

# Hypoglycaemia in adults: When should it be raised? How can hypoglycaemia be confirmed in non-diabetic adults?<sup>☆,◇</sup>

*Quand évoquer une hypoglycémie chez l'adulte ? Comment affirmer une hypoglycémie chez l'adulte non diabétique ?*

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## 1. Hypoglycaemia: when should it be raised?

### 1.1. Signs and symptoms of hypoglycaemia

Clinical hypoglycaemia is defined as a low blood glucose level, in the absence of ketone bodies, which can trigger signs and/or symptoms, particularly in the central nervous system.

Symptoms of hypoglycaemia are divided into neuroglycopenia and neurogenes or autonomes. The formers are directly related to an insufficient glucose flow, failing to insure normal brain function. The latter are related to the sympatho-adrenal release in response to hypoglycaemia.

Perception of hypoglycaemia results mainly from autonomous nervous system activation, and from catecholamine release, triggered by hypoglycaemia. Some of the signs (palpitations, tremors, anxiety, pallor) are from adrenal mechanisms; others, such as sweating, hunger or paresthesia, are from cholinergic activation [3].

### Recommendations

The work group suggests that glycaemia higher than 0.65 g/L (3.6 mmol/L) should be considered as normal. In addition to symptoms, venous glycaemia between 0.50 g/L (2.75 mmol/L) and 0.65 (3.6 mmol/L) requires monitoring. Modalities of surveillance should be on a case-by-case basis, the end-point being to confirm or rule out a diagnosis of hypoglycaemia, with the help of any useful means at the clinician's disposal.

In all cases, only the results of a venous blood sample, from a fluoro-oxalate vial should be taken into account. Results from a capillary blood sample are not sufficient to undertake a diagnostic search.

Neuroglycopenia symptoms are from a local or general alteration in the functioning of the central nervous system. These latter include fatigue, altered behaviour, confusion, seizures and loss of conscience [4]. In the specific situation of type I diabetes, seizures seem to appear only in prolonged hypoglycaemia, sometimes 2 to 4 hours before their outcome [5].

Generally, there is complete recovery after normalization of glycaemia. Sometimes, recovery however is delayed. Profound, prolonged hypoglycaemia may lead to brain death, though in type I diabetes in particular, heart arrhythmia is the main cause of sudden death. In adult diabetes, some reports indicate the possibility of definitive after-effects of hypoglycaemia, but the data remain poorly documented.

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### Recommendations

Clinical symptoms of hypoglycaemia are not specific. Moreover, an isolated low blood glucose level does not define hypoglycaemia. Thus, hypoglycaemia should only be diagnosed in the presence of the Whipple triad:

- symptoms, signs or association compatible with hypoglycaemia;
- plasma glucose levels below 0.5 g/L (2.75 mmol/L);
- rapid resolution of signs and symptoms after glucose administration [1,2].

### Main neuroglycopenic signs.

Neuroglycopenic signs are from a focal or general brain dysfunction. The signs are multiple but generally similar from one hypoglycaemia to another in the same patient:

They may include:

- concentration impairment, fatigue, slurred speech, altered behavior or overt psychiatric symptoms;
- focal or general motor deficits, hyperactivity, lack of coordination, tremors, hemiparesis, diplopia, facial paralysis, etc.;
- sensory impairment, limb paresthesia, lip paresthesia, etc.;
- blurred vision;
- general or focal seizures;
- confusion;
- at worst, hypoglycaemic coma, with distinctive features:
  - sudden onset,
  - depth is variable, sometimes coma is deep,
  - restless coma along with profuse sweating,
  - with hypothermia and pyramidal signs.

During the DCCT study, no after-effects, particularly cognitive, were observed, even in the teenage group [6,7].

Clinical symptoms of hypoglycaemia are not specific. Besides, an isolated low blood glucose level does not define hypoglycaemia. Thus, hypoglycaemia should only be diagnosed in the presence of the Whipple triad:

- symptoms, signs or association in accordance with hypoglycaemia;
- plasma glucose levels below 0.5 g/L (2.75 mmol/L);
- disappearance of signs and symptoms after providing glucose to elevate blood levels.

The literature gives several levels of glycaemia defining hypoglycaemia in non-diabetic adult subjects. Consensus within the work group has led to a venous glycaemia cut-off defining hypoglycaemia as 0.50 g/L (2.75 mmol/L).

The work group has suggested that glycaemia above 0.65 g/L (3.6 mmol/L) should be considered as normal. In the presence of symptoms, venous glycaemia between 0.5 g/L (2.75 mmol/L) and 0.65 g/L (3.6 mmol/L) requires monitoring. The modalities of surveillance should be on a case-by-case basis, the end-point being to confirm or rule out a diagnosis of hypoglycaemia, with the help of any useful means at the clinician's disposal. However, the work group suggests that the patient's age should be taken into account: glycaemia below 0.65 g/L (3.6 mmol/L) in elderly subjects should be considered as low.

The first step in investigating suspicion of hypoglycaemia is to confirm the reality of hypoglycaemia, next non-tumoral causes of hypoglycaemia should be ruled out. The last step is to confirm insulinoma.

### 1.2. Context of hypoglycaemia

In children, in addition to adult aetiologies, the framework of hypoglycaemia includes some congenital metabolism disorders [8] as well as nesidioblastosis [9]. The possibility of hypoglycaemia without hyperinsulinism, such as glucocorticoids or growth hormone insufficiency, as well as medicine-linked-adverse events, should not be overlooked. Nonetheless, hypoglycaemia in children is not the subject of the present consensus.

Hyperinsulinism related to a  $\beta$ -Langherans pancreatic tumour is the main pathophysiological mechanism of hypoglycaemia. Nevertheless, when hypoglycaemia has been confirmed, non-hyperinsulinic causes must be checked for.

In this framework, if the context may sometimes lead to an obvious cause, other less obvious aetiologies must not be overlooked.

The main causes of hypoglycaemia without hyperinsulinism include:

- toxic and drug-related hypoglycaemia:
  - hypoglycaemia related to diabetic treatment is outside of this context, as iatrogenic hyperinsulinism is the mechanism of onset. Three main drug families may be involved: sulfonylureas, repaglinide and insulin. Other antidiabetic drugs are not responsible for hypoglycaemia. Conversely, outside this context of diabetes, aetiologic diagnosis might be more difficult. Besides diabetes, parenteral nutrition with poor management of insulin flow at the end of feeding is a common cause of hypoglycaemia. The context must be taken into account, and is sometimes suggested rather than stated. Such is the case in voluntary or criminally drug-induced hypoglycaemia, related to antidiabetic drug intake. In such cases, diagnosis may be difficult,
  - alcohol inhibits gluconeogenesis. Alcohol induced hypoglycaemia occurs in fasting subjects,

Table 1  
Drugs (antidiabetic drugs excluded) related to hypoglycaemia. All other drugs suspected in the occurrence of hypoglycaemia have been listed in this review as “very poor level of proof”. This group includes beta-blockers (131 reported cases), conversion enzyme inhibitor and angiotensin II receptor antagonists (129 cases), disopyramide, trimethoprim-sulfamethoxazole (cotrimoxazole), heparin and 6-mercaptopurine.

	Number of cases	Number of publications	Clinical context
Quinolones			Development cancelled
Clinafloxacin	234	18	Infection
Gatifloxacin	16	2	Infection
Pentamidine	330	29	In immunodeficiency
Quinine	326	30	Cerebral malaria
Indometacin	330	29	Chronic hypoglycaemia during long term treatment for persisting ductus arteriosus
Cibenzoline	16	16	In kidney failure
Glucagon			During endoscopy
Artemisine/artesumate/artemeter	45	4	Cerebral malaria
IGF-1			Antidiabetic treatment or GH deficiency
Chloroquine oxaline sulphonamide	4	20	Colic neoplasm, development cancelled
Lithium	3	9	
Propoxyphene and dextropropoxyphene	10	19	Along with kidney failure

- drugs. Table 1 displays the molecules implicated in the onset of hypoglycaemia, in order of their supposed responsibility. In his systematic review, M.H. Murad [10] found 164 drugs supposedly involved in at least one case of hypoglycaemia. For most of those drugs, proof is far from being established;
- visceral failure:
  - liver failure related hypoglycaemia generally occurs during fulminant hepatitis or right ventricular failure in a context of global liver failure (with icterus and impaired coagulation),
  - primary adrenal failure should not be overlooked. It should be sought with plasma ACTH measurement and basal cortisol level (possibly with a glucocorticoid secretion stimulation test) before any other diagnostic testing,
  - anterior pituitary failure may be responsible for clinical hypoglycaemia, linked to combined corticotropic and somatotropic deficiencies. In children, they may lead to deep hypoglycaemia,
  - kidney failure [11]. Hypoglycaemia is rarely observed outside of a dialysis context and contrasts with the usual insulin resistance in kidney failure. Pathophysiology seems to involve combined loss of renal gluconeogenesis and malnutrition,
  - cerebral malaria [12], severe sepsis [13]. Hypoglycaemia mechanisms in cerebral malaria are poorly understood and occur mainly in children. Glucose consumption by parasites or effect of quinine has been forwarded as possible causes. It is more likely to be a consequence of global visceral failure;
- other aetiologies:
  - anorexia nervosa [14], and more generally malnutrition. Hypoglycaemia is linked to the absence of substrates for gluconeogenesis, as well as ketonic body synthesis, which is a worsening factor,
  - some congenital metabolism defects revealed in adulthood,
  - after bariatric surgery, particularly surgeries involving intestinal bypass (cf. below),

- IGF2 and big-IGF2 in relation with bulky mesenchymal tumours [15];
- specific place of autoimmune hypoglycaemia:
  - autoimmune hypoglycaemia is different, because it emerges from a hyperinsulinic mechanism: from the presence of anti-insulin or anti-insulin receptor antibodies [16]. It is the third cause of hypoglycaemia in the Far East. It is rare outside this geographic area (less than a hundred reported cases). Autoimmune hypoglycaemia is often postprandial, but may occur after physical exercise, along with paradoxical hyperglycaemia, either postprandial or after a glucose load. It mostly occurs in a context of other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Some cases have developed in patients with plasma cell disorder. It sometimes happens after exposure to SH-radical containing drugs (captopril, PTU, penicillamine, etc.).

### 1.3. Time of onset of hypoglycaemia

Insulinoma-linked-hypoglycaemia usually occurs in fasting states. A recent study from the Mayo Clinic [17] however shows that insulinoma symptoms can occur after meals. In this retrospective study, 6% of subjects with proven insulinoma had presented with exclusive postprandial symptoms (with a predominance of male patients) and 21% with mixed fasting and postprandial symptoms. The Mayo Clinic being a reference centre for the diagnosis of insulinoma, the above figures should be reconsidered since they probably concentrate the most difficult cases with atypical features.

Aside from these specific cases and the consequences of gastric surgery and faced with the occurrence of postprandial symptoms, which are most often adrenergic, a diagnosis of “functional” or “reactive” hypoglycaemia should be considered. This is moreover incorrectly named as most patients don’t meet the diagnostic criteria of hypoglycaemia and thus do not enter the framework of this consensus [18] (Table 1).

#### 1.4. Hypoglycaemia after proximal digestive tract surgery

Hypoglycaemia with hyperinsulinism is a well-known complication of morbid obesity cure intestinal bypasses. A recent Swedish study involving 5000 surgical intestinal bypasses assessed an overall incidence rate of 0.2% [19]. Conversely, occurrence of hypoglycaemia remained unaltered after either gastric banding or vertical banded gastroplasty surgery. In the study, mean delay for occurrence of symptoms was 2.7 years (1 to 5 years in the literature). Hypoglycaemia may be completely suppressed with dieting. Other treatments have been suggested, such as acarbose, diazoxide and somatostatin analogs. Some refractory cases required partial pancreatectomy.

These rare complications must not be mistaken for a dumping syndrome, which is common after gastric surgery. Dumping syndrome is related to both a quick gastric distension and quick gastric clearance, along with digestive hormone (GLP1, Glucagon, etc.) release impairment. After bariatric surgery, occurrence of dumping syndrome may affect 10 to 15% of patients. Dumping syndrome occurs rapidly after surgery. It is usually treated with dietetic measures including fractionated meal and simple carbohydrate exclusion [20,21].

## 2. How can hypoglycaemia be confirmed in non-diabetic adults?

Hypoglycaemia is rare outside of treated diabetes. It is however often diagnosed in patients describing one or several episodes of fainting with or without loss of consciousness. Hypoglycaemia is the consequence of an imbalance between endogenous glucose production and its use by peripheral tissue. Outside of long-term fasting, glucose is a metabolic nutrient which is mandatory in brain metabolism, as the brain has limited glucose storage capacity.

Thus, any decrease in brain glucose flow lasting more than a few minutes will lead, if uncorrected, to clinical warning symptoms and/or neuroglycopenia.

#### 2.1. Biological threshold in identification of hypoglycaemia

Hypoglycaemia is defined by consensus as a drop in plasma glucose below the threshold of 0.5 g/L (2.5 mmol/L). As the level of glucose decreases, “counter-regulation mechanisms” (i.e. defence mechanisms) are triggered, with a reproducible order corresponding to different glycaemic thresholds, as described by Cryer [22].

The first mechanism involved is insulin secretion inhibition, at a threshold of around 0.80 g/L (4.5 mmol/L). Below the threshold of 0.65–0.70 g/L (3.6–3.9 mmol/L), counter-regulating hormone secretion is triggered: first, glucagon which increases glycogenolysis and neoglucogenesis of the liver; then adrenergic hormones with similar effects on the liver and delivery of substrates for neoglucogenesis, such as lactates and alanine via glycolysis, glycerol and free fatty acids via lipolysis, in both cases reserves are released due to adrenalin. In case of hypoglycaemia lasting more than an hour, growth hormone and cortisol release are then triggered. The anti-hypoglycaemic

effect is mainly linked to a decrease in tissue sensitivity to insulin and to an increase in glucose production by the liver [23]. The outcome of all these alterations is to counteract the drop in plasma glucose flow thus avoiding hypoglycaemia symptoms that generally appear around the threshold of 0.55 to 0.5 g/L (3–2.75 mmol/L) [22]. This threshold might be lowered in patients having undergone long periods associated with frequent and iterative hypoglycaemia, such as occult insulinoma [24]. The isolated discovery of a significant drop in glycaemia in non-diabetic adults is not sufficient to establish a diagnosis of hypoglycaemia. Simultaneous association of suggestive clinical symptoms along with a drop in plasma glucose levels (i.e. Whipple triad, cf. supra) is mandatory. Conversely, glycaemia above the threshold of 0.65 g/L (3.6 mmol/L), along with neurogenic or autonomous symptoms can rule out hypoglycaemia as the cause of symptoms.

#### 2.2. Glycaemia measurement method

A decrease in measured glycaemia may indeed be related to a delay of over two hours between blood sampling and biological analysis, due to *in vivo* glycolysis activation. Abnormal blood cells consume the glucose inside the vial between sampling and centrifugation [25]. Such a phenomenon is observed only in cases of leukaemia or severe haemolytic anaemia. Prevention recommends the use of anti-glycolytic agents for sampling (fluoro-oxalate vials). In these conditions, glycaemia remains stable for 24 hours [26]. In order to ascertain unambiguous hypoglycaemia, glycaemia should be measured both after a total blood sample and measurement should be determined using the glucose oxydase reference technique.

The easy to perform capillary glucose assessment with amperometric technique on a dipstick, may give indications as to the glucose level. Nevertheless it is not proof of hypoglycaemia in a non-diabetic subject presenting symptoms in accordance with this diagnosis [27].

A threshold of 0.55 g/L (3 mmol/L) has been implemented in North America regarding diagnosis of hypoglycaemia (Cryer 2009). However, it should be underlined that a moderate drop in glycaemia, between 0.45 g/L (2.5 mmol/L) and 0.70 g/L (3.9 mmol/L) will have a diagnostic value with high sensitivity but poor specificity, whereas glycaemia below 0.45 g/L (2.5 mmol/L) will show poorer sensitivity but very good specificity in the diagnosis of hypoglycaemia. By consensus, the work group suggests that a threshold of 0.50 g/L (2.75 mmol/L) should be chosen. Lastly, the presence or absence of ketonic bodies alters the physiopathologic and aetiologic meaning of hypoglycaemia.

#### 2.3. Aetiologic arguments in hypoglycaemia

All symptoms, time of onset, especially during fasting or postprandial occurrence, intensity and duration should be thoroughly described. Close family or other witnesses of hypoglycaemic episodes should be questioned to evaluate intensity of such episodes. Trigger factors should be sought, and drug intake around hypoglycaemic episodes should also be listed.

### Recommendations

Once hypoglycaemia has been confirmed, medical history and clinical examination are crucial to guide diagnosis. Chronic visceral failure, neoplasia, hormonal deficiency particularly adrenal insufficiency, autoimmune history, presence of psychological troubles, as well as the presence in the family of a type-2 diabetic patient, alcohol consumption should be thoroughly investigated.

A complete physical examination should be performed, searching for signs of undernourishment, especially in elderly people.

#### 2.4. Diagnostic features

### Recommendation

The work group suggests an observation period to be performed during hospitalisation, if faced with unclear onset mechanisms of hypoglycaemia-like malaise, particularly if case history points to organic origins. This aims to simultaneously measure glycaemia, insulinemia and C-peptide during a malaise. It is the only way to evidence inappropriate insulin secretion combined with spontaneous hypoglycaemia.

Several situations are possible after collection of aetiological data:

- clinical features indicate diagnosis of functional hypoglycaemia: postprandial occurrence of adrenergic symptoms should be linked with hypoglycaemia in the simultaneous presence of the following three conditions (Whipple triad):
  - symptoms are part of the signs of hypoglycaemia,
  - at the same time as symptoms occur, glycaemia was below 0.5 g/L (2.8 mmol/L),
  - symptoms disappear as glycaemia rises;
    - in practice: postprandial occurrence of only dysautonomic signs will almost constantly be accompanied by glycaemia over the previously mentioned threshold [28]. A psychological evaluation will allow detection of an underlying emotional liability or anxious or depressive state [29],
    - a decrease in glycaemia below 0.5 g/L (2.7 mmol/L) leads to the occurrence of neuroglycopenic manifestations, which in turn should lead to further investigation in these patients. An oral glucose tolerance test is not recommended [30]. A mixed meal test, composed of a half solid and half liquid meal, with 50–60% carbohydrates, usually inducing symptoms should be preferred.

The meal is followed by a 5-hour follow-up clinical and biological surveillance. Blood samples should be drawn every 30 minutes to assess not only glycaemia, but also insulin, C-peptide, proinsulin blood levels if glycaemia falls below 0.6 g/L (3.3 mmol/L),

- the occurrence of symptoms simultaneous with real biological hypoglycaemia confirms diagnosis of reactive hypoglycaemia. In the absence of symptoms, other investigations should be made: first, ATCH-stimulated cortisol testing, then a fasting test, aiming at revealing a Whipple triad and making biological assessments (glycaemia, insulinemia, plasma C-peptide, checking the presence of sulfonylurea hypoglycaemic agents, etc.);
- tumoral hypoglycaemia is obvious or immediately suspected:
  - symptoms associate both adrenergic and neuroglycopenic manifestations,
  - symptom occurrence: fasting or after a short period without food intake,
  - symptoms are accompanied by glycaemia below 0.5 g/L (<2.75 mmol/L),
  - symptoms disappear, and there is a simultaneous rise in glycaemia, after glucose intake;
    - in practice: an observation period in hospital will allow measurement of glycaemia, insulinemia and plasma C-peptide. Persistent and inappropriate levels of insulin and/or C-peptide (respectively >3 mU [18 pmol]/L and >200 pmol/L) along with glycaemia below 0.55 g/L (<3 mmol/L) confirm abnormal insulin secretion [31],
    - other investigations could be performed, such as plasma proinsulin or  $\beta$ -hydroxy-butyrate assessment, or the detection of antidiabetic drug intake (sulfonylureas, glinide) and, if necessary, glucagon testing. Intravenous administration of 1 mg glucagon is followed by glycaemia assessments 0, 10, 20 and 30 minutes later (Cryer 2009). A  $\beta$ -hydroxy-butyrate level <2.7 mmol/L and a glycaemic rise above 0.25 g/L (1.4 mmol/L) after glucagon, confirm the implication of insulin or an IGF in the mechanism responsible for hypoglycaemia,
    - indirect signs of inappropriate insulin secretion will be clearly evidenced after more than 48 hours fasting. From that time on, the liver glycogen store is depleted and ketogenesis is activated. Aetiological investigations can be completed with assessment of anti-insulin antibodies. This information should avoid a “fasting test”;
- the relation between hypoglycaemic origin and symptoms is raised but remains doubtful:
  - a “fasting test” must be performed during diagnostic investigation. If an organic cause is confirmed, the pathophysiologic mechanism will be identified and the precise cause will be evidenced in fine,
  - if inappropriate insulin secretion is evidenced, and occult use of sulfonylureas or the presence of anti-insulin antibodies is ruled out, then imaging should be performed to detect insulinoma.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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