Hypoglycemia/Hyperglycemia

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The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with companies or the manufacturer(s) of any commercial product/service that will be discussed as part of this presentation.

Session Summary

During this session Dr. Clark will discuss the new AAP guidelines for management of hypoglycemia and how best to prevent hypo- and hyperglycemia. Brain injury patterns seen in infants who are hypo- or hyperglycemia will also be reviewed.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- discuss the physiology of glucose metabolism;
- state the derivation of the definition of hypoglycemia;
- identify the most common causes for hypo- and hyperglycemia;
- discuss management strategies to reduce the problems associated with both.

References


CPS Statement: Retrieved at www.cps.ca/english/states/FN/fn04-01.htm


Glucose Utilization, retrieved at http://www.umanitoba.ca/dnalab/graduate/pancreas10.htm


*Please review additional references denoted on the slides.

**Session Outline**

See handout on the following pages.
Objectives

• To discuss the physiology of glucose metabolism
• To review the derivation of the definition of hypoglycemia
• To identify the most common causes for hypo- and hyperglycemia
• To discuss management strategies to reduce the problems associated with both.

Glucose Metabolism in the NICU
Knowing When They Are Too Sweet
And When They Are Not Sweet Enough

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Physiology

Pancreas

• The pancreas secretes two important hormones that regulate glucose, lipid, and protein metabolism: glucagon and insulin.
• Two major types of tissues:
  – acini, which secrete digestive juices into the duodenum
  – islets of Langerhans, which secrete the hormones insulin and glucagon directly into the blood.
• The islets of Langerhans contain three types of hormone-secreting cells:
  – alpha cells, which secrete glucagon,
  – beta cells, which secrete insulin,
  – delta cells, which secrete somatostatin and/or gastrin.

Glucose Utilization

http://www.umanitoba.ca/dnalab/graduate/pancreas10.htm
In insulin regulation, blood glucose concentration is a reflection of the balance between glucose input into the circulation from food intake and glucose extraction for consumption by the tissues.

Pathways of glucose extraction include glucose storage as glycogen in the liver and muscles, glucose conversion to lipid, and glucose oxidation.

During feeding, increased blood glucose and amino acid levels, as well as gut hormones, stimulate insulin secretion and suppress glucagon release.

The main action of insulin is in the liver, where it stimulates conversion of glucose to glycogen and decreases gluconeogenesis and glycogenolysis.

Glucose is also stored as glycogen in the muscles. It is oxidized in the muscle and adipose tissue and converted to lipid in the liver and adipose tissue.

Insulin stimulates amino acid incorporation into protein and fatty acid incorporation into lipids.

Glycogenolysis – breakdown of hepatic glycogen yielding glucose

Glucogenesis – production of glucose from noncarbohydrate precursors

Lipolysis – breakdown of fat

Ketogenesis – creation of ketones

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During periods of fasting, the source of energy shifts from the oxidation of glucose to the oxidation of fat.
- Early in fasting, glucose is supplied by the breakdown of hepatic glycogen stimulated by epinephrine and glucagon.
- After hepatic glycogen stores are depleted, the body depends on new glucose produced from precursors in muscle and adipose tissue.
- Gluconeogenesis is stimulated by growth hormone and cortisol.
- With prolonged fasting, adipose tissue is broken down into free fatty acids (FFA) and glycerol.
- FFA can be used directly as a fuel by tissues and are oxidized in the liver to provide energy with resultant formation of ketone bodies (acetoacetate and β-hydroxy-butyrate).
- Ketone bodies can be used as an alternate fuel as previously mentioned.

Glucose Balance

Hypoglycemia

Defining Hypoglycemia is a Problem

Screening guidelines for newborns at risk for low blood glucose
Fetus and Newborn Committee, Canadian Paediatric Society (CPS)
Paediatr Child Health 2004;9(10):723-9
Reference No. FN04-01
Reaffirmed February 2009

Medscape – Persistent Hyperinsulinemic Hypoglycemia in Infants: Physiology
Lori A. Markham, MSN, RNC, NNP, CCRN, Baylor University Medical Center

Glucose Counter-regulatory Hormones: Effect on Liver
Canadian Paediatric Society (CPS) Paediatr Child Health 2004;9(10):723-9

- Neonatal hypoglycemia cannot be defined by a single value of glucose applicable to all clinical situations and to all infants.
- It appears that infants may develop signs suggestive of hypoglycemia over a range of blood glucose levels that is substantially lower than normal adult levels.


- The magnitude of concern about a medical disorder often is inversely related to the amount of accurate data defining it.
- Dr. Cornblath describes how concern for neonatal hypoglycemia has grown exponentially over the past 50 years.
- He also points out that those characteristics of low glucose concentration that might cause irreversible neuronal injury remain relatively undocumented and poorly defined.


- Blood glucose concentrations as low as 30 mg/dL are common in healthy neonates by 1 to 2 hours after birth; these low concentrations, seen in all mammalian newborns, usually are transient, asymptomatic, and considered to be part of normal adaptation to postnatal life.
- Most neonates compensate for “physiologic” hypoglycemia by producing alternative fuels including ketone bodies, which are released from fat.

Canadian Paediatric Society (CPS) Paediatr Child Health 2004;9(10):723-9

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Emedicine article -Pediatrics, Hypoglycemia

- Hypoglycemia is the most common metabolic problem in neonates.
- In children, a blood glucose value of less than 40 mg/dL (2.2 mmol/L) represents hypoglycemia.
- A plasma glucose level of less than 30 mg/dL (1.65 mmol/L) in the first 24 hours of life and less than 45 mg/dL (2.5 mmol/L) thereafter constitutes hypoglycemia in the newborn.


- There is not a specific plasma glucose concentration or duration of hypoglycemia that can predict permanent neurologic injury in high-risk infants.
- Data that have linked plasma glucose concentration with adverse long-term neurologic outcomes are confounded by variable definitions of hypoglycemia and its duration (seldom reported), the omission of control groups, the possible inclusion of infants with confounding conditions, and the small number of asymptomatic infants who were followed.
- In addition, there is no single concentration or range of plasma glucose concentrations that is associated with clinical signs. Therefore, there is no consensus regarding when screening should be performed and which concentration of glucose requires therapeutic intervention in the asymptomatic infant.
Distribution of Glucose in the NICU

Percentiles for Neonates With No Report of Glucose Problems

Glucose Day 0

Glucose Day 1

Glucose EGA = 40

Glucose Based on Growth Group
Symptoms

- Jitteriness
- Cyanosis (blue coloring)
- Apnea (stopping breathing)
- Hypothermia (low body temperature)
- Poor body tone
- Poor feeding
- Lethargy
- Seizures

Causes of Hypoglycemia

- Causes of hypoglycemia in neonates differ slightly from the causes of hypoglycemia in older infants and children.
- Hyperinsulinism, or persistent hyperinsulinemic hypoglycemia of infancy (PHHI), is the most common cause of hypoglycemia in the first 3 months of life. It is well recognized in infants of mothers with diabetes.
- Other causes in all ages include gram-negative sepsis; endotoxin shock; and ingestions, including salicylates, alcohol, hypoglycemic agents, and beta-adrenergic blocking agents.

Emedicine article - Pediatrics, Hypoglycemia
Hilarie Cranmer, MD, MPH, FACEP, Assistant Professor; Michael Shannon, MD, MPH, Professor, Department of Pediatrics, Harvard Medical School, Children’s Hospital; Updated: Aug 10, 2009.

- The overall incidence of symptomatic hypoglycemia in newborns varies from 1-3 per 1000 live births.
- Incidence varies with the definition, population, method and timing of feeding, and the type of glucose assay. Serum glucose levels are higher than whole blood values.
- The incidence of hypoglycemia is greater in high-risk neonatal groups.
- Early feeding decreases the incidence of hypoglycemia.
Harris, DL; et al. Incidence of Neonatal Hypoglycemia in Babies Identified as at Risk J. Pediatrics 2012

- Infants (n = 514) were recruited who were born in a tertiary hospital, >35 weeks gestation and identified as at risk of hypoglycemia (small, large, infant of a diabetic, late-preterm, and other).
- One-half of the babies (260/514, 51%) became hypoglycemic, 97 (19%) had severe hypoglycemia, and 98 (19%) had more than 1 episode.
- Most episodes (315/390, 81%) occurred in the first 24 hours.
- The median number of blood glucose measurements for each baby was 9 (range 1-22).
- The incidence and timing of hypoglycemia was similar in all at risk groups, but babies with a total of 3 risk factors were more likely to have severe hypoglycemia.

Transient Hypoglycemia
- Infants of diabetic mothers
- Prematurity
- Hypothermia
- Intrauterine growth restriction (IUGR)
- Small for gestational age (SGA)
- Septicemia, asphyxia/birth depression
- Erythroblastosis fetalis
- Beckwith-Wiedemann syndrome

Persistent Hypoglycemia
- Hyperinsulinemia
  - PHHI
  - Beta-cell adenoma
  - Exogenous insulin administration
  - Sulfonylurea use
- Hormone-deficiency
  - Growth hormones
  - Adrenal insufficiency
  - Glucagon
  - Hyperthyroidism
  - Panhypopituitarism
- Errors of metabolism
  - Carbohydrate metabolism disorders
  - Fat metabolism disorders
  - Amino acid metabolism disorders
  - Ketotic hypoglycemia
- Liver Disease

Diagnosis of Hyper and Hypoglycemia

Diagnosis of Hypoglycemia and Hyperglycemia

Rare Causes of Hypoglycemia
- The incidence of inborn errors of metabolism that lead to neonatal hypoglycemia are rare but can be screened in infancy:
  - Carbohydrate metabolism disorders (>1:10,000)
  - Fatty acid oxidation disorders (1:10,000)
  - Hereditary fructose intolerance (1:20,000 to 1:50,000)
  - Glycogen storage diseases (1:25,000)
  - Galactosemia (1:40,000)
  - Organic acidemias (1:50,000)
  - Phospho(enol)pyruvate carboxykinase deficiency (rare)
  - Primary lactic acidosis (rare)
Nesidioblastosis

W Zumkeller. Nesidioblastosis. Endocrine-Related Cancer (1999) 6 421-428

- The underlying genetic defects of b-cell regulation include a severe recessive disorder of the sulphonylurea receptor, a milder dominant form of hyperinsulinism, and a syndrome of hyperinsulinism plus hyperammonaemia.
- Estimates for the incidence of congenital hyperinsulinism vary from 1/40,000 live births in northern Europe to 1/2675 live births in Saudi Arabia where consanguineous marriages are common.
- This condition requires prompt medical and surgical therapy in order to prevent permanent brain damage.

Genetics

- Most cases of PHHI are sporadic. In approximately 50% of cases, no known genetic abnormality is found.
- Familial forms of PHHI are rare but well documented. These cases of PHHI involve autosomal recessive or dominant defects in 4 genes.
  - Beta-cell high-affinity sulfonamide receptor gene (ABCC8, also known as SUR1)
  - Inwardly rectifying potassium channel gene (KCNJ11, also known as Kir6.2)
  - Glucokinase gene (GCK, also called Gk): Only 5 persons have been described with this mutation.
  - Glutamate dehydrogenase gene (GLUD1, also called GUD1): This gene is associated with hyperinsulinism with hyperammonaemia. It is unclear whether this disorder (described below) is a variant of persistent hyperinsulinemic hypoglycemia of infancy or a distinct clinical entity.

- The abnormal histologic aspects of the tissue include:
  - the presence of islet cell enlargement,
  - islet cell dysplasia,
  - beta cells budding from ductal epithelium,
  - and islets in apposition to ducts.

Evaluation

Pancreatic specimen showing diffuse persistent hyperinsulinemic hypoglycaemia of infancy (PHHI) viewed at low power. The pale-staining cells are the neuroendocrine (islet) cells, which should be arranged in discrete islands within the acinar lobules. Acinar cells are the exocrine cells that have denser-staining, dark eosinophilic cytoplasm. These acinar cells are arranged in acini-small glands. In PHHI, more of the neuroendocrine cells are present, and they are arranged more diffusely throughout the lobules. Image courtesy of Phil Collins, MD; eMedicine Specialties > Pediatrics: General Medicine > Endocrinology -- Persistent Hyperinsulinemic Hypoglycaemia of Infancy Author: Robert S Gillespie, MD, MPH, Department of Pediatrics, Cook Children’s Medical Center; Coauthor(s): Stephen Ponder, MD, CDE, Director, Division of Pediatric Endocrinology, Department of Pediatrics, Driscoll Children’s Hospital; Professor, Texas A&M College of Medicine.
High-risk groups who need screening

- Newborns who weigh more than 4 kg or less than 2 kg
- Large for gestational age (LGA) infants who are above the 90th percentile, small for gestational age (SGA) infants below the 10th percentile, and infants with intrauterine growth restriction
- Infants born to insulin-dependent mothers (1 in 1000 pregnant women) or mothers with gestational diabetes (occurs in 2% of pregnant women)
- Gestational age less than 37 weeks
- Newborns suspected of sepsis or born to a mother suspected of having chorioamnionitis
- Newborns with symptoms suggestive of hypoglycemia, including jitteriness, tachypnea, hypotonia, poor feeding, apnea, temperature instability, seizures, lethargy
- Significant hypoxia; perinatal distress; or 5-minute Apgar scores less than 5
- Mother on terbutaline, beta-blockers, or oral hypoglycemic agents;
- Possibility of an inborn error of metabolism or genetic disorder.

Which infants should we screen?

- The AAP suggest that “at risk infants” should be screened.
  - SGA
  - LGA
  - IDM
  - Preterm

  “Routine screening and monitoring of blood glucose concentration is not needed in healthy term newborn infants after an entirely normal pregnancy and delivery.”


Medscape – Persistent Hyperinsulinemic Hypoglycemia in Infants: Physiology
Lori A. Markham, MSN, RNC, NNP, CCRN, Baylor University Medical Center

- When the patient is hypoglycemic (glucose <40 mg/dl), the diagnosis can usually be made by measuring
  – plasma glucose
  – serum insulin, cortisol, growth hormone
  – lactate, free fatty acids, and β-hydroxybutyrate (ketones)

Importance of Glucose to the Brain

- The brain and formed elements of blood have an obligatory glucose requirement.
- Brain cells are permeable to glucose and can utilize glucose without the intermediation of insulin.
- The brain is able to metabolize ketone bodies, acetoacetate, and beta-hydroxybutyrate for up to two-thirds of its energy requirements in the absence of glucose.

- Studied 35 term infants with early brain MRI scans after symptomatic neonatal hypoglycemia (median glucose level: 1 mmol/L) without evidence of HIE.
- Compared with equivalent data from 229 term, neurologically normal infants (control subjects), to identify risk factors for hypoglycemia.
- White matter abnormalities occurred in 94% of infants with hypoglycemia, being severe in 43%, with a predominately posterior pattern in 29%.
- Cortical abnormalities occurred in 51% of infants; 30% had white matter hemorrhage, 40% basal ganglia/thalamic lesions, and 11% an abnormal posterior limb of the internal capsule. Three infants had middle cerebral artery territory infarctions.
- Twenty-three infants (65%) demonstrated impairments at 18 months, which were related to the severity of white matter injury and involvement of the posterior limb of the internal capsule.
- Fourteen infants demonstrated growth restriction, 1 had macromelia, and 2 had mothers with diabetes mellitus.
- Pregnancy-induced hypertension, a family history of seizures, emergency cesarean section, and the need for resuscitation were more common among case subjects than control subjects.


- The impact of isolated hypoglycemia on the developing brain has been well documented in animal experiments, including those on primates.
- 3 important principles
  - First, prolonged and severe, rather than transient or minor, hypoglycemia was required for cerebral injury.
  - Second, the pattern of injury involved neuronal injury to the upper cortical layers (2 and 3), particularly affecting the parieto-occipital regions, as well as injury to the hippocampus, caudate, and white matter.
  - Finally, mild hypoglycemia combined with mild hypoxia-ischemia resulted in cerebral injury, whereas either of the 2 conditions in isolation did not.

Management
Glucose infusion

- Main treatment is to provide glucose
  - Feeding provide carbohydrates that can be used to produce glucose
  - IV infusion (normal glucose infusion rate 6-8 mg/kg/min)
  - If higher rates of glucose infusions are required a central line should be placed

CPS Statement:

www.cps.ca/english/statements/FN/fn04-01.htm

- Initiate intravenous infusion of 10% dextrose at a rate of 80ml/kg/day (5.5mg glucose/kg/min). Check glucose 30 min after any change and adjust therapy (up to 100 ml/kg/day and/or 12.5% dextrose) in order to maintain glucose level ≥ 2.6mmol/l (approximately 45mg/dl).
- If rates in excess of 100 ml/kg/day of 12.5% dextrose are required investigation, consultation and/or pharmacological intervention are indicated.
- May start weaning IV 12 hours after stable blood glucose is established. Continued breastfeeding is encouraged.

Drugs Used

- Diazoxide acts to inhibit insulin secretion. Can cause fluid retention
- Octreotide is a long-acting somatostatin analog that also acts to inhibit insulin secretion but it can suppress growth hormone, and increase abdominal distention
- Nifedipine is a calcium channel blocking agent and acts to decrease insulin secretion by closing the ATP potassium channels in the pancreatic beta cells.
- Glucagon is used as a temporizing agent and antagonizes insulin action by mobilizing hepatic glycogen stores
- Glucocorticoids have also been shown to be effective in managing hypoglycemia, but their use is minimal.

http://www.cps.ca/english/statements/fvFN04-01-fig1.pdf
Hyperglycemia

**Definition**
- Hyperglycemia is a serum glucose concentration > 125 mg/dL.
- The most common cause of neonatal hyperglycemia is iatrogenic.
- Iatrogenic causes usually involve too-rapid IV infusions of dextrose during the first few days of life in very low-birth-weight infants (< 1.5 kg).

**Causes of Hyperglycemia**
- The other important cause of hyperglycemia is physiologic stress
  - Surgery
  - Hypoxia
  - Respiratory distress
  - Sepsis
- In premature infants, partially defective processing of proinsulin to insulin and relative insulin resistance may cause hyperglycemia.
- In addition, transient neonatal diabetes mellitus is a rare self-limited cause that usually occurs in small-for-gestational-age infants
- Corticosteroid therapy may also result in transient hyperglycemia.

**Risks for Hyperglycemia**
- Preterm birth
- Higher-than-needed rates of IV glucose infusion
- Intrauterine growth restriction (IUGR)
- Increased stress hormones
  - Increased catecholamine infusions and plasma concentrations
  - Increased glucocorticoid concentrations (from use of antenatal steroids, postnatal glucocorticoid administration, and stress)
  - Increased glucagon concentrations
- Early and high rates of intravenous (IV) lipid infusion
- Insufficient pancreatic insulin secretion
- Absence of enteral feedings, leading to diminished "incretin" secretion and action, limiting their potential to promote insulin secretion.
Diagnosis of Hyper and Hypoglycemia

Among preterm infants receiving continuous glucose infusions at 8 mg/kg per minute, 11 mg/kg per minute, or 14 mg/kg per minute, practically none of the infants in the lowest glucose infusion group developed hyperglycemia. In contrast, 50% or more of the infants in the middle infusion group and all of the infants in the highest infusion group developed increased blood glucose concentrations.


- Four eligible trials
- Two trials compared lower vs. higher rates of glucose infusion in the early postnatal period. These trials were too small to assess effects on mortality or major morbidities.
- Two trials, one a moderately large multicentre trial (NIRTURE, Beardsall 2008), compared insulin infusion with standard care.
- Insulin infusion reduced hyperglycemia but increased death before 28 days and hypoglycemia.
- Reduction in hyperglycemia was not accompanied by significant effects on major morbidities; effects on neurodevelopment are awaited.


- 195 assigned infants to continuous infusion of insulin at a dose of 0.05 U per kilogram of body weight per hour with 20% dextrose support
- 194 to standard neonatal care on days 1 to 7. The efficacy of glucose control was assessed by continuous glucose monitoring.
- Compared with the control group, infants in the early-insulin group had lower mean glucose levels (112±25 vs. 121±40 mg/dl, P <0.01).
- Fewer infants in the early-insulin group had hyperglycemia for more than 10% of the first week of life (21% vs. 33%, P = 0.008).
- The early-insulin group had significantly more carbohydrate infused (51±13 vs. 43±10 kcal per kilogram per day, P=0.001) and less weight loss in the first week (standard-deviation score for change in weight, −0.55±0.52 vs. −0.70±0.47; P = 0.006).
- More infants in the early-insulin group had episodes of hypoglycemia (defined as a blood glucose level of <2.6 mmol per liter [47 mg per deciliter] for >1 hour) (29% in the early-insulin group vs. 17% in the control group, P = 0.005), and the increase in hypoglycemia was significant in infants with birth weights of more than 1 kg.
- In the intention-to-treat analysis, mortality at 28 days was higher in the early insulin group than in the control group (P = 0.04).
Complications

Treatment

- Reduction of IV dextrose concentration, rate, or both
- Rarely insulin
- "Reasonable guidelines indicate that insulin treatment should be reserved until plasma glucose concentrations exceed 16.7 to 22.2 mmol/L (300 to 400 mg/dL) despite reducing the glucose infusion rate to less than 3 to 4 mg/kg per minute. The usual method of insulin administration involves a continuous infusion, beginning at 0.02 to 0.05 U/kg per hour. Although higher infusion rates have been used, they usually are not necessary and increase the risks of hypokalemia and subsequent hypoglycemia."
- Hay, http://pedsinreview.aappublications.org/cgi/content/full/20/7/e16