Hypoglycemia

Definition:

Independent of perceptable simultaneous symptoms, hypoglycemia is defined as a blood glucose measurement in capillary blood below 40 mg/dl (2.22 mmol/l).

Blood glucose readings between 40 and 50 mg/dl (2.22-2.78 mmol/l) represent hypoglycemia, if adrenergic and/or neurological symptoms are simultaneously observed.

Comment: for patients without Diabetes mellitus

The blood glucose measurement has to be performed by means of valid enzymatical - photometrical or electrochemical - methods. Glucose-Analyzers used in laboratories are suited.

"Glucose-Meters" based upon dry chemistry strips have been developed for diabetic patients.

They are unreliable in the hypoglycemic range (<50 mg/dl) and only useful for rough estimations to be checked by laboratory chemistry.

Blood glucose levels above (> 60 mg/dl (> 3.33 mmol/l) have to be considered as normal levels, even when symptoms or complaints compatible with hypoglycemia are simultaneously observed. Such levels definitely rule out the diagnosis of hypoglycemia as a cause of the symptoms.

Low-normal blood glucose levels between 50 and 60 mg/dl (2.77-3.33 mmol/l) represent a range of uncertainty, which may occasionally be reached in completely healthy persons as well as regularly during fasting periods for more than 24 hrs.

If blood glucose in this range levels do occur in the overnight fasted patient, before main meals or 3-5 hrs. after main meals, a physician considered to be familiar with hypoglycemia should be consulted.
Symptoms

Symptoms compatible with hypoglycemia occur:

1. through activation of the sympathetic nervous system and result in uncomfortable **adrenergic symptoms** posing no danger for the patient

2. through cerebral shortage of glucose supply and may result in serious and debilitating **neurological (neuroglycopenic) symptoms.**

<table>
<thead>
<tr>
<th>general symptoms</th>
<th>nausea, dizziness, collapse, weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>adrenergic symptoms</td>
<td>sweating, tremor, palpitations, tachycardia, agitation, nervousity, hunger</td>
</tr>
<tr>
<td>neuroglycopenic symptoms</td>
<td>impairment of consciousness, mental concentration, vision, speech, memory, blurred vision, fatigue, seizures, paralyses, ataxia, loss of consciousness, aggressive behaviour</td>
</tr>
</tbody>
</table>

Typical clinical situations in patients suspected of hypoglycemia

- history of suspicious symptoms
  - blood glucose unknown
- history of suspicious symptoms
  - blood glucose "low"
- history of suspicious symptoms
  - blood glucose normal
- no history of symptoms
  - blood glucose by chance: "low"
- history of typical symptoms
  - proof of hypoglycemia and relief of symptoms by carbohydrate intake: "Whipple's triad"

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Causes

clinically healthy patient:

Diagnosis of an insulinoma in adult patients with confirmed or suspicious symptoms related to hypoglycemia has to be of prime concern in the differential diagnosis of hypoglycemia.

Despite significant disabling signs due to adrenergic and/or neuroglycopenic symptoms the patients clinically appear to be healthy and do not present with pathological findings during physical inspection and investigation.

True postpandial hypoglycemia is rare and very often the diagnosis is assumed despite lack of objective data. A different entity is the adrenergic postprandial syndrome (APS), often misclassified as reactive hypoglycemia.

Postprandial hypoglycemia should not be confused with the "early dumping syndrome" presenting with uncomfortable autonomic symptoms, which may occur shortly after intake of rapidly absorbed concentrated sugars and accelerated gastric emptying.

Disease / Cause

<table>
<thead>
<tr>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. mostly benign insulin-secreting tumors of the pancreas</td>
</tr>
<tr>
<td>2. malignant insulinoma (10-15%)</td>
</tr>
<tr>
<td>3. insulinoma in familial multiple endocrine neoplasia type I (MEN I / menin gene) - pancreatic, parathyroid, and pituitary endocrine tumors</td>
</tr>
<tr>
<td>4. rare: microadenomatosis, beta-cell-hyperplasia (*nesidioblastosis&quot; in adults ?)</td>
</tr>
</tbody>
</table>
### alimentary postprandial hypoglycemia

**a:** prototype: resection of stomach (Billroth) or
**b:** rapid gastric emptying after carbohydrate-rich nutrients

**mechanism:** GLP-1 (glucagon-like-peptide 1) ?

**c:** insulin resistance: (i.e. early type-II diabetes with postprandial hyperglycemia, >180 mg/dl) after carbohydrates (30–90 min) and late elevated insulin response / rightward shift of insulin secretion curve

**d:** increased insulin sensitivity / glucagon ?

### Alcohol

together with liver disease (cirrhosis) and malnutrition

### Medical drugs + predisposition

*see list (Drugs)*

### factitious hypoglycaemia

Insulin or anti-diabetic drugs (beta-cytotropic agents, i.e. sulfonylureas)

### extreme physical activity

extreme athletics: marathon, triathlon, ski-longrun

### mesenchymal non-islet-cell tumors

e.g. fibrosarcoma; elevated "big" IGF II levels (insulin like growth factor II)

### insulin autoimmune syndrome

**AIS / IAIS :** autoimmune insulin syndrome assoc. with autoimmune disease

1. **anti-insulin autoantibodies** (in Japan / Graves' disease, lupus erythematosus, rheumatoid arthritis, insulin injections)
2. **insulin receptor autoantibodies** (Lupus erythematosus, scleroderma, primary biliary liver cirrhosis, ITP - purpura, Hashimoto's thyroiditis)

### PHHI: familial persistent hyperinsulinemic hypoglycemia of "infancy"

diffuse nesidioblastosis / gene mutations (SUR1, Kir6.2 locus)

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### clinically ill patient

The underlying disease and impaired condition of the patient do not cause problems in the differential diagnosis.

**Hypoxia** and **metabolic acidosis** (lactic acidosis) lead to inhibition and attenuation of **hepatic gluconeogenesis**. Efficient gluconeogenesis is essentially required for a constant blood glucose level (glucose homoeostasis). In addition, gluconeogenesis in normal kidneys contributes to glucose homoeostasis.

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<table>
<thead>
<tr>
<th>Disease / Cause: Internal Medicine</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe liver failure</td>
<td>hepatic coma, severe hepatitis: impaired gluconeogenesis</td>
</tr>
<tr>
<td>renal insufficiency (uremia)</td>
<td>metabolic acidosis, retarded insulin elimination</td>
</tr>
<tr>
<td>severe cardial insufficiency</td>
<td>hypoxia with alteration of hepatic glucose metabolism, acidosis, liver congestion</td>
</tr>
<tr>
<td>(cardiomyopathy)</td>
<td></td>
</tr>
<tr>
<td>sepsis</td>
<td>acidosis, hypoxia, liver failure, renal failure</td>
</tr>
<tr>
<td>shock, multiple organ failure</td>
<td>acidosis, hypoxia, liver failure, renal failure</td>
</tr>
<tr>
<td>endocrine crises</td>
<td>pituitary insufficiency / adrenal insufficiency / hypothyroidism: lack of ACTH, GH (growth hormone), cortisol, thyroxin</td>
</tr>
<tr>
<td>medical drugs in diseases of liver / kidneys</td>
<td>see list (Drugs)</td>
</tr>
<tr>
<td>extreme malnutrition</td>
<td>anorexia, kachexia; (malignant tumor disease, malnutrition)</td>
</tr>
<tr>
<td>bone marrow and lymph node diseases</td>
<td>leucemia, lymphoma, myeloma (plasmocytoma): antibodies ?</td>
</tr>
<tr>
<td>inborn errors of metabolism</td>
<td>glycogen storage disease, fructose intolerance, galactosemia</td>
</tr>
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Source:


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postprandial Hypoglycemia

In the presence of vegetative adrenergic symptoms postprandial hypoglycemia should only be considered if biochemical hypoglycemia does occur within 2-4 hours after intake of a standardized testmeal (rich in carbohydrates) during laboratory test conditions, e.g. as compared to a testmeal rich in proteins.

Postprandial hypoglycemia typically may occur after a carbohydrate rich meal, thus also classified as "alimentary hypoglycemia". This is in contrast to fasting hypoglycemia or spontaneous hypoglycemia in insulinoma.

Evolutionally patients with insulinoma may experience hypoglycemia within 3-6 hours after an oral glucose load (depending upon the insulin secretion pattern of the tumor). The hypoglycemia cannot be efficiently counterregulated, fasting needs to be withdrawn. Patients with postprandial hypoglycemia are able to counterregulate hypoglycemia adequately and thus return to the normal range of blood glucose levels.

postprandial hypoglycemia and "diabetes"?

Very often we have to face the erroneous notion, postprandial or meal-associated hypoglycemia being mistaken as "an early sign" of diabetes mellitus ???.

It is true that real hypoglycemia after a meal may occur early in the development of type II diabetes. However, these are caused by untimely delayed and therefore increased insulin secretion when elevated hyperglycemic blood glucose levels have been detected early-postprandially (so called right-shift of the insulin secretion curve).

Typically co-existence of hyperglycemia and hypoglycemia is found but not hypoglycemia alone. The HbA1c may be normal, too.

postprandial hypoglycemia and pancreatogenous Non-Insulinoma Hypoglycemia

postprandial hypoglycemia together with clearly neuroglycopenic symptoms may be a challenging issue if caused by pancreatogenous hyperinsulinemic Non-Insulinoma Hypoglycemia (= islet cell hypertrophy). According to J.Service (Mayo Clinic Rochester MN) this is probably the correct terminus for rare islet cell hyperplasia or nesidioblastosis in adults.
The oral glucose tolerance test (OGTT) does not allow the diagnosis of postprandial hypoglycemia, since the "meal" is not physiological and the availability of glucose in the gastrointestinal tract of short duration. Glucose tolerance testing is suitable for screening purposes.

The term "reactive" or "functional" hypoglycemia is outdated and should not be used.

Postprandial hypoglycemia is to be differentiated from the

**Adrenergic Postprandial Syndrome - APS**

(Normoglycemia)

Despite normal concentrations of blood glucose patients face unspecific symptoms (sweating, tremor, palpitations, anxiety, nausea) caused through autonomic adrenergic counterregulation. The adrenergic tone elicits the symptoms and simultaneously avoids hypoglycemia through biochemical mechanisms (action of epinephrine / adrenaline; see "Gluco-Homeostasis").

APS represents a reactive or functional dysregulation of the autonomic nervous system and should not be classified as "hypoglycemia". Terms like "pseudohypoglycemia" or even "non-hypoglycemia" should be avoided, since they do not address the virtual presence of discomfort reported by these patients.

The biochemically defined cutoff for hypoglycemia as tolerated in the brain is 2.8 mmol/l (50 mg/dl). A counterregulatory response (epinephrine/adrenaline and glucagon) is triggered at higher blood glucose levels in the range of > 60 mg/dl (cutoff 3.1-3.3 mmol/l). Glucagon does not cause symptoms, but epinephrine does.

**Dumping - Syndrome**

The early dumping-syndrome does occur within 30 minutes in 10-15% of patients after resective gastric surgery. These are orthostatic hemodynamic symptoms induced secondary to a rise in intestinal osmotic pressure due to a rapid emptying of the osmotically active gastric content. Symptoms are characterized as adrenergic symptoms, in addition patients experience nausea, intestinal rumors, fullness, falling blood pressure with tachycardia/bradycardia.

Causes are: catecholamines, serotonin, vasoactive kinines; intraluminal pressure. Eventually and depending upon the carbohydrate content transient hyperglycemia may even be seen.

The late dumping-syndrome is identical with true postprandial hypoglycemia in patients after gastric surgery caused by an imbalance of postprandial hyperinsulinemia and availability of carbohydrates.

It may occur in patients with dysfunction of intestinal motility without prior gastric surgery. Increase of the intestinal passage and contractions are mediated by the secretion of intestinal hormones / peptides (cholecystokinin - CCK, gastrin, motilin, neurotensin (?), substance P).

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Causes of postprandial hypoglycemia:

Increased **insulin secretion** (triggered through increased **glucagon-like peptide 1** - secretion ("early responder")

Rapid **gastric emptying** (after **gastric surgery**):
- a. stimulation of **insulin secretion**
- b. stimulation of **GLP-1-secretion**, GIP

Renal **glucosuria**

**Increased insulin sensitivity** (increased non-oxidative glucose metabolism)

**Decreased insulin sensitivity** ("insulin resistance") with initially decreased insulin response, thereafter right-shifted increased insulin response ("late responder").

? Decreased **glucagon secretion** / glucagon resistance (hyposensitivity of glucagon receptors)

**Literature postprandial hypoglycemia:**


Lefebvre PJ, Andreani D, Marks V, Creutzfeldt W. Statement on postprandial or reactive hypoglycemia. Diabetes Care 11: 1988, 439


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Drugs - Pharmaceuticals

Medical drugs and pharmaceuticals potentially causing hypoglycemia:

Hypoglycemia has been described in context with several pharmaceuticals of quite different origin. Often these were single and quite rare observations or reports without known mechanisms of action. They should, however, always be considered as one reason of causing hypoglycemia.

1. A cause of hypoglycemia may be drug-induced toxic liver and kidney lesions. Hypoglycemia may become evident due to prescription of drugs despite preexisting liver or kidney failure. Quite often this is the case during simple pain relieving therapy with salicylates or antibiotic therapy with sulfonamides containing sulfamethoxazol.

2. The stimulatory action of several drugs (including salicylates and antiarrhythmics) is still unknown, although stimulatory actions on insulin secretion have been observed.

3. Never should the hypoglycemia provoking action of alcohol be underestimated. In patients under influence of alcohol presenting with unclear impaired consciousness a determination of the blood glucose is always mandatory!

4. Therapy with acetylsalicylic acid in the range of grams may clinically be relevant due to its widespread use, predominantly when overdosed in children.

5. We do not comment here upon the use of blood glucose lowering drugs designed for the treatment of diabetes (including insulin) - the oral antidiabetic agents, predominantly the sulfonylureas, if taken by non-diabetic patients.

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<table>
<thead>
<tr>
<th>Category</th>
<th>Example Drugs</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIARRHYTHMICS</strong></td>
<td>Disopyramide, Chinidine, Flecainide, Propafenone</td>
<td>stimulation of insulin secretion</td>
</tr>
<tr>
<td><strong>ANTIMALARIAL DRUGS</strong></td>
<td>Chinin - Derivatives</td>
<td>Chinin, Chloroquine, Mefloquine</td>
</tr>
<tr>
<td></td>
<td><strong>ANTIBIOTICS</strong></td>
<td>insuline stimulation, inhibition of gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>Sulfonamides</td>
<td>Trimethoprim + Sulfamethoxazol</td>
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<tr>
<td></td>
<td>Tetracyclines</td>
<td>renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>Pentamidine</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>Betablocker</td>
<td>Pneumocystis carinii - infection</td>
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<tr>
<td></td>
<td>unselective β-blockers</td>
<td>?</td>
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<tr>
<td></td>
<td>Psychopharm. drugs</td>
<td>?</td>
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<tr>
<td></td>
<td>Butyrophenones</td>
<td>Haloperidol</td>
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<td></td>
<td>MAO-Inhibitors</td>
<td>Fluoxetine, Clomipramine</td>
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<td></td>
<td>Antithyroid drugs</td>
<td>?</td>
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<tr>
<td></td>
<td>Methimazole</td>
<td>Thiamazole</td>
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<tr>
<td></td>
<td>other drugs</td>
<td>MAO-Inhibitors ?</td>
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<tr>
<td></td>
<td>ACE - inhibitors</td>
<td>Enalapril</td>
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<tr>
<td></td>
<td>Antiarrhythmic</td>
<td>Procainamide</td>
</tr>
<tr>
<td></td>
<td>Antihypertensive</td>
<td>Dihydralazine</td>
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<tr>
<td></td>
<td>Antihistaminics</td>
<td>?</td>
</tr>
<tr>
<td><strong>Toxic Substances</strong></td>
<td>Alcohol, Colchicine, Chloroform, Phosphorus</td>
<td>Inhibition of gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>Insectizides</td>
<td>Liver necrosis</td>
</tr>
<tr>
<td></td>
<td>Toxins</td>
<td>Liver necrosis</td>
</tr>
<tr>
<td></td>
<td>Amanita phalloides</td>
<td>Liver necrosis</td>
</tr>
</tbody>
</table>

Source:

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PHYSIOLOGY

Glucohomeostasis

Mathematics of Glucohomeostasis

During normal conditions the **basal glucose requirement** amounts to 2 mg/kg/min. This results in **10 grammes per hour** for a normal weight adult of 75 kg. The **brain** requires around **5-6 g/h**, day or night, during rest or "work". About 4 g/h are used by the muscles, fat tissue, the organs (liver, heart) and the red blood cells, mostly requiring insulin for glucose uptake. The liver thus has to produce 10 g/h, mostly achieved by glucagon.

<table>
<thead>
<tr>
<th>A blood volume of 70 ml / kg results in <strong>5.25 L of blood</strong> in an adult of 75 kg body weight.</th>
</tr>
</thead>
<tbody>
<tr>
<td>At an <strong>arterial blood glucose concentration</strong> of 50 mg / dl we just find <strong>2.75 gramm</strong> of free circulating glucose.</td>
</tr>
<tr>
<td>A <strong>cerebral blood flow</strong> of 15 % of the total circulation (CMV) will result in <strong>900 ml / minute</strong> (60 ml/100 g/minute) resp. <strong>54 liters / hour</strong> for a normal brain mass of 1500 g. This means a total calculated glucose content of 27 grammes (≈ 0.45 g/minute).</td>
</tr>
<tr>
<td>At least <strong>20 % (≈ 5.4 g)</strong> thereof are <strong>extracted by the brain</strong>, which will result in a decrease of the <strong>arterial blood glucose concentration</strong> from <strong>50 mg / dl</strong> to a <strong>venous concentration of 40 mg / dl</strong> (difference: 10 mg / dl = 90 mg / 900 ml per minute = 5.4 g / 54 l per hour).</td>
</tr>
</tbody>
</table>

This simple calculation demonstrates the essential and critical requirement of a **minimal arterial blood glucose concentration of 50 mg/dl** in order to guarantee the demands of the brain for proper functionality. **These are not met at 40 mg/dl** and thus would cause neurological symptoms. Normal brain blood flow and cardiac output are essential. Attenuation of cardiac function (insufficiency, cardiomyopathy) and attenuation of cerebral blood flow (stroke, sclerosis) demonstrate the fragile equilibrium in case of prevailing hypoglycemia.

"**Stress-Hyperglycemia**" during the postaggressive metabolic state essentially means the physiological adaptation to jeopardized cerebral blood flow in order to meet the fuel needs by the brain. This is achieved by a **biochemical centralisation of the glucose metabolism** analogous to the **hemodynamic centralisation** of the circulation during shock (cardiogenous, hemorrhagic, hypovolemic). Metabolic centralisation physiologically resembles a **glucagon-mediated "endogenous infusion of glucose"**.
Literature Glucohomeostasis


Unger RH: Glucagon physiology and pathophysiology in the light of new advances. Diabetologia 28 (1985) 574-578


Physiology of Glucoregulation

Basal glucoregulation

Glucoregulation during physical activity

Glucoregulation during famine

Alimentary postprandial glucoregulation

Glucoregulation during postaggression ("fight or flight")

(surgery, trauma, shock)

Glucose - Counterregulation

HIERARCHY of Hypoglycemia - Counterregulation

Level 1: Attenuation of Insulin-Sensitivity

("physiological Insulin-Resistance")

Level 2: Suppression of Insulin-Secretion

Level 3: Stimulation of Glucagon-Sensitivity

Level 4: Stimulation of Glucagon - Secretion

Level 5: Stimulation of the autonomic adrenergic nervous system

Level 6: Potentiation of counterregulation

(Cortisol, Growth hormone, Endorphins)

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