Spontaneous hypoglycaemia

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Definitions of Hypoglycemia

Definitions for hypoglycemia are variable, which complicates both the study and tracking of hypoglycemic events.

Rather than refer to a specific blood glucose concentration for all individuals, hypoglycemia in patients with diabetes can be defined as:

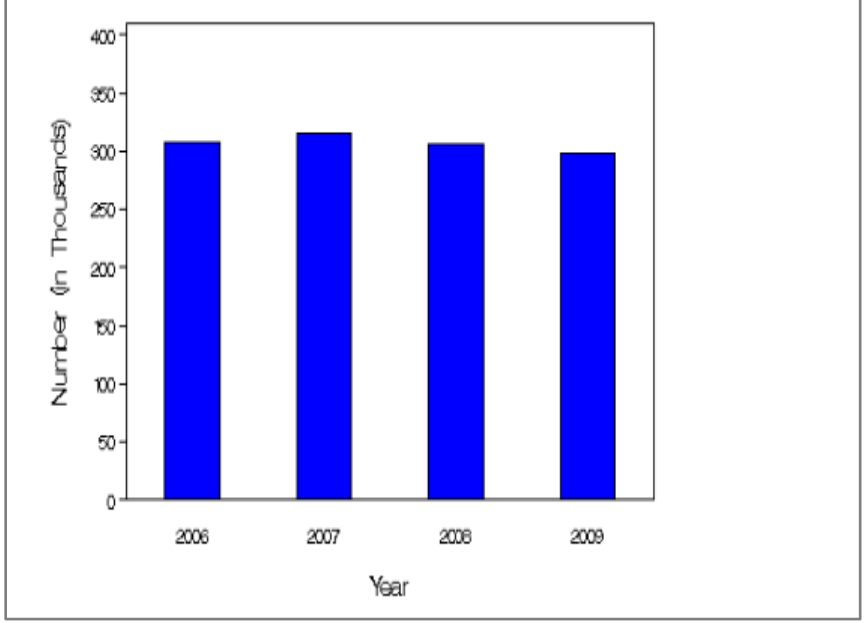
An abnormally low plasma glucose concentration that exposes the individual to potential or actual harm.

Office of Disease Prevention and Health Promotion and the Centers for Disease Control and Prevention. (2014, September). Slides for Preventing Adverse Drug Events: Individualizing Glycemic Targets Using Health Literacy Strategies. (Continuing Education Course) CDC Training and Continuing Education Online. Chapter 2.

Emergency department visits, with hypoglycemia as first-listed diagnosis

DM patients 18 years or older, 2006-2009, USA

Number remained stable, about 300,000/yr



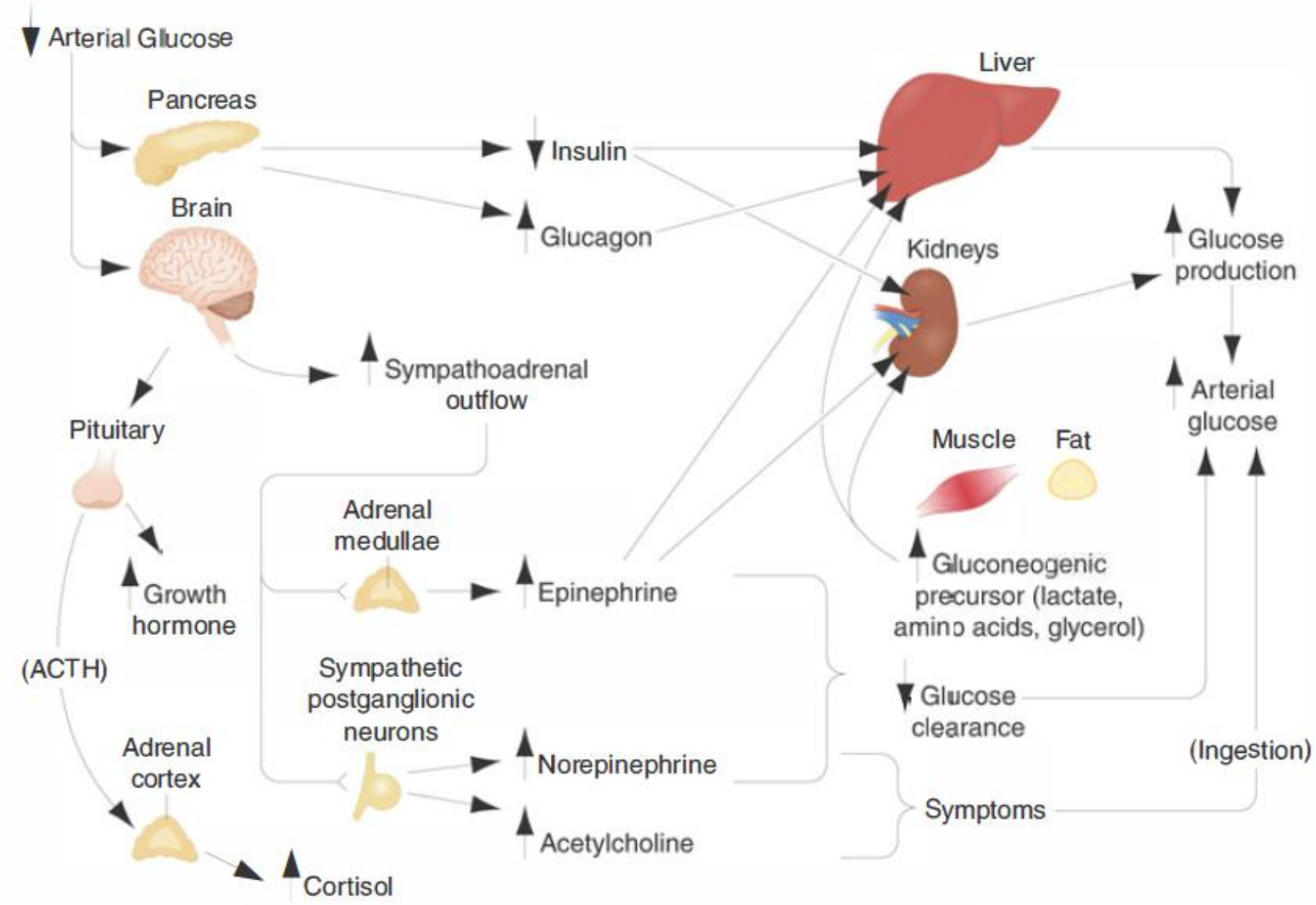
Centers for Disease Control and Prevention. "Hypoglycemia." <http://www.cdc.gov/diabetes/statistics/hypoglycemia> Accessed 5/22/2015.

Spontaneous hypoglycaemia

- When hypoglycaemia develops in non-diabetic people, it is called ‘spontaneous’ hypoglycaemia.
- There is no specific blood glucose concentration at which spontaneous hypoglycaemia can be said to occur.
- For this reason, and because the symptoms of hypoglycaemia are non-specific, a hypoglycaemic disorder should only be diagnosed if all three conditions of Whipple’s triad are met.

Whipple's triad

- Patient had symptoms of hypoglycaemia
- Low blood glucose measured at the time of symptoms
- Symptoms resolved on correction of hypoglycaemia



Physiology of glucose counterregulation

PHYSIOLOGIC RESPONSES TO DECREASING PLASMA GLUCOSE CONCENTRATIONS

Response	Glycemic threshold, mmol/L (mg/dL)	Role in Prevention or Correction of Hypoglycemia (Glucose Counterregulation)
↓ Insulin	4.4-4.7 (80-85)	Primary glucose regulatory factor/first defense against hypoglycemia
↑ Glucagon	3 .6-3 .9 (65-70)	Primary glucose counterregulatory factor/second defense against hypoglycemia
↑ Epinephrine	3.6-3.9 (65-70)	Third defens against hypoglycemia, critical when glucagon is deficient
↑ Cortisol and GH	3.6-3.9 (65-70)	Involved in defense against prolonged hypoglycemia; not critical

Most common symptoms of hypoglycaemia

Autonomic

- Sweating
- Trembling
- Pounding heart
- Hunger
- Anxiety

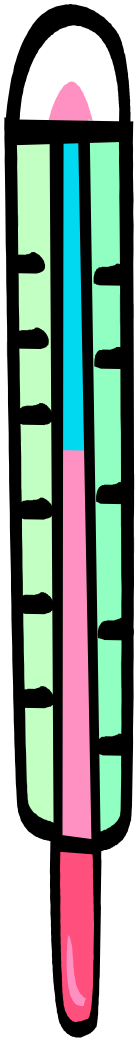
Neuroglycopenic

- Confusion
- Drowsiness
- Speech difficulty
- Inability to concentrate
- Incoordination
- Irritability, anger

Non-specific

- Nausea
- Tiredness
- Headache

Hypoglycemia Symptoms



90 ← Normal

70 ← Counterregulatory hormone release

60 ← Adrenergic symptoms

50 ← Neuroglycopenic symptoms

40 ← Lethargy

30 ← Coma

20 ← Seizure

CAUSES OF HYPOGLYCEMIA

Ill or medicated individual

1 . Drugs

Insulin or insulin secretagogue, alcohol

2 . Critical illness

Hepatic, renal or cardiac failure

Sepsis, inanition

3 . Hormone deficiency

Cortisol

4. Non-islet cell tumor

Seemingly well individual

5 . Endogenous hyperinsulinism

Insulinoma

Functional ß-cell disorders

Insulin autoimmune hypoglycemia

6. Accidental, surreptitious, or malicious hypoglycemia

Drugs

- Insulin and insulin secretagogues suppress glucose production and stimulate glucose utilization.
- Ethanol blocks gluconeogenesis but not glycogenolysis.
- Many other drugs have been associated with hypoglycemia. These include commonly used drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists, ß-adrenergic receptor antagonists, quinolone antibiotics, indomethacin, quinine, and sulfonamides.

Critical illness

- Among hospitalized patients, serious illnesses such as renal, hepatic, or cardiac failure; sepsis; and inanition are second only to drugs as causes of hypoglycemia.
- Rapid and extensive hepatic destruction (e.g., toxic hepatitis) causes fasting hypoglycemia because the liver is the major site of endogenous glucose production.

Critical illness

- Sepsis is a relatively common cause of hypoglycemia. Increased glucose utilization is induced by cytokine production in macrophage rich tissues such as the liver, spleen, and lung.
- Hypoglycemia develops if glucose production fails to keep pace. Cytokine-induced inhibition of gluconeogenesis in the setting of nutritional glycogen depletion, in combination with hepatic and renal hypoperfusion, may also contribute to hypoglycemia.

Hormone Deficiencies

- Hypoglycemia can occur with prolonged fasting in patients with primary adrenocortical failure (Addison's disease) or hypopituitarism.
- Cortisol deficiency is associated with impaired gluconeogenesis.

Non-β-Cell Tumors

- Fasting hypoglycemia, often termed non-islet cell tumor hypoglycemia, occurs occasionally in patients with large mesenchymal or epithelial tumors (e.g., hepatomas, adrenocortical carcinomas, carcinoids).
- In most instances, hypoglycemia is due to overproduction of an incompletely processed form of insulin-like growth factor II ("big IGF-II") that does not complex normally with circulating binding proteins and thus more readily gains access to target tissues.

Endogenous Hyperinsulinism

1. A primary ß-cell disorder-typically a ß-cell tumor (insulinoma), sometímes multiple insulinomas, or a functional ß-cell disorder with ß-cell hyperplasia or hypertrophy
2. An antibody to insulin or to the insulin receptor
3. Ectopic insulin secretion, among other very rare mechanisms.

None of these causes is common.

Diagnosis

- Establishing fasting hypoglycemia
- Establishing the cause

Supervised 72 hour fast test

- In hospital setting to lower risk to the patient
- Usually hypoglycemia develops in first 48 hours of the fast in 95% of cases

Supervised 72 hour fast test

Protocol

- Discontinue all non essential medications
- Allow the patient to drink calorie-free and caffeine-free beverages
- Collect blood specimens for measurement of plasma glucose, insulin, C-peptide, and proinsulin every six hours until the plasma glucose concentration is below 60 mg/dL (3.3 mmol/L) at this point, the frequency of sampling should be increased to every one to two hours.

Test end points and duration

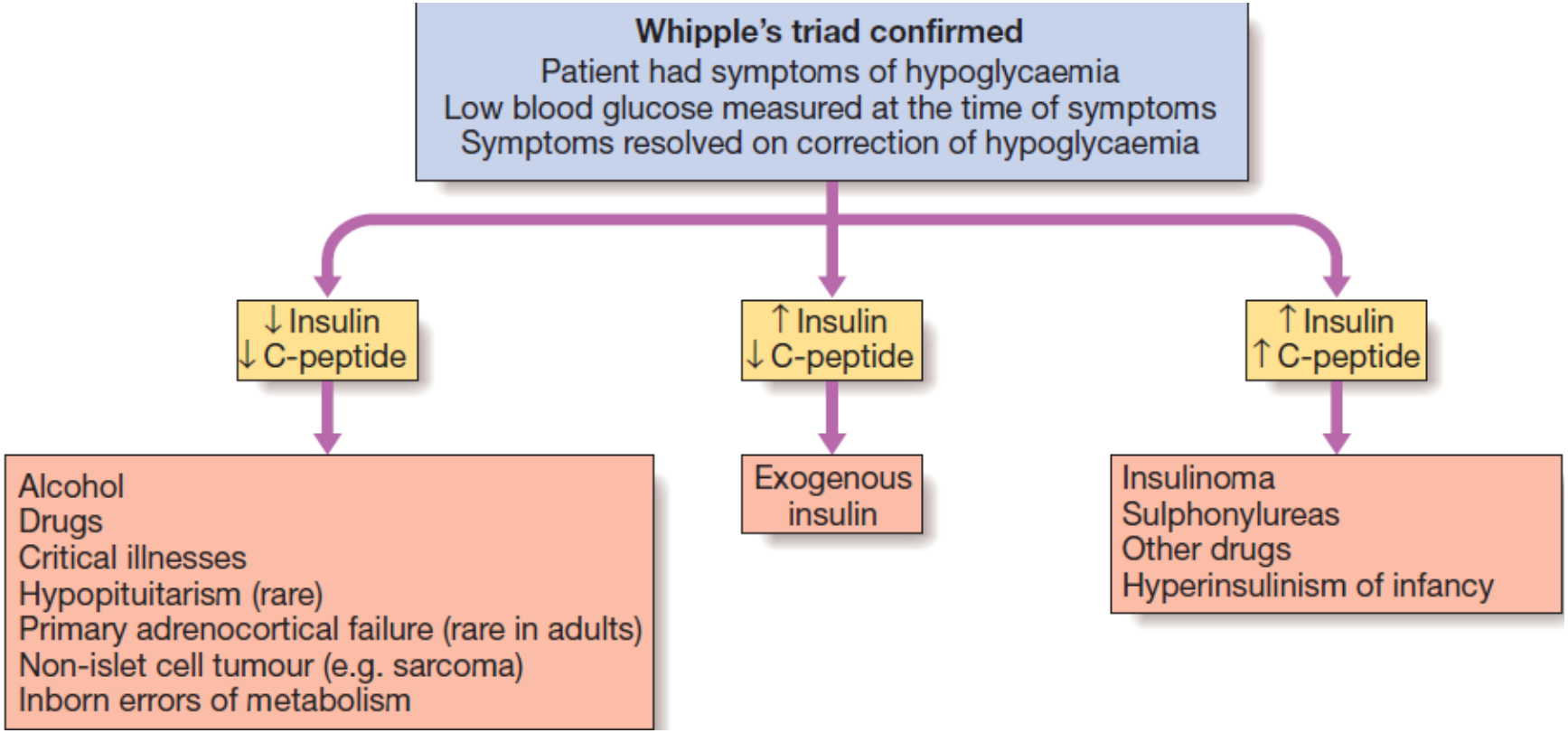
- The plasma glucose concentration is ≤45 mg/dL (2.5 mmol/L)
- The patient has symptoms or signs of hypoglycemia
- 72 hours have elapsed
- Plasma beta-hydroxybutyrate and sulfonylurea levels are measured with glucose, insulin, C-peptide, proinsulin.
- 1 mg of glucagon is given intravenously and the plasma glucose measured 10, 20, and 30 minutes later.

INTERPRETATION

- Normals do not become hypoglycaemic.
- If hypoglycaemia with raised insulin but low C peptide, consider self administration of insulin.
- If hypoglycaemia with raised insulin, and raised C-peptide, make sure sulphonylurea screen is negative!

INTERPRETATION

- With hypoglycaemia, insulin and endogenous insulin production (estimated by C-peptide) should be low.
  - Insulin <3 mU/l; C peptide <75 pmol/l = normal response
  - Insulin >3-6 mU/l; C peptide 100-300 pmol/l = possible insulinoma but needs further tests
  - Insulin >6 mU/l; C peptide >300 pmol/l = insulinoma
- Ketones should be suppressed with insulinoma even though patient is fasting because of the excess insulin.



Differential diagnosis of spontaneous hypoglycaemia

Management

- Treatment of acute hypoglycaemia should be initiated as soon as laboratory blood samples have been taken.
- Intravenous dextrose (5% or 10%) is effective in the short term in the obtunded patient, and should be followed on recovery with oral unrefined carbohydrate.

Management

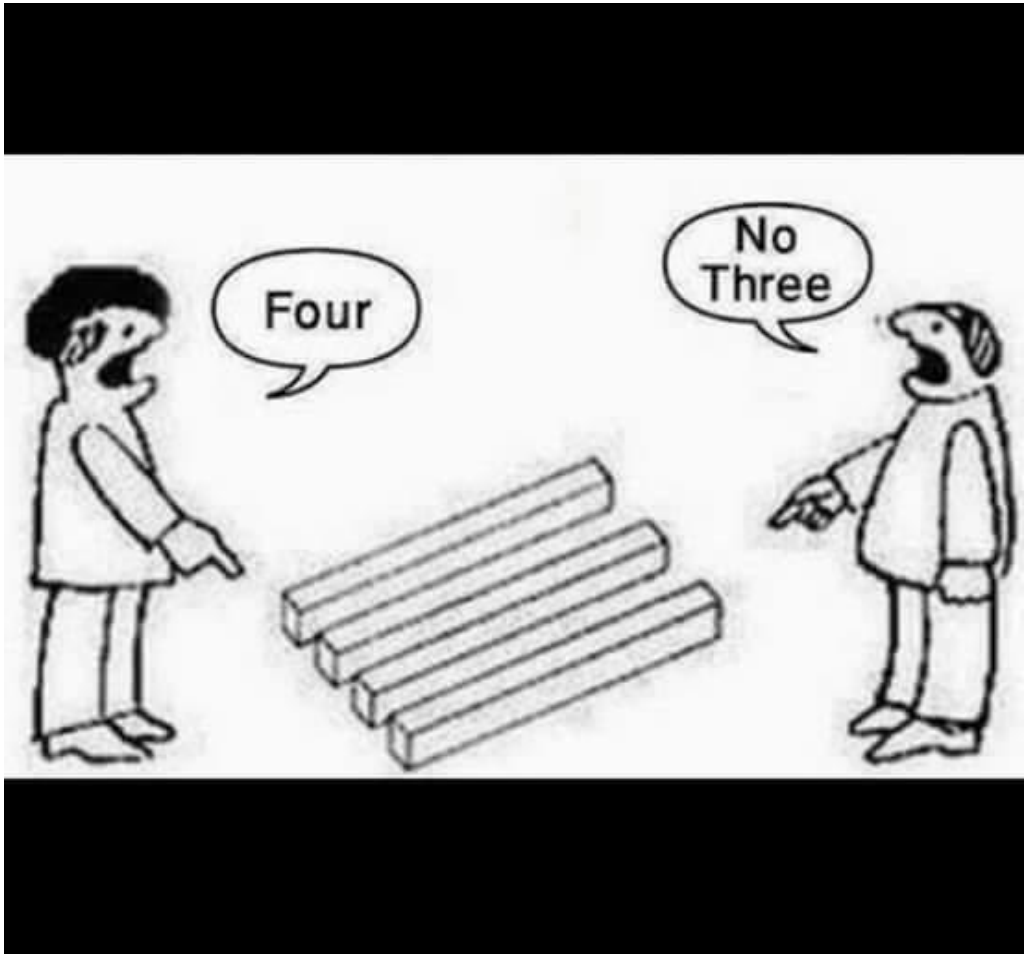
- Chronic recurrent hypoglycaemia in insulin-secreting tumours can be treated by regular consumption of oral carbohydrate combined with agents that inhibit insulin secretion (diazoxide or somatostatin analogues).
- Insulinomas are resected when benign, providing the individual is fit enough to undergo surgery.

Management

- Patients with autoantibodies against the insulin receptor can be treated with high-dose glucocorticoid (prednisone, 60 mg/d) to prevent hypoglycemia.
- The treatment of hypoglycemia related to hepatic or renal disease, cardiac failure, or sepsis includes short-term measures and, treatment or management of the underlying disease process.

Conclusion

- Definition
- Establishing hypoglycemia
- Establishing the cause
- Treatment


Four
No
Three