HYPOGLYCEMIA IN ADULTS

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SUMMARY - Hypoglycemia is a clinical and biological syndrome, caused by an abnormal decrease in plasma glucose levels to below 0.55g/l (3.0 mmol/l). Hypoglycemia is responsible for non-specific signs and symptoms which should be noted in a particular pathological context, and for secretion of counterregulatory hormones (mainly glucagon and catecholamines). Difficulty in identifying the etiology is variable, based upon history and physical examination, and hormonal investigations or imaging procedures, according to the results. Drug-related hypoglycemia is the most frequent observed cause (mainly in insulin-treated diabetic patients, but many drugs may be involved), followed by toxicity (alcohol mainly). Tumor-induced hypoglycemia is secondary to inappropriate insulin secretion by a beta-cell pancreatic tumor (insulinoma), and, rarely to an extrapancreatic mesenchymal large tumor secreting IGF-II. Hypoglycemia is present in other diseases, such as hormonal deficiencies, hepatic, or renal failure, or acute cardiac insufficiency. Multifactorial hypoglycemia seems to be underdiagnosed, mainly in hospitalised, underfed older patients with severe disease or sepsis. Autoimmune hypoglycemia is rare, due to insulin or insulin-receptor autoantibodies. Reactive hypoglycemia is observed after gastrectomy, but true primitive hypoglycemia appears to be rare, with false excess diagnosis in the majority of the cases.

Key-words: Hypoglycemia, adults, diabetes mellitus, insulinoma, extrapancreatic hypoglycemic tumor, review.

RÉSUMÉ - Hypoglycémies de l’adulte.
L’hypoglycémie est un syndrome clinique et biologique défini par un abaissement anormal de la glycémie au-dessous de 0.55 g/l (3,0 mmol/l). Elle est responsable de manifestations cliniques non spécifiques mais évocatrices selon le contexte pathologique, et d’une sécrétion d’hormones hyperglycémiantes (principalement le glucagon et les catécholamines). Le diagnostic étiologique est de difficulté variable. Il repose sur l’anamnèse, l’examen physique et des examens complémentaires dont le choix est dicté par les données de ceux-ci : dosages hormonaux, imagerie. Les hypoglycémies iatrogènes (surtout chez les diabétiques insulinotraité, mais de nombreux médicaments peuvent être en cause), et toxicité (intoxications alcooliques) sont les plus fréquentes. Les hypoglycémies d’origine tumorale sont liées en premier lieu à une hyper-sécrétion inappropriée d’insuline par une tumeur insulaire pancréatique (insulinome), plus rarement à une tumeur extra-pancréatique, souvent d’origine mésenchymateuse, de grande taille et sécrétant de l’IGF-II. Une hypoglycémie peut s’observer dans certains contextes pathologiques tels que l’insuffisance surrénale ou antéhypophysaire, l’insuffisance cardiaque, hépatique ou rénale. Les hypoglycémies multifactorielles s’observent surtout chez des patients âgés hospitalisés, infectés et dénutris. Dans quelques cas, un mécanisme auto-immun est à l’origine de l’hypoglycémie, par le biais d’autoanticorps anti-insuline ou antirécepteurs de l’insuline. Les hypoglycémies fonctionnelles s’observent après gastrectomie, ou chirurgie digestive haute, mais les formes primitives authentiques sont rares, et le diagnostic plutôt porté par excès.

Mots-clés : Hypoglycémie, adulte, diabète sucré, insulinome, tumeur hypoglycémisante extra-pancréatique, revue.
Hypoglycemia is a clinical and biological syndrome, causing a variety of diagnostic and therapeutic problems. Recognition of fasting (postabsorptive) hypoglycemia is easy in a patient known to be taking antidiabetic agents, or in the setting of apparent illness (hepatic failure, hypopituitarism, or huge retroperitoneal or thoracic tumors). In other cases, the non-specificity of the clinical manifestations, such as paroxysmal neurological or psychiatric disorders makes the diagnosis difficult. On the other hand, hypoglycemia should not be overdiagnosed in the case of non-specific autonomic symptoms occurring in a non-fasting state, and evidence of low plasma glucose levels is required for the diagnosis.

**DEFINITION-CLINICAL MANIFESTATIONS**

Hypoglycemia is a clinical and biological entity defined as an abnormal decrease in plasma glucose concentrations and the clinical consequences thereof. Hypoglycemia-related symptoms are multiple, non-specific and with many guises, and thus cannot be used to define hypoglycemia. Their only common feature is that they can be reverted by glucose administration. However, it is also difficult to set a plasma glucose level to define hypoglycemia. Physiological responses to hypoglycemia are hierarchical, as documented with the stepped hypoglycemic clamp technique in normal control subjects [1-3]. The first event to be elicited by a progressive decrement in plasma glucose levels is an inhibition of insulin secretion, for a mean arterialised venous glucose of 4.5 mmol/l (0.80 g/l). This inhibition has a major role in the defence against hypoglycemia, as recovery is negatively correlated with peripheral and portal insulin levels [4]. The second event is counterregulatory hormone release, which occurs at a glucose threshold of 3.3 to 3.6 mmol/l (0.60 to 0.65 g/l). Glucagon is the first line of defence, mainly for correcting brief hypoglycemia [5]. Glucagon stimulates a cascade of phosphorylation, inducing an increase in hepatic glucose production by stimulation of glycolysis and neoglucogenesis. Epinephrine becomes of primary importance when glucagon secretion is deficient, and is important in correcting prolonged hypoglycemia, by direct and indirect mechanisms. Epinephrine increases hepatic glucose output by stimulation of glycolysis and neoglucogenesis, directly and through its action on insulin and glucagon secretion. Epinephrine increases substrates for neoglucogenesis (lactates, alanine) via an increase in muscle glycolysis, and free fatty acids via lipolysis. As their action is delayed, cortisol and growth hormone are not involved in the correction of brief hypoglycemia but they do have a role later, in the defence against prolonged hypoglycemia. They reduce peripheral glucose uptake, by decreasing insulin sensitivity, and increase hepatic glucose production.

Clinical symptoms, both autonomic and neuroglycopenic, (Table I), appear when plasma glucose levels fall below 3 mmol/l (0.55 g/l). Neurogenic or autonomic symptoms result from autonomic nervous system response to hypoglycemia. Some symptoms mediated by catecholamines are “adrenergic”, others mediated by acetylcholine are “cholinergic” (Table I). Neuroglycopenic symptoms are the result of brain glucose deprivation. Finally, cognitive function deteriorates when the levels fall below 2.7 mmol/l (0.50 g/l). This last threshold value usually appears in classic textbooks to define clinical or “organic” hypoglycemia, but the threshold for counterregulatory hormone response might be more appropriate for clinical purposes and for defining plasma glucose targets for treatment of diabetes.

**DIAGNOSIS OF HYPOGLYCEMIA**

Careful interview of the patient, including personal and family history, description and chronology of symptoms, as well as possible treatments or toxic substances is required, together with physical examination. In many cases, recognition of the cause of hypoglycemia is easy, as hypoglycemia induced by antidiabetic drugs (insulin or sulfonylureas) is the most frequently observed.

Hypoglycemia either symptomatic or not, occurring in an hospitalised patient who presents with one or more causes of hypoglycemia (organ failure, drugs or toxicity) does not require further investigations, if follow-up indicates the complete resolution after suppression of the cause.

Patients presenting with paroxysmal neurological or psychiatric manifestations, related to fasting or to physical exercise, associated with low plasma glucose levels and reverted by glucose, require investigations to look for an organic cause: insulinoma, more frequent than extra-pancreatic tumor, or autoimmune or induced hypoglycemia. The first step is to obtain blood samples during a spontaneous episode for simultaneous assay of glucose, insulin, and C-peptide. If it is not available, the patient should be hospitalised in a specialised unit for a 48-hour fasting. Inappropriately high insulin levels for a low plasma glucose associated with high C-peptide values is diagnostic of endogenous hyperinsulinism. Differential diagnosis of insulinoma is difficult in cases of surreptitious use of sulfonylureas, or autoimmune hypoglycemia. Psychological or autoimmune context, plasma proinsulin and sulfonylurea assays are then useful. Use of sulfonylureas induces an increase in proinsulin proportional to insulin, contrary to the more marked increase of proinsulin than insulin observed in insulinomas. High
plasma insulin levels together with undetectable C-peptide concentrations are characteristic of hypoglycemia induced by exogenous insulin. If plasma insulin levels are suppressed or appropriately low at the time of hypoglycemia, an extrapancreatic tumor should be sought by free IGF-II plasma assay and imaging. Finally, if a fasting test does not induce any significant fall in plasma glucose, the hypothesis of organic hypoglycemia should be ruled out.

**EXOGENOUS OR INDUCED HYPOGLYCEMIA**

Exogenous or induced hypoglycemia includes hypoglycemia related to toxics and drugs. By far the leading cause is treatment of diabetes mellitus, and particularly insulin therapy.

**Hypoglycemia related to non-antidiabetic drugs**

Hypoglycemia due to non-antidiabetic drugs can be recurrent or protracted, severe with neuroglycopenic signs including coma, and responsible for sequelae or death. Some drugs potentiate antidiabetic agents, or are active alone, usually in a particular setting: elderly, inanition, prolonged fasting, renal or hepatic failure, sepsis. The most frequently reported drugs associated with hypoglycemia are listed in *Table II*, with the indication of the putative mechanisms of hypoglycemia. According to cases notified to French Pharmacovigilance Centers [7], the most frequent are cibenzoline (24%), dextroproxyphene and disopyramide (both 16%), beta-blockers, pentamidine, antidepressant drugs (5%), and angiotensin-converting enzyme inhibitors (3.7%). In this series, hypoglycemia is observed mainly in polymedicated old patients (age ranging from 75 to 81 for the first 3 drugs). The true incidence of these events is underevaluated, as hypoglycemias due to ancient drugs with well-known side-effects are not notified.

**Hypoglycemia related to diabetes treatment**

Hypoglycemia related to the treatment of diabetes represents the major cause of hypoglycemia. Insulin treatment is responsible for the majority of severe episodes (25-fold more frequently than sulfonylureas [13]. Hypoglycemia is thus the limiting factor in the management of diabetes [14].

**Type 1 diabetes-insulin-treated type 2 diabetes** – Hypoglycemia occurring in type 1 insulin-dependent diabetic patients represents the leading cause of hypoglycemia. Its frequency increases due to the search for the best glycemic control or for “near-normoglycemia” in order to prevent long term complications after the DCCT (Diabetes Control and Complications Trial) results. Hypoglycemic events observed in diabetic patients may be classified on a clinical basis as silent hypoglycemia, moderate hypoglycemia, and severe hypoglycemia (defined according to DCCT criteria as requiring external assistance for recovery).

**Hypoglycemia unawareness** – i.e. the absence of autonomic symptoms (*Table I*), affects about 25% of type 1 diabetic patients [18], mainly after long disease duration [19]. Incidence of severe hypoglycemia is

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**Table I.** Autonomic signs and symptoms by decreasing frequency and neuroglycopenic symptoms (according to cerebral stage) related to hypoglycemia. After Towler et al. [6].

<table>
<thead>
<tr>
<th>AUTONOMIC</th>
<th>NEUROGLYCOPENIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>Cortical</td>
</tr>
<tr>
<td>Tremors</td>
<td>disorientation, confusion dizziness, difficulty in concentration</td>
</tr>
<tr>
<td>Weakness, fatigue</td>
<td>(^a)</td>
</tr>
<tr>
<td>Pallor</td>
<td>Corticodiencephalic</td>
</tr>
<tr>
<td>Hunger</td>
<td>incoordination, sympathetic hyperactivity incapacity to discriminate sensation and to respond to stimuli, pupillary dilation</td>
</tr>
<tr>
<td>Tingling</td>
<td>Mesencephalic</td>
</tr>
<tr>
<td>Anxiety, nervousity</td>
<td>seizures, diplopia, hemiparesis, extensor plantar response</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Myelencephalic</td>
</tr>
<tr>
<td>Nausea</td>
<td>coma, superficial breathing, myosis bradycardia, hypothermia death</td>
</tr>
<tr>
<td>Thirst</td>
<td></td>
</tr>
<tr>
<td>Hypertension, cardiac rhythm abnormalities</td>
<td></td>
</tr>
<tr>
<td>Angor, pulmonary artery hypertension</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)adrenergic, \(^b\)cholinergic.
seven-fold higher when hypoglycemia unawareness is present [20, 21]. It is associated with a lower threshold for counterregulatory hormone release [22, 23]. This threshold varies according to antecedent mean plasma glucose: it is lower in patients with intensive treatment [24, 25], and higher in patients with poor metabolic control [26]. Cognitive alteration thresholds do not seem to be influenced by intensive treatment [27]. The role of cortisol hypersecretion induced by antecedent hypoglycemia has been proposed to explain decreased autonomic response to hypoglycemia [28, 29]. Recent, even silent, hypoglycemic episodes lead to a decrease in glycemic threshold for counterregulation and for autonomic symptoms [30, 31]. A self-aggravating circle then ensues. Desensitisation to hypoglycemia by hypoglycemia itself is supported by restoration of awareness after institution of screening and meticulous prevention of silent hypoglycemia [32], or by fixation of higher plasma glucose goals for metabolic control [33]. Evidence is also given by restoration of hypoglycemia awareness after removal of insulinoma [34]. Hypoglycemic episodes in patients treated with beta-blockers are due in part to autonomic symptom masking [35]. Finally, caffeine administration seems to prevent hypoglycemia by increasing plasma glucose threshold for autonomic symptoms, without changes in cognitive alteration threshold [36]. Caffeine may thus be helpful in patients with hypoglycemia unawareness.

Frequency of a given symptom is variable from one series to another [37], and from one patient to another. However, variability in a given patient is more limited, which gives good confidence for each symptom.

The frequency of silent hypoglycemia is high in type 1 diabetes, and is negatively related to the median of blood glucose levels. It occurs mainly during the night (56%) [38], reaching even 80% when bedtime blood glucose is 6 mmol/l or less [39]. The frequency of severe hypoglycemia is variable from one series to another, ranging from 50 to 1,400 episodes/1,000 patient-years) [8]. The DCCT indicates the relative risk of conventional and intensive treatment. A cohort of 1,441 young type 1 diabetic patients (19-39 years) was randomized into an intensive treatment group (n = 711) which aimed at reaching normal blood glucose and HbA1c levels, and a conventional treatment group.

<p>| TABLE II. | Drugs (INNs) associated with hypoglycemia [7-9], with indication of the putative mechanisms. |</p>
<table>
<thead>
<tr>
<th>DISEASES TREATED</th>
<th>DRUGS</th>
<th>MECHANISMS</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>cibenzoline, disopyramide, flecaïnide, propafenone</td>
<td>a</td>
<td>7, 8</td>
</tr>
<tr>
<td>Depression, psychiatric disorders</td>
<td>fluoxetine, clomipramine, monoamine oxidase inhibitors</td>
<td>a</td>
<td>7, 8</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>methimazole, carbimazole</td>
<td>d</td>
<td></td>
</tr>
<tr>
<td>Pain, inflammation</td>
<td>acetylsalicylic acid, diclofenac, indomethacin, acetaminophen, propoxyphene</td>
<td>a</td>
<td>7</td>
</tr>
<tr>
<td>Infections</td>
<td>sulfamethoxazole</td>
<td>a</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>pentamidine</td>
<td>e</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>quinine, chloroquine, mefloquine</td>
<td>a, c</td>
<td>7, 8</td>
</tr>
<tr>
<td>Hypertension, heart disease</td>
<td>beta-blockers</td>
<td>b, c</td>
<td>7, 8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>angiotensin-converting enzyme inhibitors</td>
<td>b</td>
<td>12</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
<td>fibrates</td>
<td>b</td>
<td>7, 8</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>penicillamine</td>
<td>d</td>
<td>7, 8</td>
</tr>
<tr>
<td></td>
<td>streptozotocin</td>
<td>e</td>
<td></td>
</tr>
</tbody>
</table>

*a increase in insulin secretion; 
*b increase in insulin sensitivity; 
*c decrease in gluconeogenesis; 
*d insulin autoantibodies; 
*e beta-cell cytotoxic effect.
(n = 730) for a 6.5-year mean duration follow-up, 3,778 episodes of severe hypoglycemia have been recorded, associated with coma or seizures in 1,027 [40]. Overall incidence of severe hypoglycemia was 612 vs 187/1,000 patient-years in the intensive and in the conventional group respectively, with a risk-ratio of 3.28. As hypoglycemia unawareness was among exclusion criteria, the actual incidence of hypoglycemia may be underestimated in this study. The increased incidence observed in the intensive group was the same during the 5 first years of treatment, and persisted after adjustment for HbA1c levels.

Insulin treated type 2 diabetic patients have less frequent and severe hypoglycemia than type 1 patients. A protective role for insulin resistance has been proposed. The UKPDS (United Kingdom Prospective Diabetes Study) indicates that in the intensive treatment group, the mean proportion of any hypoglycemic episodes was 23/1,000, a figure far lower than that of the DCCT [41]. A similar incidence has been reported in the Kumamoto Study [42].

The consequences of severe hypoglycemia – occurring in type 1 and in type 2 diabetic patients are controversial: the DCCT does not attribute to them any excess mortality, nor any alteration in cognitive functions [43]. One patient from the UKPDS intensive group died suddenly at home, and death has been attributed to hypoglycemia [41]. However, evidence of hypoglycemia responsibility is lacking. Some conflicting results have appeared in the literature: higher prevalence of cognitive functions alterations in patients with hypoglycemia unawareness [44] or history of severe hypoglycemia [45], and presence in these patients of magnetic resonance imaging cerebral abnormalities [46]. Moreover, hypoglycemia may be associated with alterations in cardiac ventricular repolarisation or with arrhythmia which could underlie sudden death [47].

Type 2 diabetes treated with sulfonylureas – In a cohort of 32,343 sulfonylureas-treated patients, Van Staa et al. [48] reported an annual risk of any hypoglycemic episodes of 18/1,000 patients/year (605 out of 34,052). In the UKPDS, the mean proportion of patients with one or more severe hypoglycemic episodes was 4/1,000 with chlorpropamide and 6/1,000 with glibenclamide, the corresponding values for any hypoglycemic episodes being 110 and 177/1,000 respectively [41]. The type of sulfonylurea and the associated drugs determine this risk. In the Van Staa et al. series, the risk was higher in glibenclamide users than with other sulfonylureas (relative risk 0.6 to 0.75). In a recent study [49], the incidence of severe hypoglycemia requiring hospitalisation was 2.29/1000 patient-years with glibenclamide and 0.73 with gliclazide, close to previously reported data from the same group [50]. Severity of hypoglycemia related to sulfonylureas is variable, ranging from simple hunger or sweating before lunch or in the evening [51] to prolonged coma. In a Swedish series of 57 cases of severe hypoglycemia in glibenclamide users, death was reported in 10 cases [52]. Predisposing factors to hypoglycemia in sulfonylurea users are known:

- Age, over 70 [53]: in old patients, use of long acting drugs (carbutamide, glibenclamide) or with prolonged release (gliclazide GTS) is not recommended.
- Undernutrition and fasting: sulfonylurea treatment should be stopped in these circumstances.
- Interactions with associated drugs [54], mainly in older patients: metformin, insulin, angiotensin converting enzyme inhibitors, sulfamides, antiarythmic drugs, beta- blockers, fibrates, antalgics, antioxidant K, psychotropic drugs.
- Alcohol consumption.

As hypoglycemia induced by sulfonylureas may be prolonged or recurrent, due to the long half-life of certain derivatives, hospitalisation is recommended. Glucagon administration should be avoided, as it stimulates insulin secretion. Long-acting somatostatin analog octreotide use is logical, as it inhibits insulin secretion, but it has been used only in rare cases, in non-diabetic patients [55].

Factitious hypoglycemia

Factitious hypoglycemia is due to self-administration of sulfonylureas (27 reported cases) [56-58], or of insulin. Hypoglycemia from sulfonylureas is difficult to distinguish from that of insulinoma from a clinical and biological point of view. Inappropriately high insulin, together with C-peptide plasma levels, characteristic of endogenous insulin hypersecretion [56], or C-peptide non-suppressibility by insulin [59] are similar to those observed in insulinomas. Surreptitious use of sulfonylureas is not admitted by the patient, even if laparotomy is planned: surgical exploration has been performed in 9 cases, with partial pancreatectomy in 5, followed by death in one. Some features should draw attention, mainly if pancreatic imaging remains negative in the setting of hypoglycemia with hyperinsulinemia: abrupt onset of symptoms without any prodromic phase (11/27 cases), history of psychiatric or behavioral disorders (7 cases), paradoxical tolerance to fasting test (5 cases), opportunity to know the effects of the drugs, or to have access to them by the profession of the patient or by that of his or her spouse (10 cases). In 11 cases, a type 2 diabetic patient treated with sulfonylureas was a member of the family. The diagnosis is made by the assay of sulfonylureas in the plasma or the urines (19 cases), or by the discovery of the tablets in the room or the possessions of the patient (6 cases). Treatment is difficult, as the patient will not admit taking hypoglycemic drugs, nor accept any psychiatric counseling.
Accidental use of sulfonylureas (46 reported cases) [56], instead of drugs with nearly similar INNs or trade names (chlorpropamide for chloroquine for instance) is recognised by the examination of the tablets, or by assaying sulfonylureas in plasma [56]. Factitious or criminal administration of insulin is suspected when hypoglycemia with hyperinsulinemia is associated with undetectable C-peptide plasma levels [60]. Diagnosis relies on the presence of polyclonal insulin antibodies in the serum [60], or specific assay [61], in the case of insulin of animal origin.

Hypoglycemia related to toxicity

Except for alcohol, toxic hypoglycemias are rare, and usually easy to recognize. They occur in the setting of hepatic failure secondary to acute liver necrosis due to intoxication by carbon tetrachloride, ethylene glycol, Ammanitis phalloida, hypoglycin (ackee-fruit from Jamaica), or certain species of thistle (Actratylis gummifera).

Excess of alcohol consumption can be responsible for hypoglycemia in fasting or underfed patients. Hypoglycemia is usually severe, with coma, and should be distinguished from acute alcohol poisoning itself by systematic blood glucose determination. High mortality rates have been reported [62]. During fasting, hepatic glycogen stores decrease, and glucose needs are covered by neoglucogenesis [62, 63]. Alcohol excess decreases both neoglucogenesis (by inhibition of malate-oxaloacetate conversion, secondary to an increase in NADH/NAD ratio), and the accessory catalytic alcohol pathway by catalase. Glucagon should not be administered to correct hypoglycemia, as hepatic glycogen stores are depleted. In insulin treated diabetic patients, alcohol excess may be responsible for severe hypoglycemia, either during fasting or by insulin effect potentiation [64]. Furthermore, alcohol has been shown to cause hypoglycemia unawareness [65]. In type 2 diabetic patients, alcohol can potentiate sulfonylurea-insulin secretory effects, and induce reactive hypoglycemia [62].

**TUMOR HYPOGLYCEMIA**

Insulinoma

Pancreatic beta-cell tumors, or insulinomas, are the most common cause of hypoglycemia due to endogenous hyperinsulinism [66]. Insulinomas are rare, with an estimated incidence of 1/250,000 patient-years [67]. Age of onset is usually 40-60 years, ranging from 6 weeks to 70 years. There is no sex difference [68]. Insulinoma is solitary in most cases, with no predilection for any area of the pancreas, so that the majority is corporeocaudal (42%), cephalic or isthmic (34%) [69]. Ectopic insulinomas (1-3%) have been found in the wall of the duodenum, the porta hepatis, and in the vicinity of the pancreas. Most insulinomas are small, with 90% less than 2 cm in diameter and 50% less than 1.3 cm, but ranging from 0.5 to 15 cm [69]. The majority of insulinomas are benign, well limited adenomas. Approximately 10% of the insulinomas occur in association with MEN 1 (primary hyperparathyroidism, pancreatic islet tumors, and pituitary adenomas, inherited as an autosomal dominant trait). These tumors are usually multiple. Malignant insulinomas are rare. Familial insulinomas have been reported [70]. Hyperinsulinism in such patients has been attributed to beta-cell hyperplasia, including a histologic pattern termed nesidioblastosis, clusters of beta-cells appearing to bud from pancreatic ducts. This syndrome is observed mainly in childhood, but is responsible for 0.5 of 5% of hypoglycemia in adults [70]. It is usually associated with mutations in the sulfonylurea-receptor gene [71], except in some adult cases [72]. Another cause is autosomal dominant familial hyperinsulinism with hypoglycemia due to a mutation of glucokinase gene, resulting in increased activity of the enzyme for glucose, and thus a decreased threshold for insulin secretion [73].

**Clinical manifestations** – Whipple’s triad (symptoms of hypoglycemia, low plasma glucose levels and rapid resolution of symptoms after glucose administration) is the main basis of the diagnosis [67]. The interval from the onset of symptoms to diagnosis ranges from 10 days to 30 years (median 2 years). The hypoglycemic episodes happen at irregular intervals with a varying duration. The symptoms of hypoglycemia occur more often in the late afternoon, in the early morning, or during exercise. Manifestations of reactive (post-prandial) hypoglycemia without readily demonstrable postabsorptive hypoglycemia are rare. Symptoms the most characteristically diagnostic of insulinoma are those of neuroglycopenia, as neurogenic symptoms are rare or absent [74]. Episodes of confusion or abnormal behavior are common as are various combinations of diplopia, blurred vision, sweating, palpitations and weakness. Loss of consciousness or amnesia have been reported in more than 50% of cases. The initial diagnosis is more often a neurological and/or neuropsychiatric disorder. Their intermittency and non-specific, multifaceted characters delay the diagnosis, although all signs and symptoms are usually recognized rapidly by oral or parenteral glucose. Peripheral neuropathy and gradual neurological deterioration resulting from recurrent episodes of hypoglycemia have been reported in rare instances [75]. Obesity or weight gain is present in 25% of the patients, explained by the need for frequent feeding. Physical examination is otherwise normal. Insulinoma may occur in a patient with pre-existing type 2 diabetes, but the co-occurrence of the two diseases seems to be coincidental [76].
Localisation of insulinomas – Insulinomas are usually small and difficult to detect. Many localisation procedures have been proposed for their detection.

Preoperative localisation techniques. Transabdominal ultrasound has a poor value in detecting tumors, with a sensitivity ranging from 26 to 75% [69]. The abdominal CT scan rarely detects tumors less than 1 cm in diameter and may fail to detect up to 20% of lesions larger than 3 cm. In most series, detection rates of CT scan for insulinomas ranges between 30 and 75%, with a sensitivity of 12.5%. Small tumors usually appear as enhancing lesions after contrast, but are rarely identified because of decreased vascularity [69]. New-generation CT scans with higher resolution may demonstrate better specificity [77]. Angiography is particularly useful in detecting small primary insulinomas. Angiographic detection rates have been enhanced by the use of digital subtraction images and are most effective when contrast product is injected into the smallest branch arteries following highly selective catheterisation. The sensitivity of angiography is about 70%, ranging from 18% to 94%, with a specificity of almost 100% [69]. Transhepatic portal venous sampling (THPVS) involves percutaneous cannulation of an intrahepatic branch of the portal vein, the catheter then being moved forward into the tributaries of the portal vein and blood sampled for hormone assay. The highest hormonal gradient indicates the site of the tumor. In most series, regionalisation rates range from 62.5 to 100% [69]. Selective intraarterial pancreatic stimulation (SIPS) relies on the secretary response of pancreatic endocrine tumors to secretagogue (calcium glucose). The secretagogue is injected into each artery that supplies the pancreas (gastrroduodenal, superior mesenteric, splenic, and hepatic artery). Serial samples are taken from a catheter in the right suprahepatic vein for insulin assay following the injection. The advantages of SIPS over THPVS are that it is performed at the same time as angiography and does not require transhepatic catheterisation (reducing morbidity). It gives also a greater predictability for tumor regionalisation. The SIPS is a reliable preoperative procedure, when other imaging techniques have failed to locate the tumor. However, it remains invasive, and its place is not still clearly defined among imaging techniques.

Endoscopic ultrasound (EUS) has been reported to be extremely effective in localising small tumors, with a detection rate of about 80% [78, 79]. The technique requires considerable additional expertise. It is better at identifying lesions in the pancreatic head than in the tail, because the latter has to be viewed through the wall of the stomach. Despite the fact that most insulinomas are found in the body or tail, a 80% localisation rate with endoscopic ultrasound has been reported in all series, comparing favourably with other preoperative techniques [76, 77]. The sensitivity and positive predictive value are 77% and 94% respectively [80]. Somatostatin receptor scintigraphy has been more recently proposed. Pancreatic endocrine tumors usually contain a high density of somatostatin receptors. In vitro studies have demonstrated high affinity binding sites for the 123I-labelled somatostatin analogue Tyr3-octreotide in 50 to 72% of insulinomas [81]. Somatostatin receptor scintigraphy is likely to be of limited value in identifying primary tumors. However, it may have a role in treatment in identifying the extent of the metastatic process (lymph nodes, lungs and bone). Furthermore, the positivity of scintigraphy is correlated with response to octreotide treatment [82]. The sensitivity and positive predictive value are 60% and 100%, respectively [80].

Peroperative localisation techniques. Intraoperative ultrasound (IOUS) appears to be more effective than palpation in detecting insulinomas, probably because they are more readily accessible to the probe. The sensitivity of IOUS ranges from 75 to 100% [15]. IOUS and palpation are complementary techniques, and are far more sensitive than preoperative techniques for localising small tumors.

In conclusion localisation of insulinomas can be achieved in a first step using abdominal CT scanning and possibly transabdominal ultrasonography. These techniques should be the initial investigations, and are particularly useful in identifying large tumors or metastatic disease. Endoscopic ultrasonography can significantly enhance detection rates for small tumors in centres with this expertise. It is the investigation of choice for those tumors not localized by CT. The calcium-stimulation test is invasive, and its place remains still to define. Somatostatin receptor scintigraphy may have a role in localising extrapancreatic tumors and/or metastatic disease and in selecting patients likely to respond to treatment with somatostatin analogs. Peroperative localisation by palpation and ultrasonography can direct the surgeon to limited tissue resection.

Analytical methods – Diagnosis of insulinomas is based on the demonstration of hypoglycemia with hyperinsulinemia at the time of hypoglycemic symptoms. Repeated daily determinations of plasma glucose and insulin concentrations sometimes make the diagnosis. Although insulin levels may or not be elevated in an absolute way, they are invariably inappropriately high, relative to the low plasma glucose concentrations. The association of increased insulin values > 6 µU/ml, (> 36 pmol/l) with a low glucose value (< 2.2 mmol/l) confirms the diagnosis. Assay of plasma C-peptide concentrations, as a marker of endogenous insulin secretion, is useful in distinguishing an endogenous secretion from exogenous insulin administration. Plasma C-peptide concentrations are suppressed from exogenous and increased with endogenous insulin [84]. Proinsulin and proinsulin to insulin ratio are elevated disproportionately in insulinomas.
Non-suppressibility of C-peptide can be assessed by hypoglycemia induced by insulin (C-peptide suppression test). The lack of an appropriate negative feed-back response of C-peptide of at least 50% from baseline levels during hypoglycemia is characteristic of insulinomas [84]. However, C-peptide responses are influenced by age and body mass index (BMI); suppressibility is lower as BMI and age increase [86]. The Tolbutamide test and other stimulatory tests are not useful either. The key diagnosis test is the prolonged fast with sampling for plasma glucose, insulin and C-peptide every 4 hours during 48 hours. The interval between the last meal and the onset of symptomatic hypoglycemia may vary from 7 to 60 hours, being less than 12 hours in 30% of cases and of 24 hours in 60% of the cases [67]. Insulinoma is confirmed by non suppressed plasma insulin concentrations in association with hypoglycemia, i.e. an increased insulin/glucose ratio during the fast. Turner’s amended ratio (100 x insulinemia uU/ml/glycemia mg/100 ml — 30; normal < 30, < obese < 100, insulinoma > 150) is less useful as it fails to identify all insulinomas.

Multiple endocrine neoplasia (MEN I) should be considered when an insulinoma has been diagnosed, by screening for pituitary and parathyroid adenomas. Finally, pancreatic malignant insular tumor may secrete other peptides like glucagon, somatostatin, pancreatic polypeptide, ACTH, VIP, gastrin, serotonin, creta other peptides like glucagon, somatostatin, pancreatic polypeptide, ACTH, VIP, gastrin, serotonin, partly pancreatic insulinomas and when surgery is contraindicated.

Medical Treatment – Several drugs can be used to improve hypoglycemia in patients with malignant insulinomas and when surgery is contraindicated.

In advanced malignant tumors, chemotherapy is the treatment of choice, and is influenced by the distribution and bulk of tumor, the aggressiveness of the disease, and the nature and severity of the associated endocrine syndromes. Streptozotocin has been proposed specifically for the treatment of islet-cell carcinoma. It selectively destroys pancreatic B-cells by inhibiting the synthesis of deoxyribonucleic acids. A progressive increase in therapeutic effectiveness has been observed if streptozotocin is associated either to fluorouracil or to doxorubicin. The combination of streptozotocin and doxorubicin has been shown to be the most effective [88]. Hepatic artery embolization has been used as palliative treatment of metastatic islet carcinomas.

Persistent hypoglycemia, whether from a benign or malignant insulinoma, or inoperable tumors, can usually be controlled by diazoxide. This drug inhibits the release of insulin but has no effect in reduction of tumor mass. Potentiation of its effects can be obtained by combination with a thiazide diuretic [89]. This combination may be used preoperatively for preventing hypoglycemia. Side effects of diazoxide are hirsutism, edema and, rarely, hypotension and granulocytopenia. Streptozotocin and diazoxide may be used in combination.

Long-acting somatostatin analog (octreotide) has been used in the treatment of a variety of neuroendocrine tumors with apparent success. Its actions on pancreatic endocrine function mimic those of natural somatostatin, including the ability to lower plasma insulin levels, and other pancreatic peptide hormones [90]. Few reports of insulinomas treated with octreotide have been reported. The response seems mainly to depend on the presence of somatostatin receptors. Octreotide has not been shown to induce tumor regression [91, 92]. It can inhibit tumor growth in some cases but duration of response is as yet unpredictable. Moreover, octreotide can worsen fasting hypoglycemia by reduction in glucagon and growth hormone release [93]. Ca2+-channel blockers have been shown to inhibit insulin release and reduce incidence of hypoglycemia in some [94] but not all patients [95] with insulinoma. Further studies are needed to confirm their long-term beneficial effects.

Surgical treatment – Surgery therapy is the treatment of choice, the type depending on the size and the location of lesions. Enucleation should be preferred, but for body and tail lesions, distal pancreatectomy is often required. More extensive pancreatectomy is warranted for multiple adenomas or malignant tumor. Even when total tumor resection is not possible, tumor mass reduction often alleviates hypoglycemia, at least temporarily. When lesions are not apparent despite intraoperative ultrasonography (8 to 20% of cases), partial pancreatectomy is often performed. Intraoperative hormonal measurements may be used to direct surgical treatment. It is highly reliable in patients with atypical causes, such as insulinoma associated with MEN, insulin-secreting carcinoma, or pancreatic neidoblastosis [96].

Postoperative complications including pancreatitis, pancreatic fistula, and abscess depend on the choice of surgery. Hyperglycemia usually follows effective surgery, but it is transient over a few days. Permanent diabetes mellitus occurs in about 10% of cases.

Minimally invasive surgery is feasible and appropriate for selected insulinomas. Videolaparoscopic resection is indicated in unique and benign insulinomas, superficially located to the anterior wall of the pancreas, to be resected by enucleation or distal pancreatectomy with splenic preservation. This approach is contraindicated in multiple insulinomas, in insulinomas located on the posterior wall or deeply located in the head of the pancreas, and in malignant tumors. Advantages are the lack of parietal incision and the quality of postoperative comfort. Disadvantages are the absence of palpation and difficulty exploring the whole pancreas [97, 98].
Extrapancreatic tumors

Hypoglycemia can be caused by a variety of rare extrapancreatic, non-beta-cell tumors. More than 300 cases have been reported. The majority are mesenchymal in origin: fibrosarcoma, mesothelioma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, hemangiopericytoma, neurofibroma, and lymphosarcoma [63, 99]. They are slow growing, although many are malignant and usually large at diagnosis. Their localization is retroperitoneal (40%), intra-abdominal (30%) and intrathoracic (30%). Epithelial non-beta-cell tumors are hepatocarcinomas (20% of cases), malignant adrenocortical tumors (10% of cases), usually large and silent, and carcinoid tumors (ileum, bronchus, pancreas). Hypoglycemia occurs occasionally in patients with leukemia, lymphoma, or multiple myeloma, as well as melanoma, teratoma, or pseudomyxoma. Hypoglycemia has also been reported in rare cases of neuroblastoma or paraganglioma, including pheochromocytoma [70].

Hypoglycemic episodes occur in the early morning or during exercise, and characteristically symptoms are neuroglycopenic and severe. The patients are usually old, in a poor general condition. The diagnosis is easy in most cases, as the tumor is usually large.

Biological alterations associate low concentrations of plasma glucose, insulin, C-peptide, proinsulin, growth hormone, and insulin-like growth factor-I (IGF-I). High rates of glucose turnover are common, consistent with an increase in glucose uptake by the muscle and tumor, and a low hepatic glucose production [70]. Other studies have demonstrated a decrease in neoglucogenesis, together with an inhibition of glycolysis, lipolysis and ketogenesis. Insulin secretion is suppressed appropriately and serum IGF-I levels are typically low. Hypoglycemia is due to an overproduction of IGF-II, and particularly of an incompletely processed form (“big” IGF-II). The 150-kDa complex of IGF-II, IGF-binding protein-3 and an acid-labile subunit, that normally transports most of the IGF-II in the circulation, is markedly decreased in affected patients. Most of IGF-II is transported in a smaller complex thought to enter target tissues more readily, and serum-free IGF-II concentrations are elevated. Hypoglycemia is attributed to the direct insulin-like action of IGF-II. Glucagon and growth hormone levels are suppressed by IGF-II, contributing to hypoglycemia. IGF-II to IGF-I ratio is typically high, as growth hormone secretion and, consequently, IGF-I production is suppressed. Free serum IGF-II and pro-IGF-II levels are elevated [63, 101-103]. In rare instances hypoglycemia is related to insulin hypersecretion by a small-cell carcinoma of the cervix [104].

AUTOIMMUNE HYPOGLYCEMIA

Insulin autoimmune syndrome – The insulin autoimmune syndrome (IAS) is characterised by the combination of fasting hypoglycemia, high concentrations of total serum immunoreactive insulin, and presence of autoantibodies to native human insulin in serum. The first case was described in 1970 by Hirata et al. [105]. Actually, 244 cases have been reported in Japan, and only 29 cases in Caucasian patients from Europe and the USA [106]. In Japanese patients, IAS is the third leading cause of spontaneous hypoglycemic attacks, after insulinoma and extrapancreatic tumors. Age of onset is usually 60-70 years, except for young female patients with Graves’ disease. Sex-ratio is 1. Hypoglycemia is transient, with a duration less than one month in 30%, and of less than 3 months in 40% of the cases. A few patients continue to present with mild hypoglycemic attacks for more than 1 year. In nearly 80% of the cases, IAS is associated with other autoimmune disorders such as Graves’ disease (25%), rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and chronic hepatitis [107]. The role of autoimmunisation induced by drugs has been suggested as a drug containing sulfhydryl groups had been introduced in 50% of the cases 4 to 6 weeks before the onset of the hypoglycemic attacks: methimazole, carbimazole, penicillamin, captopril, α-mercaptopropionyl glycine, glutathion, pyritinol and imipenem [106, 107]. The clinical diagnosis of IAS is based upon the presence of hypoglycemic attacks occurring a few weeks after initiation of treatment.

The disease course is benign in the majority of the cases, with spontaneous remission in less than 3 months, and disappearance of insulin autoantibodies 4 to 12 months after withdrawal of the drug. Some patients need medication to stop the persistent hypoglycemic attacks: steroids, azathioprine, or 6-mercaptopurine. Paradoxically, insulin autoantibodies may disappear spontaneously in some instances in spite of the continuation of carbimazole or methimazole treatment. The current treatment recommended is frequent feeding (6 meals or more/day) and to avoid sweets except at the time of hypoglycemic attacks. Alpha-glucosidase inhibitors may be helpful in decreasing insulin plasma levels after meals [106].

A large increase in plasma insulin levels is observed, in excess of 1,000 pmol/mL, and may attain 150,000 pmol/ml in some cases. The structure of circulating insulin is normal. C-peptide plasma concentrations are elevated, reflecting free C-peptide concentrations and secreted proinsulin bound by insulin autoantibodies. C-peptide or insulin-receptor autoantibodies are absent. The majority of insulin autoantibodies are polyclonal, belonging to the IgG class. Two subtypes of antibodies are produced: antibodies with low affinity and high binding capacity, and antibodies with high affinity and low binding capacity, the former being associated with hypoglycemic attacks [108].
A strong association between IAS and HLA DR4 has been evidenced in 96% of the Japanese patients (HLA frequency is 43% in normal Japanese controls). Analysis of the nucleotide sequences indicates that the haplotype of all the patients with IAS is DRB1*0406/DQA1*0301/DQB1*0302 (14% of controls) [109]. The DRB1*0406 allele seems to play an important role in presenting insulin peptides to T cells [110]. Dissociation of insulin from the insulin-antibody complex is thought to result in increase in free insulin plasma concentrations and hypoglycemia during fasting.

Autoantibodies to the insulin receptor – Autoantibodies to the insulin receptor are usually observed in extreme insulin resistance syndrome B associated with acanthosis nigricans and other autoimmune diseases (lupus erythematosus, Sjögren syndrome). Hypoglycemia is due to the insulin-like agonist action of the receptor antibodies.

Autoantibodies to the β-cell – The presence of β-cell-stimulating antibodies has been reported in the serum of patients with hypoglycemia or insulin dependent diabetes mellitus [111]. The target action of these autoantibodies is not known.

MULTIFACTORIAL HYPOGLYCEMIA

This most common cause of hypoglycemia is observed among hospitalised patients with failure of one or more critical organ systems [112]. These include hepatic, cardiac, and particularly renal failure, as well as sepsis and inanition.

Hepatic diseases – Endogenous glucose production requires a structurally and enzymatically intact liver. Hypoglycemia results from generalized hepatic damage (80%): fulminant hepatitis (viral and toxic), primary malignant hepatic tumors resulting for a gluconeogenic regulatory abnormality rather than hepatic destruction [113]. Hypoglycemia is unusual in metastatic liver disease, in common forms of cirrhosis and hepatitis.

Cardiac diseases – Hypoglycemia occurs occasionally in patients with severe cardiac failure of different causes. The pathogenesis of hypoglycemia is not known. Suggested possibilities include hepatic congestion, hepatic hypoxia, inanition, and gluconeogenic substrate limitation.

Renal diseases – Hypoglycemia occurs in some patients with renal failure. Some patients are cachectic and hypoglycemia is attributed to substrate limitation of gluconeogenesis (alanine, lactate). An inhibition of gluconeogenesis and a decreased glycemic response to exogenous glucagon have been reported [112, 114]. In patients with diabetes mellitus and renal failure, insulin requirements are reduced and the risk of hypoglycemia is enhanced, due to a decreased renal metabolism and clearance of insulin. In patients with end-stage renal disease, reduced renal glucose production may contribute to the pathogenesis of hypoglycemia, but this is not expected to cause hypoglycemia if the capacity of liver to produce glucose is normal [115].

Sepsis – Hypoglycemia is not infrequent in patients with sepsis. Hypoglycemia is due to an increased glucose utilisation (by macrophage-rich tissues such as liver, spleen, and ileum), an increased glucose turnover and a decreased hepatic glucose production [116]. Cytokines, such as tumor necrosis factor (TNF) and interleukin 6 (IL6) increase initially glucose production in stimulating glucagon and catecholamine secretion, and increase glucose utilisation. The later decline in glucose production is caused by decreased hepatic responsiveness to the appropriate glucoregulatory stimuli to hepatic glucose production [117].

Inanition – Hypoglycemia can result from prolonged starvation, but nutritional hypoglycemia is thought to be rare in developed countries where it is mainly due to severe inanition and anorexia nervosa. The pathogenesis seems to be multifactorial: substrate limitation of gluconeogenesis, total body fat depletion, and glucose utilisation exceeding the capacity of glucose production [118].

Hormonal deficiencies – Hormonal glucoregulatory abnormalities causing hypoglycemia are not common, except in patients with type 1 diabetes, because counterregulatory systems are effective in compensating for a selective defect in one hormone.

Cortisol and Growth hormone deficiency – The majority of adults with deficient secretion of cortisol, growth hormone, or both do not develop clinical hypoglycemia. Plasma glucose concentrations and hepatic glucose production are normal. However, clinical hypoglycemia can occur when glucose utilisation or losses are increased, as during exercise or pregnancy, or when glucose production is impaired, following alcohol ingestion, for instance. Severe hypoglycemia may occur in young children with chronic deficiencies of these hormones, particularly in the neonatal period and before age 5. Hypoglycemia is generally preceeded by a period of caloric deprivation. Cortisol deficiency results in reduced epinephrine, but not glucagon secretion.

Glucagon and epinephrine deficiency – Postabsorptive hypoglycemia occurs when both glucagon and epinephrine are deficient in the setting of relative or absolute therapeutic insulin excess only in people with type 1 diabetes. Hypoglycemia is not a feature of the
epinephrine deficient state that results from bilateral adrenalectomy when glucocorticoid replacement is adequate.

Isolated glucagon deficiency does not result in hypoglycemia if epinephrine, cortisol and growth hormone secretions are intact and insulin secretion is suppressed appropriately.

## REACTIVE (POSTPRANDIAL) HYPOGLYCEMIA

Reactive or postprandial or stimulative hypoglycemia occurs after meals, typically within 3–4 hours of food ingestion. Congenital deficiencies of enzymes of carbohydrate metabolism (hereditary fructose intolerance, galactosemia) are rare causes of postprandial hypoglycemia and become apparent early in life. Postprandial hypoglycemia has been reported in patients who have undergone gastric surgery resulting in rapid absorption of ingested food into the small intestine (gastrectomy, gastroenterostomy, pyloroplasty, gastric bypass). Hypoglycemia results of marked early hyperinsulinemia caused by rapid absorption of ingested nutrients, via an enhanced secretion of insulinotropic gut factors (secretin, enteroglucagon, cholecystokinin, gastric inhibitory polypeptide (GIP), or both [119]. Symptoms of hypoglycemia should be distinguished from the dumping syndrome (abdominal fullness, nausea, weakness) which occurs less than 1 hour after meal.

The frequency, and even the existence, of idiopathic reactive hypoglycemia is a matter of debate. Idiopathic reactive hypoglycemia is too often erroneously diagnosed by patients and by physicians. Some investigators have found that most patients thought to have hypoglycemic symptoms as well as low glucose levels after glucose ingestion have normal glucose levels after a mixed meal. Also, when glucose is assayed during symptomatic episodes, only 5% of 132 episodes are associated with blood glucose levels of 2.8 mmol/l or less [120]. However we have seen above that the glycemic threshold for autonomic symptoms is higher than 2.8 mmol/l.

The diagnosis of reactive hypoglycemia requires appropriate symptoms temporally related to a low plasma glucose concentration; the diagnosis should not be made on the basis of an oral glucose tolerance test (both not specific and not sensitive).

The pathogenesis of true idiopathic reactive hypoglycemia is unknown. There is no evidence that insulin secretion is excessive, but insulin response is high and delayed. Increased sensitivity to insulin, increased cellular responsiveness to insulin and decreased counterregulatory hormone secretion have been reported [121]. Deficient glucagon secretion, including compensatory enhancement in epinephrine secretion may be another explanation [122].

A low carbohydrate high-protein diet is recommended to patients with reactive hypoglycemia. Its efficacy has to be established. Frequent feedings (6/day) and avoidance of simple sugars are also advised. Anticholinergic drugs have been reported to be beneficial, but produce undesirable side effects. Propanolol reduces symptoms in patients with postgastrectomy hypoglycemia.

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