Understanding the Hormone-Related Health Challenges in Congenital Disorders of Glycosylation (CDGs)

A Patient-Friendly Summary of "Endocrine Implications of Congenital Disorders of Glycosylation." *Original article by Drs. Yağmur Ünsal and Zeynep Alev Özön published in the Journal of Clinical Research of Pediatric Endocrinology, 2025. Summarized by Dr. Kristen Skvorak, Director of Research, CDG CARE*

Summary

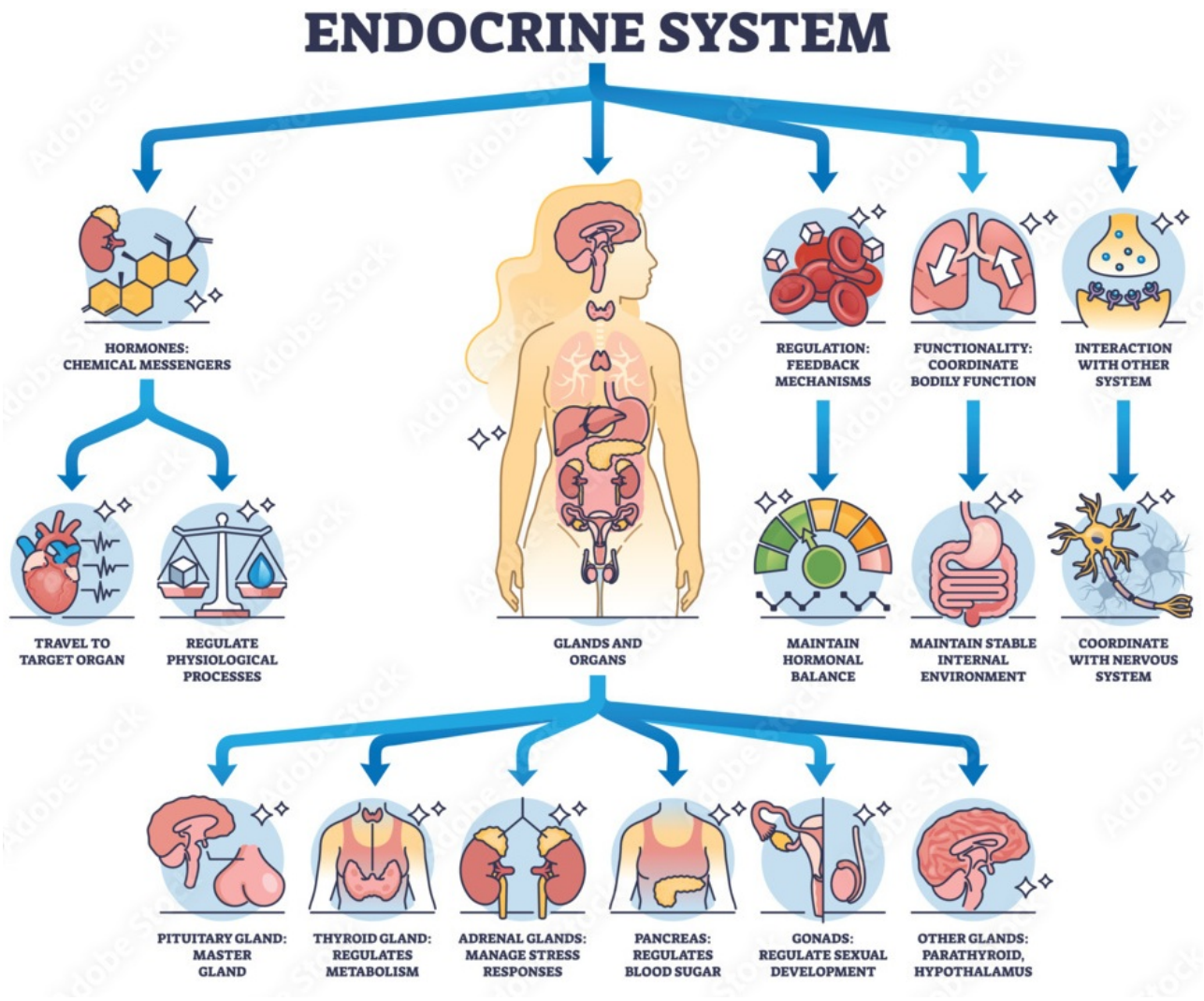
- Endocrine (hormone) issues are common in CDGs because many hormones, and their carrier proteins, rely on glycosylation. Hormone-related problems are reported in over half of people with CDG, and in some types, up to 85%
- CDGs can change:
  - How long hormones last in the body (i.e. their stability)
  - How much hormone is available in the blood
  - How well hormones bind to and activate their targets
  - How the body senses hormone levels and keeps them in balance (i.e. feedback systems and regulation)
- Many hormone systems may be involved, including:
  - Growth and growth factors
  - Thyroid hormones
  - Stress hormones
  - Puberty and reproductive hormones
  - Blood sugar regulation
  - Bone health
- Significant knowledge gaps remain, as most data comes from small studies. This review brings all the information together from both laboratory and patient studies to highlight key changes

Key Takeaway – Hormone-related problems are a common and important part of CDGs, affecting many body systems, but they are often underrecognized and not well studied, highlighting the need for greater clinical awareness and more systematic research.

Hormone (Endocrine) Problems in CDGs

Because glycosylation is so important, **CDGs can cause a wide variety of symptoms impacting many body systems**. Almost any organ can be affected, the nervous system being the most frequent (76%). This can lead to developmental delays or learning differences, low muscle tone (ataxia), balance and coordination issues, and seizures or nerve problems. Feeding and growth challenges are also common, and some also experience problems with digestion, vision, the immune system, blood clotting, the bones and spine, and other unique issues.

This summary specifically focuses on the **endocrine system**, which is the system of glands that produce hormones. Hormones are chemical messengers that control many important body functions, such as growth, metabolism, and puberty. The original research paper highlights that **hormone-related problems are quite common in people with CDGs**, reported in half of people with CDG, and can affect **up to 85% of individuals** in some CDG types.



Growth Issues

Many children with CDGs experience **growth failure**. While they may be born with a normal weight and length, their growth often slows down significantly within the first few years of life. This is **partly due to feeding difficulties** and poor nutrition, but it's also because of **problems with the hormones that control growth**, particularly the Growth Hormone/IGF-1 axis. The proteins involved in this system need to be properly glycosylated to work, and in CDGs, their function is impaired. For some specific types of CDG, like **MPI-CDG**, treatment with a specific sugar called mannose has been shown to help with catch-up growth.

Thyroid Problems

The thyroid gland produces hormones that **regulate metabolism**. Many of the proteins involved in making and transporting thyroid hormones are glycoproteins. In CDGs, the most common finding is a low level of the main thyroid hormone carrier protein (TBG). This can sometimes lead to an underactive thyroid (**hypothyroidism**), especially in infants with **PMM2-CDG**. Hypothyroidism is easily missed in CDGs because it looks similar to symptoms commonly seen in these disorders (i.e. slow growth, low energy, constipation, low muscle tone, developmental delays). According to clinical guidelines, it is recommended that individuals with PMM2-CDG have their thyroid function checked every six months for the first two years of life, and then once a year.

Adrenal Gland and Stress Hormones

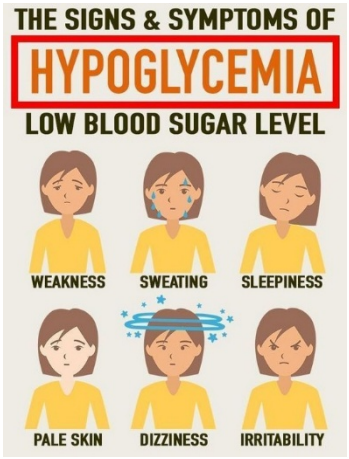
The adrenal glands produce important hormones like **cortisol**, which **helps the body respond to stress**. The system that controls the adrenal glands can also be affected in CDGs. Some individuals with CDGs, including those with **PMM2-CDG**, **ALG6-CDG**, and **ALG3-CDG**, may have adrenal insufficiency, meaning their **bodies don't produce enough cortisol**. This can lead to low blood sugar episodes, low energy and poor recovery, digestive and GI issues, or becoming very sick with minor illnesses, which is often triggered in times of stress. **Low cortisol can be a serious condition**, so clinical guidelines recommended that people with PMM2-CDG have their levels checked annually.

Puberty and Development

CDGs can have a **variable impact on puberty**. Some individuals may experience delayed puberty, while others may have a complete lack of pubertal development. This is because the hormones that control puberty (FSH and LH) and their receptors are all glycoproteins. In some cases, hormone replacement therapy can be used to help with pubertal development, but this needs to be done carefully due to an increased risk of blood clots in some individuals with CDGs.

Blood Sugar Control (Hypoglycemia)

Low blood sugar, or hypoglycemia, is another potential problem in CDGs, especially in infancy. It is most frequently seen in **PMM2-CDG** and **MPI-CDG**. In many cases, this is caused by the body **producing too much insulin** (hyperinsulinism), but can also be **due to low cortisol**. High insulin can happen because the channels that control insulin release from the pancreas are also affected by faulty glycosylation. Hypoglycemia can show up as clammy or pale skin, sleepiness, unusual irritability or feeding issues, shaking, sweating, vomiting, dizziness or loss of coordination, and **can become severe if unchecked** (seizures, unresponsiveness). Careful monitoring of blood sugar levels and a special diet are important for management. In some cases, medication like diazoxide can be helpful.



Bone Health in CDGs

Skeletal problems, such as **weak bones** (osteopenia/osteoporosis), **curvature of the spine** (scoliosis), and frequent **fractures**, are common in many types of CDGs, particularly **PMM2-CDG**. This is because many of the proteins that make up our bones and cartilage are glycoproteins. The health of the bones is also affected by other problems common in CDGs, such as poor nutrition, lack of movement, and hormonal imbalances. Regular monitoring of bone health is recommended, and physical therapy can be beneficial.

Monitoring and Treatment

The following table summarizes the key endocrine issues and monitoring recommendations for some of the more common CDG types.

CDG Type	Key Endocrine Problems	Recommended Monitoring
PMM2-CDG	Problems with all pituitary hormones, hypothyroidism, adrenal insufficiency, puberty issues, low blood sugar, weak bones.	Thyroid tests every 6 months for the first 2 years, then yearly. Annual cortisol check. Regular growth and puberty monitoring. Bone health evaluation.

CDG Type	Key Endocrine Problems	Recommended Monitoring
MPI-CDG	Low blood sugar due to high insulin.	Regular blood sugar monitoring.
ALG6-CDG	Low blood sugar, hypothyroidism, low cortisol carrier protein.	Regular monitoring of blood sugar, thyroid, and adrenal function.
ALG3-CDG	Problems with all pituitary hormones, low blood sugar, weak bones.	Comprehensive endocrine evaluation.
PGM1-CDG	Low blood sugar, growth hormone deficiency, hypothyroidism, adrenal insufficiency, puberty issues.	Comprehensive endocrine evaluation.

Treatments are generally focused on managing the specific symptoms. For example, hormone replacement therapy can be used for hypothyroidism or adrenal insufficiency. For certain CDG types, specific treatments like mannose for MPI-CDG or galactose for PGM1-CDG and TMEM165-CDG can be very effective.

Why this Matters for Families Living with CDG

Hormone-related problems are a significant aspect of Congenital Disorders of Glycosylation. Because glycosylation helps hormones work properly, **any hormone system in the body can be affected in CDG**. Hormone problems may be overlooked, especially when more obvious CDG symptoms (like neurologic or feeding issues) are present. Lab tests can also be hard to interpret since hormone-related proteins may function abnormally before blood levels appear clearly abnormal. For this reason, regular check-ups with an endocrinologist are crucial for early detection and management of these issues, which can significantly improve the health and quality of life for individuals living with CDGs.

Researchers are still learning how glycosylation changes affect specific hormones. Most current knowledge comes from small studies, and **larger international natural history studies are needed** to better understand:

- Growth and puberty over time
- Bone strength and mineralization
- Thyroid and adrenal involvement
- The long-term endocrine course of CDGs

There is also interest in understanding whether **disease-specific treatments (such as galactose or mannose in certain CDGs)** may improve hormone-related symptoms.

Bottom line: Hormone health is an important, evolving area of CDG care, and more research is underway to improve monitoring and treatment guidance for families.

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