www.insulinoma.net - www.gep-net.com
Prof. Dr. A.A.R. Starke – Dr. Christiane Saddig
Heinrich-Heine-Universität Düsseldorf – Medizinische Klinik

Hypoglycemia

Definition:

<u>Independent</u> 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 <u>simultaneously</u> observed.

<u>Comment:</u> 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 debiliating ***neurological (neuroglycopenic) symptoms.***

general symptoms	**nausea, dizziness, collapse, weight gain**
adrenergic symptoms	**sweating, tremor, palpitations, tachycardia, agitation, nervosity, hunger**
neuroglycopenic symptoms	impairment of consciousness, mental concentration, vision, speech, memory, blurred vision, fatigue, seizures, paralyses, ataxia, loss of consciousness, aggressive behaviour

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"**

Causes

clinically healthy patient:

Diagnosis of an **insulinoma in adult patients** with confirmed orfsuspicious 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	Remarks
Insulinoma	**1. mostly benign insulin-secreting tumors of the pancreas** **2. malignant insulinoma (10-15%)** **3. insulinoma** in familial **multiple endocrine neoplasia type I** (**MEN I** / menin gene) - pancreatic, parathyroid, and pituitary endocrine tumors **4.** rare: **microadenomatosis, beta-cell-hyperplasia** ("nesidioblastosis" in adults ?)

alimentary postprandial hypoglycemia ***"reactive or functional" 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**	**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)

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.

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

Source:

Starke A, Saddig C. Hypoglykämien im Erwachsenenalter. In: Diabetes mellitus. Urban & Fischer, München Jena, 2. Aufl. 2000, S. 775-782

Service FJ. Hypoglycemic disorders. New Engl J Med 332, 1995, 1144-1152

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.

! Eventually **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 adaequately and thus return to the normal range of blood glucose levels .

postprandial hypoglycemia and “ d i a b e t e s “ ?

! Very often we have to face the **erroneus** 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 developement 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 hypogylcemia, since the *"meal"* is not physiological and the availibility 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 (**cholecystokinine - CCK, gastrin, motilin, neurotensin (?), substance P**).

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:

Hogan MJ, Service FJ, Sharbrough FW, Gerich JE. Oral glucose tolerance test compared with a mixed meal in the diagnosis of reactive hypoglycemia. Mayo Clin Proc 58:1983, 491-496

Gastineau CF. Is reactive hypoglycemia a clinical entity? Mayo Clin Proc 58:1983, 545-549

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

Brun JF, Fedou C, Mercier J. Postprandial reactive hypoglycemia. Diabetes & Metabolism 26:2000, 337-351

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 **acetyl salicylic 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.

© Starke/Saddig 2001 www.insulinoma.net	Drug class	Drug name (Generic)	Remarks
ANALGETICS	**Salicylic acid derivatives**	**Acetylsalicylic acid (Aspirin®)**	stimulation of insulin secretion renal insufficiency; in children; inhibition of cerebral glucose metabolism
	Pyrazolone-Derivatives	**Phenazone, Propyphenazone**	
	p-Aminophenol-Derivatives	**Phenacetine, Paracetamol (Acetaminophen)**	acute liver necrosis; renal failure
		Diclofenac, Indomethacine	

ANTIARRHYTHMICS		**Disopyramide, Chinidine, Flecainide, Propafenone**	stimulation of insulin secretion
ANTIMALARIAL DRUGS	**Chinin - Derivatives**	**Chinin, Chloroquine, Mefloquine**	insulin stimulation, inhibition of gluconeogenesis
ANTIBIOTICS	**Sulfonamides**	Trimethoprime + **Sulfamethoxazol**	renal insufficiency
	Tetracyclines	**-**	?
		Pentamidine	Pneumocystis carinii - infection
Betablocker	**unselective ß-blockers**	**Propanolol**	? : gluconeogenesis; glucose uptake in muscle
Psychopharm. drugs	**Butyrophenones**	**Haloperidol**	?
		Fluoxetine, Clomipramine	stimulation of insulin secretion
	MAO-Inhibitors	**?**	Tryptophane metabolism ?
Antithyroid drugs	**Methimazole**	**Thiamazole**	Insulin-Auto-Immune-Syndrome (= IAIS)
other drugs	**ACE - Inhibitors**	**Enalapril**	possible increase of insulin sensitivity
	Antiarrhythmic	**Procainamide**	Lupus erythematosus & IAIS
	Antihypertensive	**Dihydralazine**	Lupus erythematosus & IAIS
	Antihistaminics	**?**	?
Toxic Substances	**Alcohol** Colchicin Chloroform Phosphorus		Inhibition of gluconeogenesis Liver necrosis
Insectizides	Parathion		Liver necrosis
Toxins	Amanita phalloides		Liver necrosis

Source:
Starke A, Saddig C. Hypoglykämien im Erwachsenenalter. In: Diabetes mellitus. Urban & Fischer, München Jena, 2. Aufl. 2000, S. 775-782
Service FJ. Hypoglycemic disorders. New Engl J Med 332, 1995, 1144-1152
Virally ML, Guillausseau PJ. Hypoglycemia in adults. Diabetes & Metabolism 25, 1999, 477-490

PHYSIOLOGY

Glucohomeostasis

Mathematics of Glucohomeostasis

During normal conditions the **basal glucose requirement** amounts to **2 mg/kg/min**. This results in **10 gramms 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.

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

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: The milieu interieur and the islets of Langerhans. Diabetologia 20 (1981) 1-11

Unger RH, Orci L: Glucagon and the A-cell. Physiology and pathophysiology. N Engl J Med 304 (1981) 1518-1524

Unger RH: Insulin-glucagon relationships in the defense against hypoglycemia. Diabetes 32 (1983) 575-583

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

Starke AAR, Imamura T, Unger RH: Relationsship of glucagon suppression by insulin and somatostatin to the ambient glucose concentration. J Clin Invest 79 (1987) 20-24

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-Sensitvity ("physiological Insulin-Resistence")**
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)**