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Hypoglycemic Disorders

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A fine balance between glucose production and glucose utilization maintains glucose levels in the normal range, both in the fasting and the "fed" states. Glucose enters the blood stream either from ingestion of carbohydrate-containing foods (in the fed state) or as a result of the breakdown of hepatic glycogen (glycogenolysis) or the formation of glucose from non-carbohydrate precursors (gluconeogenesis) in the fasting (post-absorptive) state. The latter process takes place primarily in the liver and to a lesser extent in the kidneys. The balance between production and utilization of glucose is maintained by an orchestrated interplay between insulin and insulin-counter-regulatory hormones: glucagon, catecholamines, cortisol, and growth hormone.

Failure to maintain the above balance may result in either hyperglycemia or hypoglycemia. The term "hypoglycemia" describes a symptom complex that may result from several underlying conditions.¹ While the symptoms are often typical, they are non-specific. The symptoms of hypoglycemia result from stimulation of the autonomic nervous system and from depriving the brain of its favourite fuel, glucose. The classical symptoms of hypoglycemia are therefore classified into neurogenic (autonomic) or neuroglycopenic. Table 1 shows the effects of glucose lowering on the compensatory mechanisms that we are equipped with to maintain euglycemia and the levels of glucose at which symptoms start to develop. It is, however, prudent to realize that the classical symptoms are not the only symptoms encountered in association with hypoglycemia. The symptoms seen in patients with insulinomas are detailed in Table 2.

To be certain that hypoglycemia is the cause of a patient's symptoms, Whipple's triad has to be fulfilled (Table 3).² Measurement of glucose to diagnose hypoglycemia has to be done by laboratory testing, rather than by self-measured capillary blood glucose.³

Classification of hypoglycemia

Hypoglycemia is classified into postprandial (reactive) and fasting (post-absorptive) hypoglycemia.⁴

I. Postprandial hypoglycemia

Postprandial hypoglycemia usually occurs within 4 hours of food intake. This entity is well-documented in the early life of patients with hereditary fructose intolerance and galactosemia that result from congenital deficiencies of enzymes necessary for carbohydrate metabolism. In adults, one of the best-described causes of postprandial hypoglycemia is alimentary hypoglycemia, a condition that occurs in patients who have undergone gastric surgery that results in rapid emptying of food into the small intestine.⁵ Hypoglycemia results from marked early insulin secretion due to a rapid increase in blood glucose levels. Incretins contribute to the enhanced insulin secretion,



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Table 1: Response to falling glycemia	
Response	Threshold
Decreased insulin secretion	4.4 mmol/L
Increased counter-regulatory secretion	3.6 mmol/L
Symptoms	3.0 mmol/L
Cognitive dysfunction	2.5 mmol/L

thereby exaggerating glucose-stimulated insulin release.⁶ Idiopathic reactive hypoglycemia has been documented only in a few patients after a 5-hour oral glucose tolerance test (OGTT) and measuring glucose levels following mixed meals; therefore, the existence of such an entity is debatable.^{7,8} The diagnosis of post-prandial hypoglycemia should not be made on the basis of glucose levels in an OGTT. Values as low as 2.4 mmol/l can be obtained in totally healthy people.

Several interventions in these patients have been suggested, but the evidence for their benefit and effectiveness is lacking. The use of frequent low-carbohydrate, high-protein meals, anti-cholinergic drugs, propranolol, acarbose, or miglitol are among the interventions used in such patients.

II. Fasting (post-absorptive) hypoglycemia

The causes of post-absorptive hypoglycemia include:

Drugs: Drugs are the most common cause of hypoglycemia.⁹ Antihyperglycemic agents – insulin and insulin secretagogues – are common causes of hypoglycemia in patients with diabetes mellitus. These agents can also cause hypoglycemia in patients who do not have diabetes if taken surreptitiously, given intentionally by a second party, or inadvertently through a

Table 2: Symptoms of hypoglycemia reported by patients with insulinoma	
Symptoms	Incidence
Various combinations of diplopia, blurred vision, sweating, palpitations	85%
Confusion or abnormal behavior	80%
Unconsciousness or amnesia	53%
Convulsions	12%

Table 3: Whipple's triad
<p>Definition of "Whipple's Triad"²</p> <ul style="list-style-type: none"> – Blood glucose < 2.8 [< 2.5 (Service) or < 3 mmol/L (Marks and Teal)] – Classical symptoms: neurogenic (autonomic) and neuroglycopenic – Symptoms corrected by intake of "glucose"

dispensing error. Table 4 lists some of the drugs implicated in fasting hypoglycemia.^{10,11} Alcohol-induced hypoglycemia is usually associated with a prolonged fast. It is less common, but more severe in children. Alcohol predisposes to hypoglycemia by its effect on decreasing hepatic gluconeogenesis¹²⁻¹⁴ and the counter-regulatory hormone response to hypoglycemia.¹⁵ Pentamidine, a drug used for the treatment of *pneumocystis carinii* pneumonia (PCP) in immunocompromised hosts, has been associated with hypoglycemia as a result of an inflammatory process of the beta cells with increased insulin secretion. This may be followed by permanent destruction of the beta cells resulting in hyperglycemia.

Severe illness: Severe illness contributes to fasting hypoglycemia by depletion of hepatic glycogen and decreased gluconeogenesis. It is seen in patients with fulminant hepatitis, ethanol-induced fatty liver, cholangitis, biliary obstruction, primary hepatic malignancy, severe cardiac failure, renal insufficiency, severe sepsis, and inanition. In most of these cases, fasting hypoglycemia occurs in the context of prolonged fasting or malnutrition. Fasting hypoglycemia is uncommon in hepatic metastatic disease.

Hormonal deficiencies: Hypopituitarism and hypoadrenalism have been described as causes of fasting hypoglycemia. They usually manifest with other symptoms of hormonal deficiencies. The hypoglycemia is usually precipitated by prolonged fasting.¹⁶⁻¹⁹ Decreased cortisol levels result in decreased gluconeogenesis, and epinephrine secretion. Replacement therapy with glucocorticoids corrects the tendency for hypoglycemia.

Non-beta cell tumours: Large retro-peritoneal, intra-abdominal, or intra-thoracic slow-growing tumours like hepatoma, adrenal cortical carcinoma, or neuroendocrine tumours cause fasting hypoglycemia via different mechanisms, including increased glucose utilization,^{20,21} ectopic insulin secretion,^{22,23} and by increased IGF II or Pro-IGF II.^{24,25}

Table 4: Drugs causing fasting hypoglycemia

Disorder treated	Drugs Established
Diabetes mellitus	Insulin, insulin secretagogues, metformin, alcohol
Infections	Pentamidine, Quinine, Sulphonamides
Arrhythmias	Quinidine, dispyramide, cibenzoline
Pain	ASA
Disorder treated	Drugs Putative
Pain	Acetaminophen, indomethacin, propoxyphene, phenylbutazone
Hypertension, Heart disease	ACEI, β -adrenergic antagonists
Edema	Furosemide, Acetazolamide
Depression	MAOI, Fluoxetine, imipramine
Psychosis	Haloperidol, chlorpromazine
Dyslipidemia	Fibrates
Allergies	Orphenadrine, diphenylhydramine
Gastric disorders	Cimetidine, ranitidine
Gout	Colchicine, sulfinpyrazone
Seizures	Phenytoin
Miscellaneous	Akee fruit, thalidomide

Hypoglycemia in infancy and childhood

A detailed description of this entity is beyond the scope of this publication. Several entities have been described with both common and rare etiologies. Hypoglycemia may occur in infants of diabetic mothers or of mothers using such medications as sulfonylureas or beta-adrenergic agonists. Transient intolerance to fasting occurs pre-term or in infants who are small for gestational age. Infants and children may also present with fasting hypoglycemia due to islet cell hyperplasia or the presence of an insulinoma. Enzyme defects of carbohydrate metabolism have been alluded to earlier. Enzyme defects of fat and protein metabolism are rare causes of fasting hypoglycemia.

Immune hypoglycemia

This category of hypoglycemia has been described in Japan, mostly in patients with type 1 diabetes.²⁶

The mechanism is thought to be related to dissociation of insulin from insulin-insulin antibody complexes in patients with insulin-treated diabetes mellitus. The degree of antibody formation is higher in patients treated with beef and pork insulin as compared to human insulin. The occurrence of this type of hypoglycemia is therefore suggestive of treatment with insulin;²⁷ however, antibodies to insulin have also been described in patients with type 1 diabetes prior to insulin treatment, in patients with other autoimmune diseases, and in those with an insulinoma.²⁸ In patients with severe insulin resistance due to anti-insulin receptor antibodies, the antibodies occasionally act as insulin agonists, thereby causing hypoglycemia.^{29,30}

Endogenous hyperinsulinemia

There are several causes for increased secretion of insulin.

Primary pancreatic beta-cell disorders:

- Solitary insulinoma (incidence 1/250,000)
- Multiple insulinomas (\pm MEN-1. MEN 1 gene is present in one-third of insulinomas)
- Functional beta-cell disorders: Beta-cell hyperplasia: in infants and children, and rarely in adults.
- Malignant insulinoma (5%-10%)

Beta-cell secretagogues:

- Sulfonylureas (SU)
- Non-SU insulin secretagogues: repaglinide and nateglinide

Diagnosing hypoglycemia

Normal plasma glucose levels at the time that a patient's symptoms occur practically rules-out hypoglycemia. If it is not possible to document Whipple's triad or if the results seem unreliable, further investigations need to be performed. The 72-hour fast has the benefit of confirming the presence of fasting hypoglycemia and is also instrumental in differentiating between endogenous and exogenous hyperinsulinemia. Table 5 provides a detailed description of this test. The test was terminated within 12 hours in 35% of patients with insulinoma, within 24 hours in 75%, and within 48 hours in 92%. No patient with a negative result at 72 hours had a change to a positive test by extending the fast to 96 hours.³¹ For interpretation of the results, see Table 6.

Some caveats of the 72-hour fast are worth discussing.

- Some lean women and men can have blood glucose < 2.5 mmol/L during a prolonged fast without underlying pathology.³²

Table 5: Diagnostic approach

- **The 72-hour fast:**⁸
 - Date the onset as the time of last food ingestion
 - Patient can drink calorie and caffeine-free drinks
 - Ensure the patient is active during waking hours
 - Measure: glucose, insulin, C-peptide, and pro-insulin q 6h.
 - If blood glucose is <3.3 mmol/L, measure every 1-2 hr.
 - End fast when glucose is <2.5 mmol/L and patients has S, S or both of hypoglycemia
 - At the end of the fast: measure glucose, insulin, C-peptide, pro-insulin, β-hydroxybutyrate, SU.
 - Inject 1 mg glucagon i.v., measure glucose at 10, 20, and 30 min.³⁴
 - Feed the patient

SU = sulfonylureas; S = signs, symptoms

- Markedly elevated insulin levels (>600 pmol/L) suggest insulin intake rather than insulinoma.

- In non-insulin mediated hypoglycemia, insulin levels are <30 pmol/L (in sensitive assays <18 pmol/L).³³ β-hydroxybutyrate is <2.7 mmol/L with insulin-mediated hypoglycemia, but is much higher with other causes of hypoglycemia.³⁴ Hyperinsulinemia decreases ketogenesis, by decreasing substrate availability (FFA) and decreasing ketone formation in mitochondria.

- In terms of the response to glucagons, patients with insulin-mediated hypoglycemia have a glucose increment of >1.4 mmol/L, while in those with non-insulin mediated hypoglycemia, the increase is less. Insulin is glycogenic and anti-glycogenolytic.

Table 6: Hyperinsulinemic hypoglycemia Interpretation of the results of the 72-hour fast

	Insulin	C-peptide	Proinsulin	SU
Exogenous insulin	↑	↓	↓	–
Insulinoma	↑	↑	↑*	–
Insulin secretagogues	↑	↑	↑	+

* >25% of insulin value

Table 7: Procedures to localize insulinomas

- Ultrasonography:
 - transdermal
 - endoscopic
 - intra-operative³⁵⁻³⁸
- Abdominal CT scanning with contrast
- Abdominal MRI
- Octreotide scanning
- Celiac arteriography
- Trans-hepatic portal vein catheterization (PVC)³⁹
- Selective arterial calcium stimulation with hepatic venous sampling⁴⁰

Recommended investigations for an insulinoma

Biochemical diagnosis should be confirmed before imaging techniques are embarked upon. The procedures used to localize insulinomas are listed in Table 7. Sensitivity and confidence intervals for the different procedures are listed in Table 8. Octreotide scintigraphy is expensive and the opinion of the author is not to recommend it. Palpation of the pancreas by an experienced surgeon and intraoperative pancreatic ultrasonography have a much higher yield with sensitivities approaching 100%. In the hands of experienced operators, endoscopic ultrasonography also has high sensitivity.

Treatment of an insulinoma

Surgery is the treatment of choice, with enucleation or partial pancreatectomy as the procedures of choice. The possibility of multiple endocrine neoplasia type 1 (MEN-1) should be

Table 8: Localization of insulinomas

Procedure	Sensitivity	CI
Calc. stimulation	88%	68%-97%
Trans-dermal U/S	9%	1%-23%
Abdominal CT	17%	5%-39%
Abdominal MRI	43%	22%-66%
Arteriography	36%	18%-57%
Trans-hepatic PVC	67%	30%-93%
Octreotide scan	60%	
Intra-op U/S	80%-100%	

CT = computed tomography
MRI = magnetic resonance imaging
PVC = portal vein catheterization

entertained. With this syndrome, insulinomas usually present as multiple lesions and a total pancreatectomy is usually required. Family screening should be entertained. Insulinomas are malignant in 5%-10% of cases. Surgical resection in operable cases and debulking in more advanced cases are recommended. Surgical treatment is followed by treatment with somatostatin analogues, usually the long-acting formulation. Medical treatment can prepare patients with operable insulinomas for surgery, or can be used as an alternative to surgery in patients with inoperable disease, or if surgery fails to correct the problem. Medical treatment initially consists of frequent meals. If this does not maintain euglycemia, the use of intravenous 10% glucose at a rate that keeps blood glucose within the normal range is recommended for short-term use. Oral diazoxide (at a dose of 100-800 mg per day given in divided doses) is effective in maintaining glucose levels within the normal range. This drug is associated with fluid retention, possible heart failure, and hirsutism. Concomitant use of diuretics is indicated. Given intravenously, diazoxide is a potent antihypertensive. Octreotide is a synthetic octapeptide, a somatostatin analogue that inhibits insulin, glucagons, and growth hormone secretion. Used to control hypoglycemia in patients with insulinoma, the dose is 100-1500 µg given in 3-4 divided doses or in long-acting format once per month. The response rate is about 50%. If the suppression of glucagon is significant, hypoglycemia could become worse.

Summary

When presented with a patient with hypoglycemia, a confirmation of the presence of low blood glucose associated with symptoms that abate with intake of glucose fulfills Whipple's triad. Reactive hypoglycemia occurs in patients with a previous gastrectomy, but rarely in those with inborn errors of carbohydrate and protein metabolism. Idiopathic reactive hypoglycemia is a questionable entity and, if present, represents very few cases. Fasting hypoglycemia is usually caused by drugs that lower glycemia by stimulating insulin secretion/ release. If this is ruled-out, other causes of hypoglycemia (as indicated above) should be investigated in detail in a medical centre with expertise in the investigation and management of these disorders.

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