

# Hypoglycemia in congenital hyperinsulinism



## How a normal body works:

Our body is constantly at work. Our cells need a source of energy, and this source of energy is called glucose. The process is quite simple; think of it like an assembly line. Foods we eat that contain carbohydrates (sugar) are broken down and absorbed as glucose. Some foods that contain simple carbohydrates have pure sugar (such as table sugar, corn syrup, fruit juice and candy), which causes the blood glucose to rise quickly. Others have more complex carbohydrates (such as bread, broccoli, wild rice and apples), which cause the blood glucose to rise slowly.

When the blood glucose rises after you eat, the pancreas releases insulin. Insulin helps take sugar out of the blood and into the cells to be used. The end results is falling blood sugar.

## What is glucose and where does it come from?

Glucose is a form of sugar, which is part of the carbohydrate family. After consuming food, carbohydrates are broken down into glucose in the digestive tract and carried by the blood to all parts of the body. Some of the glucose is used right away and some is stored in the liver for later use. This stored sugar in the liver is called glycogen and is what is released when you give a glucagon injection.

## What is a normal blood glucose level and when is it dangerous?

The normal blood glucose level is between 70 and 110 mg/dL. When the blood glucose drops below 50 mg/dL we call it hypoglycemia. When this happens, the cells in the brain are not able to get enough glucose and they stop working. If the glucose is too low for a long time or very low (<30mg/dL) for a short time the brain cells can die, which can lead to brain damage. Children are at more risk of damage from low glucose levels than adults because their brains need more glucose to grow and function properly.

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## Why is glucose so important for brain function?

The brain is a very important organ. It requires a certain amount of energy to function. This energy comes from glucose, lactate or ketones. To make sure that the brain has enough glucose, babies release glucose that is stored as glycogen in the liver after all the carbohydrates in their food are used up. When all the glycogen is used up in the body, the body breaks down fat and converts it to ketones.

In a normal child who does not eat for 12 to 18 hours, these ketones replace glucose in the brain for energy. However, in hyperinsulinism, when there is too much insulin being secreted, the liver cannot release sufficient amounts of glycogen, nor can the body breakdown fat for ketones. Therefore, dangerous hypoglycemia may occur. If the infant has a seizure and stops breathing, the amount of brain damage may be worsened. When the brain runs out of energy, the cells stop working and may die. This can result in signs and symptoms of lethargy, seizures or coma.

Long term, repeated episodes of hypoglycemia cause energy failure and may cause irreversible brain damage. This is why congenital hyperinsulinism is such a dangerous disease and why 20 to 40 percent of infants with this disease suffer from brain damage.

## What are fats and ketones?

When we eat more food than needed, the excess food gets stored as fat. Fat is later used as energy when our body does not have enough glucose to maintain glucose levels in the normal range. When our blood glucoses fall below 70 mg/dL, our body knows to stop making insulin. This allows the stored fat to be converted into ketones. Ketones can be used by muscle and the brain instead of glucose for energy. Hence, when ketones are present it means the body is in starvation state.

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## Why does our body needs glucose and ketones?

The human body and brain need energy in order to function and perform daily activities. The main sources of energy are sugar and ketones. This concept is very similar to a hybrid automobile, a car that runs on electricity and gasoline. For example, the hybrid automobile will run on electricity as its main energy source until it needs more power or the battery is low; then the automobile can run on gas. Without these sources, the car can't function. This is similar to how the human body needs glucose and ketones for daily activities. Therefore, if the blood glucose and ketone concentrations fall below a certain level, the brain is in danger. The lower the glucose is and the longer it stays below 50 mg/dL, the greater the risk of danger for the child.

## What does the pancreas do?

The pancreas is located just below the stomach. It has two jobs. The first job is making pancreatic juices. These juices contain enzymes that help break down and digest food in the small intestine and help the body absorb the carbohydrates, fat and protein in food. The second job is making hormones such as insulin, glucagon and somatostatin, all which control the blood glucose levels.

## What is insulin and what is its function?

Insulin is a hormone that plays an important role in our body. There are cells within the pancreas called islet cells. In each islet cell there are beta cells that secrete insulin. The main role of insulin is to transport sugar to cells, help the cells use glucose for energy and help control the amount of sugar in the blood. When glucose levels are high, insulin lowers the glucose level. When glucose levels fall below 70 mg/dL, insulin secretion is turned off, which allows the glycogen in the liver to be released and the fat to be made into ketones.

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## How do high insulin levels affect a child?

Normally, after consuming food carbohydrates are broken down to glucose in the digestive tract and carried by the blood to all parts of the body. Some of the glucose is used right away, with the help of insulin, and some is stored in the liver. When our body is experiencing a drop in blood sugar it goes through an adaptation process to prevent hypoglycemia. The liver will use the stored glycogen and convert it to glucose. When all the glycogen is used up in the body, the body breaks down fat and converts it to ketones. These pathways help prevent low blood glucose.

Normally, when the blood glucose drops below 50 mg/dL, there will be no insulin production and blood ketone levels are high. However, in hyperinsulinism, when there is too much insulin being secreted the liver cannot release glycogen, nor can the body breakdown fat for ketones. Therefore, dangerous hypoglycemia may occur.

## What are these processes/pathways?

- Glycogenolysis: the breakdown of glycogen to glucose.
- Gluconeogenesis: the generation of glucose from protein.
- Lipolysis: the breakdown of fats to fatty acids.
- Fatty acid oxidation: the breakdown of fats into ketones.
- Ketogenesis: the formation of ketones.

In the presence of high insulin levels these pathways are suppressed, leaving the body unable to compensate for low glucose.

## What is hypoglycemia?

Hypoglycemia happens when your body does not have enough glucose. It is defined as abnormally low blood glucose that is less than 50 mg/dL.

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## Why is blood glucose important?

Anything below 50 mg/dL is too low for our body to function adequately. Our body and brain cells depend on glucose to function. If hypoglycemia lasts for a long time it can lead to seizures and permanent brain damage. This is why early identification and screening is a key factor.

## How is hyperinsulinism diagnosed?

- Hyperinsulinism is diagnosed by taking a patient history, reviewing symptoms and collecting specific lab tests when the blood glucose is less than 50 mg/dL. The diagnosis is confirmed by drawing critical labs to identify inappropriate insulin secretion at the time of hypoglycemia.
  - It is important that these labs are drawn when your child has a low blood sugar.
- Sometimes we have to provoke a low blood sugar by doing a study called a diagnostic fasting study.
  - A diagnostic fasting study will identify if your child is able to fast appropriately for their age.
  - It will also confirm if your child is making too much insulin or if they are deficient in other hormones (for example, growth hormones or cortisol).

## What are the signs and symptoms of hyperinsulinism?

Everyone is different; signs and symptoms may vary. Symptoms of hypoglycemia can be grouped into two types- neurogenic and neuroglycopenic.

## What are the neurogenic symptoms?

- |             |                        |            |
|-------------|------------------------|------------|
| • Pallor    | • Trembling            | • Weakness |
| • Sweating  | • Increased heart rate | • Hunger   |
| • Shakiness | • Anxiety              | • Nausea   |

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## What are the neurological symptoms?

- Headache
- Visual disturbances
- Unresponsiveness
- Difficulty with speech/thinking
- Inability to concentrate
- Mental confusion
- Lack of breathing
- Twitching and convulsions (seizures)

## What are the signs and symptoms of low blood sugar in neonates and children?

In neonates and children up to 5 years of age, it is hard to tell if he or she has hypoglycemia because they do not show the neurogenic symptoms clearly. They usually present with breathing difficulty, seizures or unresponsiveness as the first sign of a low blood glucose.

## Are there genetic studies for congenital hyperinsulinism?

Yes. Genetic testing can help us determine the type of hyperinsulinism, as there are at least ten. Hyperinsulinism genetics can give us a clue as to whether a baby has focal (only some cells make too much insulin) or diffuse (all the cells make too much insulin) hyperinsulinism.

## What are the options for treatment?

The goal of treatment is to keep the glucose  $>70$  mg/dL. This is done using breast or bottle feeds with intravenous glucose. Once a diagnosis of hyperinsulinism is made, medicine taken by mouth is started (Diazoxide, also known as Proglycem).

## What is Diazoxide?

Diazoxide is an drug given 2-3 times a day by mouth. It makes the KATP channels in the pancreatic cells work better and stop insulin secretion. The main immediate side effects of this drug are water retention and puffiness. A longer term problem may be excessive hair growth all over the body. Rare side effects include heart failure, pulmonary hypertension, bleeding from low platelets and infection from low white cells in the blood. The goal is to maintain blood glucose levels above 70 mg/dL.

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## What is Octreotide?

Octreotide is an injection that may be initiated when Diazoxide treatment alone is inadequate and the baby is old enough to tolerate it safely. Octreotide works by suppressing insulin secretion. It often works very well for 2-3 days and then the effect on the glucose levels wear off. This is called tachyphylaxis. To prevent this, your doctor may use it twice a day in conjunction with tube feeds during the night. Sometimes, the child may have to take Diazoxide and Octreotide together to maintain adequate blood sugars.

## Can X-rays look at the pancreas?

Yes, but X-rays (and ultrasounds) do not help diagnose hyperinsulinism. X-rays can show a lump in the pancreas, but hyperinsulinism is not caused by a lump; it is caused by some or all the cells making too much insulin.

Diagnostic imaging, such as the 18F-DOPA PET scan, may help. This scan looks at cell function and can tell which cells make too much insulin and which do not. Therefore, it can tell the difference between focal and diffuse hyperinsulinism and it can show where the focal area is located.

## Is surgery an option?

Surgery is indicated when medical therapy fails. The type of hyperinsulinism, focal or diffuse, will determine how much of the pancreas needs to be removed. For example, if the infant has the KATP diffuse form of hyperinsulinism, 98 percent of the pancreas will be removed if the infant is not medically responsive. In this case, the infant has a 95 percent risk of developing diabetes by age 15 and will likely still have some hypoglycemia after surgery. However, it will be easier to control. With focal hyperinsulinism, only the focal part is removed; the baby can be cured and have a very low risk of diabetes later in life.

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## Why do we need a team approach?

Congenital hyperinsulinism is a rare and severe condition that requires a team approach for success. Our specialized center has a multidisciplinary team that includes doctors specializing in endocrinology, pediatric surgery, neonatology, neurology, gastroenterology, pathology and radiology. The team is also supported by a nurse practitioner, nutritionist and social worker, as well as clinical therapists, child life specialists, and feeding/speech therapists.

## What is discharge planning?

Discharge planning enables a safe medical program that might include feeding therapy, drug therapy and surgery. Once a stable program is established, we prepare for home. Preparation includes patient education, provision of medication and equipment and a long-term care plan. The final step includes the family handling all of the baby's care in the hospital for a day or two, until they are comfortable they can manage home care.

## What is the future of hyperinsulinism?

Congenital hyperinsulinism is a rare condition, but one of the most common causes of persistent hypoglycemia in neonates and infants. We are researching and improving the understanding, diagnosing and treating of infants with this condition. You may be offered the opportunity to participate in several research studies while at Cook Children's Hyperinsulinism Center.

## When should blood sugars be checked?

A normal blood sugar range is 70 -120 mg/dL. Check your child's blood sugar before feeds/meals. Please check with your doctor on how many times per day you need to check blood sugar, as every child is different and will require a different schedule. If a glucometer is not available and your child is showing signs of abnormal blood sugar (for example, shaky, weak, severe hunger, sweaty, pale, poor concentration and/or dizziness), treat the symptoms.

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## How to treat a low blood sugar:

The rule of 15:

- If a blood sugar is below 60 mg/dL, treat with 15 grams of a carbohydrate (preferably liquid). This is about 4 ounces of juice or 6 ounces of regular soda.
- Recheck blood sugars in 15 minutes, repeat as necessary until blood sugars are over 60 mg/dL and then provide a snack or meal.

## How to treat seizures:

### Signs and symptoms to look for

- Seizures can present in many forms.
- Staring spells.
- Unusual twitching of the arms and legs.
- Uncontrollable muscle spasms.
- Loss of consciousness.
- Uncontrolled urination or bowel movement.

### What to do if your child is having a seizure

- Gently place your child on the floor in a safe place.
- Do not try to stop the seizure.
- Do not try to put anything in your child's mouth.
- Check blood sugar. If less than 50 mg/dL:
  - Administer glucagon.
  - Lay your child on their side.
  - Glucagon can cause vomiting; if your child vomits, keep him or her on side.
- Do not give your child anything to eat or drink.
- Call 911 and your local Endocrine doctor.

## How to prevent low blood sugar:

- Know the cause of your child's hypoglycemia; this will eliminate unnecessary hypoglycemic events and decrease the risk of brain damage.
- Understand all aspects of the child's condition to provide the best home care.
- Monitor your child's blood sugar more closely during times of illness (like vomiting and diarrhea).
- Know your child's fasting tolerance.