone mineralization. Large scale proteomic and metabolomic profiling may help delineate these shortcomings in the literature and help illuminate specific endocrine effects as well as the natural course of disease. Long term studies with international participation focusing on growth, puberty, bone mineralization and thyroid and adrenal involvement are necessary. Results of disease specific treatments (ie. galactose, and mannose) focusing on endocrine systems should be sought.

**Footnotes**

**Authorship Contributions**

Concept: Zeynep Alev Özön, Design: Zeynep Alev Özön, Data Collection or Processing: Yağmur Ünsal, Zeynep Alev Özön, Analysis or Interpretation: Yağmur Ünsal, Zeynep Alev Özön, Literature Search: Yağmur Ünsal, Zeynep Alev Özön, Writing: Yağmur Ünsal, Zeynep Alev Özön.

**Conflict of Interest:** Zeynep Alev Özön is an Associate Editor of the Journal of Clinical Research in Pediatric Endocrinology. However, the reviewers evaluating this manuscript were blinded and were from different institutions. She was not involved in the editorial review of this manuscript to avoid prejudice that may disrupt impartiality. The other author declares no conflict of interest.

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