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Review

Non-diabetic hypoglycemia

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ABSTRACT

Glucose is the main substrate utilized by the brain, and therefore numerous counterregulatory mechanisms exist to maintain plasma glucose concentration. This makes it rare for hypoglycemia to develop in people who are not taking hypoglycemic drugs, such as insulin or sulfonylureas, for diabetes. The symptoms of hypoglycemia are nonspecific. The presence of Whipple's triad is necessary for diagnosis. When symptoms occur spontaneously, the patient can be evaluated for hypoglycemia. If this is not possible, then a 72-hour fasting test or a mixed meal tolerance test can be performed to create conditions for symptoms to occur. Non-diabetic hypoglycemia is mainly divided into two main groups: insulin-mediated (hyperinsulinism) and insulin-independent. The main causes of hypoglycemia due to endogenous hyperinsulinism are insulinoma and islet cell hyperplasia (nesidioblastosis), post-bariatric surgery, and autoimmune hypoglycemia with the presence of anti-insulin antibodies. Other important causes of hypoglycemia include hypoglycemic drugs, non-islet cell tumors, hormonal deficiencies (primary adrenal insufficiency, anterior pituitary insufficiency), and critical illnesses (liver/kidney failure). In this article, we provide an overview of the pathogenesis and treatment of hypoglycemia.

Keywords: Hypoglycemia, non-diabetic hypoglycemia, insulinoma, nesidioblastosis, postprandial reactive hypoglycemia

DEFINITION OF HYPOGLYCEMIA

Hypoglycemia is a decreasing in plasma glucose concentration enough to cause symptoms. Even when blood glucose is within biochemical norms, rapid and sudden decreasing may cause symptoms. As a result, the definition of hypoglycemia includes the presence of low serum blood glucose, the presence of symptoms, and the improvement of symptoms with glucose intake. Hypoglycemia is usually defined by a plasma glucose concentration below 70 mg/dL; however, there may be no obvious signs and symptoms until the plasma glucose concentration falls below 55 mg/dl. The Whipple triad has been used to define hypoglycemia since 1938.[1] Symptomatic hypoglycemia is clinically diagnosed using the Whipple triad.[2]

The Whipple's triad should be present in cases of true hypoglycemia:

Classic Whipple Triad

1.Symptoms and signs of hypoglycemia
2.A plasma glucose level of 55 mg/dl or less
3.Disappearance of symptoms with glucose administration

Hypoglycemia is a condition frequently encountered in the community during diabetes mellitus treatment. It is rare in older children and adults not receiving diabetes mellitus treatment and may be because of various or multiple etiologies.[2] In healthy individuals, symptoms of hypoglycemia usually develop when the mean plasma glucose is <55 mg/dl. If plasma glucose is <60 mg/dl, it is suspicious; if it is 55 mg/dl, it should be investigated.

Hypoglycemia is rare in people without diabetes mellitus who are not taking hypoglycemic drugs due to the good physiologic efficiency of the counterregulatory mechanisms, i.e., the counter-regulatory system. However, non-diabetic hypoglycemia constitutes a class of endocrine emergencies that should be examined.

SYMPTOMS OF HYPOGLYCEMIA

In the presence of hypoglycemia, the counterregulatory system shows very good physiologic activity.[3] When plasma glucose falls below 70 mg/dl, activation of the counterregulatory system begins, and below 60 mg/dl, increased autonomic activation occurs and symptoms become prominent. Severe symptoms are usually seen when plasma glucose falls below 50 mg/dl. There is a consensus that the threshold for hypoglycemia is 55 mg/dl, but what is important is not the threshold but the association of low blood glucose levels with accompanying clinical symptoms. Hypoglycemia is mostly associated with the following symptoms:[4]

1. Adrenergic symptoms

Symptoms associated with an increased catecholaminergic response, such as sweating, tremors, and palpitations

2. Neuroglycopenic symptoms

Symptoms ranging from dysarthria, confusion, epilepsy, visual and behavioral impairment, and coma caused by a decrease in cerebral glucose concentration

Increased adrenergic activation usually results in minor symptoms, including mild-to-moderate hypoglycemia. Symptoms may vary between individuals, but each individual experiences a similar episode. If plasma glucose decreases even further, glucose entry into the nervous system, especially the brain, is reduced, resulting in neuroglycopenic symptoms. Major symptoms occur, including severe hypoglycemia. ECG changes may also occur in severe hypoglycemia, and QT prolongation may be observed.[5] Hypoglycemia may be asymptomatic or silent, and it is common and often asymptomatic, especially in cases of non-diabetic acute coronary syndrome. Silent hypoglycemia has been associated with silent cardiac ischemia. Silent hypoglycemia is associated with a significantly higher frequency of ventricular extrasystole or non-sustained ventricular tachycardia in patients with acute coronary syndrome.[6] Table 1 shows the minor and major symptoms and signs observed in hypoglycemia. Table 2 shows adrenergic and neuroglycopenic symptoms and signs. Figure 1 shows the glycemic threshold for counterregulatory hormones and the onset of changes in hypoglycemia symptoms in response to hypoglycemia in non-diabetic subjects.[7]

Table 1. Minor and major symptoms and findings in hypoglycemia

Minor Hypoglycemia	Major Hypoglycemia
(The person can handle it himself)	(The person needs someone else's help)
- Feeling of hunger	- Confusion
- Tachycardia, Palpitation	- Cognitive changes
- Shaking, Sweating	- Personality changes
- Paleness	- Coordination difficulty
- Restlessness	- Diplopia
- Dizziness	- Headache
- Defect of vision	- Disorientation
- Tiredness	- Loss of consciousness
- To yawn	- Coma

Table 2. Adrenergic and neuroglycopenic symptoms and findings

Adrenergic	Neuroglycopenic
- Paleness	- Diplopia
- Tremor	- Lethargy
- Irritability	- Difficulty concentrating
- Anxiety	- Confusion
- Tachycardia	- Behavior change
- Palpitations	- Paresthesia
- Sweating	- Fainting
- Weakness	- Convulsion
- Feeling of hunger	- Coma
- Nausea	- Death

ETIOLOGY OF NON-DIABETIC HYPOGLYCEMIA

There are many etiologic factors involved in non-diabetic hypoglycemia. They are generally divided into two main groups:[8]

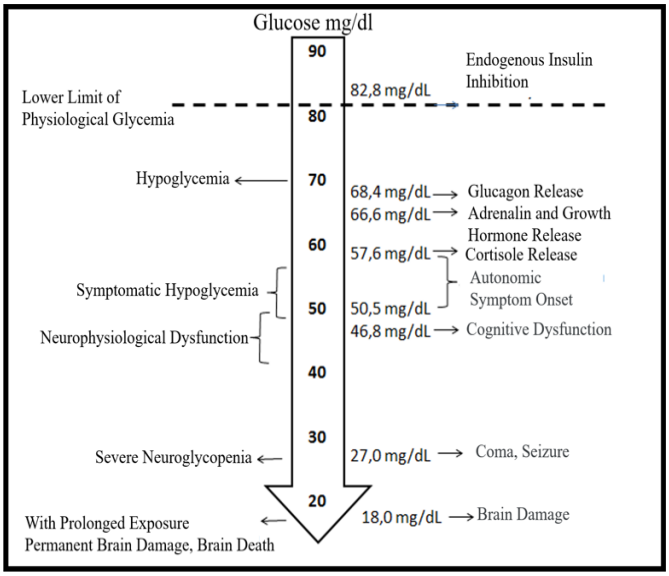

Figure 1. Glycemic threshold for counterregulatory hormones and baseline values of changes in hypoglycemia symptoms in response to hypoglycemia in non-diabetic individuals

1.Insulin-mediated nondiabetic hypoglycemia (hyperinsulinism)

2.Insulin-independent nondiabetic hypoglycemia

Insulin-mediated nondiabetic hypoglycemia is characterized by hyperinsulinism. It is divided into endogenous and exogenous causes. Endogenous causes include insulinoma and islet cell hyperplasia (nesidioblastosis), post-bariatric surgery, and autoimmune hypoglycemia with the presence of anti-insulin antibodies. Exogenous causes are iatrogenic hyperinsulinism and include hyperinsulinemia resulting from the intake of exogenous insulin or insulin secretagogues (sulfonylureas and glinides) in a healthy person, especially factitious hyperinsulinism.

Insulin-independent hypoglycemia; alcohol, visceral insufficiency (liver/kidney failure), critical illness, primary adrenal insufficiency, anterior pituitary insufficiency, severe sepsis, cerebral malaria, anorexia nervosa, cachexia, glycogen storage disease, gastric surgery, mesenchymal tumors with high insulin-like growth factor-2 (IGF-2) levels, autoimmune hypoglycemia with the presence of anti-insulin receptor antibodies, and drugs that cause hypoglycemia. Table 3 lists the causes of nondiabetic hypoglycemia, and Table 4 lists the drugs that may cause or trigger hypoglycemia.

CLASSIFICATION OF NON-DIABETIC HYPOGLYCEMIA

There are two types of non-diabetic hypoglycemia; fasting hypoglycemia and reactive hypoglycemia.[9,10] Table 5 shows the types of non-diabetic hypoglycemia and possible causes.

1. Fasting Hypoglycemia (Postabsorptive)

Occurs in the morning when a meal is skipped or in the time frame of 5 hours after a meal, may be associated with a disease.

2. Reactive Hypoglycemia (Postprandial)

Occurs several hours after eating, usually within 1-4 hours after a meal.

Traditionally, non-diabetic hypoglycemic disorders are classified in this way. This classification has been criticized as being unhelpful diagnostically. This is because some causes of hypoglycemia, such as insulinoma, may present

Table 3. Causes of non-diabetic hypoglycemia

Hypoglycemia with high insulin levels	Hypoglycemia with normal or low insulin levels
Endogenous Causes	**Non-pancreatic Tumors**
• Insulinoma	• Tumors with increased IGF-2 secretion or more frequent precursors (Doege-Potter syndrome)
• Nesidioblastosis	➢ Fibrosarcoma
• Reactive hypoglycemia (hyperinsulinism)	➢ Hemangiopericytoma
• Autoimmune hypoglycemia	➢ Hepatocellular carcinoma
➢ Anti-insulin antibody (Hirata disease)	• Liver-associated malignancies
• Post-bariatric surgery associated hyperinsulinism	➢ Multiple metastases
• Ectopic insulin secretion of non-pancreatic tumors	➢ Hepatocellular carcinoma
• Genetics (congenital hyperinsulinism)	• Medicines
➢ Monogenic causes	• Alcohol
- Beckwith-wiedemann syndrome	➢ Especially excessive drinking -binge drinking-
- Perlman syndrome	• Critical illnesses
- Simpson-Golabi-Behmel syndrome	➢ Liver failure
- Kabuki syndrome	➢ Heart failure
- Sotos syndrome	➢ Kidney failure
- Timothy syndrome	➢ Sepsis
- Costello syndrome (HRAS gene mutation)	➢ Cerebral malaria
- Ondine syndrome	➢ Anorexia nervosa
- Usher type 1c syndrome	➢ Cachexia
- Congenital glycosylation disorder	➢ Malnutrition
➢ Insulin receptor mutation	• Hormone deficiencies
➢ Beta cell insulin secretion regulation gene mutations	➢ Cortisol insufficiency (peripheral adrenal insufficiency)
➢ Channel anomalies	➢ Growth hormone deficiency (hypopituitarism)
- ABCC8 mutation (most common)	➢ Glucagon deficiency
➢ Congenital metabolism errors	➢ Adrenalin deficiency
- Congenital fructose intolerance	• Autoimmune hypoglycemia
- Exercise induced hyperinsulinemia (autosomal dominant)	➢ Anti-insulin receptor antibody
Exogenous Causes	• Early dumping syndrome
• Accidental, covert, or malicious hypoglycemia (iatrogenic or factitious)	➢ After bariatric surgery
➢ Bound to exogenous insulin	- Gastric bypass surgery (roux-en-y operation) – especially
➢ Bound to sulfonylureas or glinides	- Sleeve gastrectomy
• Medications used for therapeutic purposes	➢ Gastrectomy (total or partial)
➢ Tramadol	➢ Esophagectomy (total or partial)
➢ Methadone	➢ Fundoplication (gastroesophageal reflux or hiatal hernia operation)
➢ Cinacalcet	➢ Vagotomy (stomach ulcer treatment)
➢ Topiramate	➢ Pyloroplasty (pyloric stenosis treatment)
➢ Quinolone	• Toxic substances
• Physiological	➢ Toxic hypoglycemic syndrome
➢ pregnancy	- Ake fruit
	• Genetics
	➢ Congenital metabolism errors
	- Glycogen storage disease
	- Fatty acid oxidation disorders
	- Gluconeogenesis disorders
	- Organic aciduria
	- Biotin sensitive multiple carboxylase deficiency
	• Physiological
	➢ Heavy exercise
	➢ Very prolonged hunger

Table 4. Drugs that may cause or trigger hypoglycemia	
- Insulin	- Cinacalcet
- Insulin secretagogues (especially sulfonylureas, meglitinides)	- Ciprofloxacin
- Sulfonamides	- Chloramphenicol
- Tramadol	- Ketoconazole
- Methadone	- Oxytetracycline
- Topiramate	- Isoniazid
- Tyrosine kinase inhibitors	- PAS
- Quinolones (especially 3rd and 4th generations; moxifloxacin, levofloxacin, more rarely ciprofloxacin)	- Ethionamide
- Tigecycline	- P-aminobenzoate
- Anti-malarial drugs (quinine, hydroxychloroquine)	- Acetaminophen
- Derivatives of artemisinin (artesunat, artemeter)	- Indomethacin, propoxyphene, Phenylbutazone
- Quinidine	- MAOI
- Salicylate	- Fluoxetine
- Disopyramide	- Imipramine
- Cibenzoline	- Lithium
- Pentamidine	- IGF-1
- Glucagon (during endoscopy)	- Gabapentin
- Angiotensin converting enzyme inhibitors	- Mifepristone
- Angiotensin receptor blockers	- Heparin
- Non-selective beta-blockers	- 6-Mercaptopurine
	- Trimethoprim-sulphamethoxazole

Table 5. Types of non-diabetic hypoglycemia and possible causes	
Type of Non-diabetic Hypoglycemia	**Possible Causes**
Fasting hypoglycemia	• Tumors or similar formations; tumors that secrete insulin in the pancreas -insulinoma- or hyperplasia -nesidioblastosis-, increased IGF-2 secretion from non-pancreatic tumor • Medicines • Alcohol; especially binge drinking • Serious diseases; those affecting the liver, heart, or kidneys • Serious diseases; those affecting the liver, heart, or kidneys • Low levels-deficiencies of contrainsular hormones such as cortisol, growth hormone, glucagon, or epinephrine • Carbohydrate enzyme defects • Autoimmune (insulin antibodies, insulin receptor antibodies) • Factitious hypoglycemia • Toxic substances; for example, ake fruit causing toxic hypoglycemic syndrome
Reactive hypoglycemia	• Presence of pre-diabetes or risk of diabetes; increased endogenous insulin after meals due to insulin resistance – hyperinsulinemia • Food passes very quickly into the small intestine after stomach surgery. • Rarely, hypoglycemia due to inherited metabolic diseases
* Adapted from reference no 9	

with both postabsorptive and postprandial hypoglycemia. Factitious hypoglycemia may present with symptoms that occur irregularly, independent of food intake. A more useful approach for clinicians is a classification based on clinical features (Table 6). People who appear healthy are likely to have different hypoglycemic disorders than those who are ill.[9]

DIAGNOSTIC APPROACH TO NON-DIABETIC HYPOGLYCEMIA

The diagnostic approach should be started by confirming Whipple's tirade.[11] In patients with Whipple's tirade, non-pancreatic causes should be excluded. Renal, hepatic, and cardiac failure, cortisol and growth hormone deficiency, alcohol intake, drug use, recent surgery, especially bariatric surgery, and psychiatric history should be obtained in detail. It should be borne in mind that the incidence of factitious hypoglycemia is high among healthcare workers.

Blood tests should be evaluated during symptomatic episodes. If hypoglycemia is detected during the symptom, blood samples are taken for tests, and glucose, insulin, c-peptide, proinsulin, and beta-hydroxybutyrate values are examined.[11] Blood tests largely distinguish hypoglycemia caused by endogenous (or exogenous) insulin from hypoglycemia caused by other mechanisms.[10]

In patients who define the Whipple triad but in whom a spontaneous hypoglycemia episode cannot be observed, interventions aimed at triggering hypoglycemia may be performed. The most important tests that can be performed for this purpose are the 72-hour prolonged fasting test and the mixed meal tolerance test.[10] The oral glucose tolerance test (OGTT) is not recommended as a trigger test in the diagnosis of non-diabetic hypoglycemia.[12] There are opinions that limiting the prolonged fasting test to 48 hours is also sufficient to reach the diagnosis.[13] A prolonged fasting test is recommended to determine fasting hypoglycemia, and a mixed meal tolerance test is recommended to confirm postprandial hypoglycemia. Since prolonged fasting test may require fasting for up to 72 hours, this test should be performed in a hospital setting to reduce the risk of hypoglycemia development.[10]

Table 6. Classification of hypoglycemia in adults based on clinical features

Healthy Appearing Individuals	Sick Appearing Individuals
•Medicines	•Medicines
• Insulin or insulin secretagogues	• Insulin or insulin secretagogues
• Alcohol	• Alcohol
• Other drugs	• Other drugs
• Accidental, latent or malicious hypoglycemia	• Critical illnesses
• Endogenous hyperinsulinism	• Hepatic, renal or cardiac failure
- Insulinoma	• Sepsis
-Functional beta cell disorders (Nesidioblastosis)	• Malnutrition
-Non-insulinoma pancreatogenous hypoglycemia	- Anti-insulin antibody
- Post-gastric bypass hypoglycemia	- Anti-insulin receptor antibody
• Insulin autoimmune hypoglycemia	• Hormone deficiency
- Anti-insulin antibody	• Cortisol
- Anti-insulin receptor antibody	• Glucagon and adrenaline
• Idiopathic postprandial hypoglycemia	• Non-islet cell tumor
• Physiological	
- Pregnancy	
- Exercise	

*Adapted from reference no 10

With symptomatic hypoglycemia, blood tests should be measured simultaneously, and a screening for oral hypoglycemic agents (sulfonylureas and meglitinides) should be performed if possible. The glucose response can then be monitored every 10 minutes for 30 minutes with 1 mg intravenous (IV) glucagon stimulation, which strengthens the diagnosis.[2] If the blood glucose level increases more than 25 mg/dl at the end of 30 minutes, these patients have sufficient glycogen storage, and the result is in favor of insulinoma. The absence of an elevation in glucose level indicates that hypoglycemia is due to poor hepatic glycogen reserve/liver failure.[11,14] These tests differentiate hypoglycemia due to hyperinsulinism (endogenous and exogenous) from other causes.[2] Insulin has an anti-ketogenic effect, and plasma beta-hydroxybutyrate levels in insulinomas remain below 2.7 mmol/L during prolonged fasting.[8] In addition, urea and electrolytes, liver function tests, and early morning cortisol; if uncertain, then a short ACTH stimulation test may be performed, and IGF-1 levels, IGF-2 levels if there is a history of weight loss and malignancy, insulin-insulin receptor antibodies may be ordered for differential diagnosis if insulin levels are elevated and partially suppressed c-peptide is present.[8]

The main pathophysiologic feature of endogenous hyperinsulinism is inappropriately high insulin secretion when plasma glucose concentration drops to hypoglycemic levels. In the presence of hypoglycemia-related symptoms, signs, or both, endogenous hyperinsulinism is documented if plasma concentrations of glucose are less than 55 mg/dl (3 mmol/L), insulin is at least 3 mU/L (18 pmol/L), C-peptide is at least 0.6 µg/L (0.2 nmol/L), and proinsulin is at least 5.0 pmol/L.[10] Table 7 shows the differential diagnosis of symptomatic hypoglycemia in prolonged fasting, and Figure 2 shows the diagnostic algorithm for spontaneous hypoglycemia.

48-72 Hour Fasting Test (Prolonged Fasting Test)

The patient must be hospitalized for the test. The patient can consume calorie-free, caffeine-free beverages and should continue normal activity during the test. Unnecessary medications should be discontinued.[11,15] Fingertip capillary blood glucose measurement is performed until the blood glucose value reaches 60 mg/dl; close symptomatic follow-up of the patient is necessary.[11,15] Plasma insulin, c-peptide, proinsulin, and beta-hydroxybutyrate samples should only be sent for analysis in samples with plasma glucose concentrations of less than 60 mg/dl. Fasting is terminated when the plasma glucose concentration falls below 45 mg/dl and the patient has symptoms and/or signs of hypoglycemia (or 72 hours without symptoms). Alternatively, if the Whipple triad has been previously documented with certainty, fasting may be terminated when the plasma glucose concentration is below 55 mg/dl without symptoms or signs.[11] If hypoglycemia

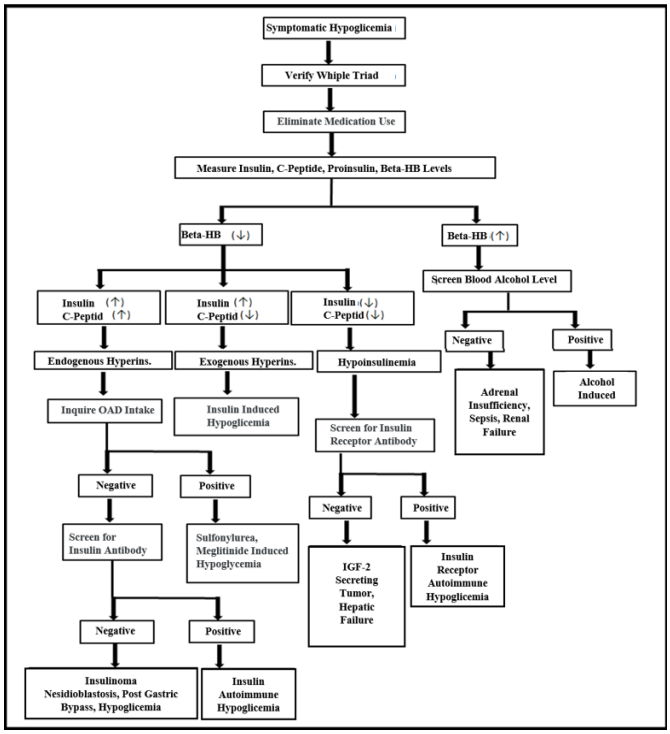

Figure 2. Diagnostic algorithm for spontaneous hypoglycemia
*Beta-HB: Beta-Hydroxybutyrate, *Adapted from reference no. 11

Table 7. Differential diagnosis of fasting hypoglycemia (glucose <55 mg/dl)

Insulin (mU/L)	C-peptide (µg/L)	Proinsulin (pmol/L)	Sulfonylurea	Antibody	Beta-HB (mmol/L)	Glucose response to glucagon (mg/dl)	Diagnosis
↑ ≥3	→ <0.6	→ <5	-	-	→ <2.7	↑ >25	Exogenous insulin intake
↑ ≥3	↑ ≥0.6	↑ ≥5	-	-	→ <2.7	↑ >25	Insulinoma, NIPHS, PGBH
↑ ≥3	↑ ≥0.6	↑ ≥5	+	-	→ <2.7	↑ >25	Sulfonylurea purchase
↑ ≥3	↑ ≥0.6	↑ ≥5	+	+ (Insulin)	→ <2.7	↑ >25	Insulin autoimmune syndrome
→ <3	→ <0.6	→ <5	-	+ (Insulin receptor)	→ <2.7	↑ >25	Insulin receptor autoimmune syndrome
→ <3	→ <0.6	→ <5	-	-	→ <2.7	↑ >25	IGF-2 secreting tumor

* NIPHS: Non-insulinoma pancreatogenous hypoglycemia syndrome, PGBH: Post-gastric bypass hypoglycemia

occurs at the end of the test, 1 mg of IV glucagon is given, and the response in glucose levels is observed. Insulin antibodies can also be measured, but they do not necessarily need to be measured during hypoglycemia.[11]

Mixed Meal Tolerance Test (MMTT)

In postprandial hypoglycemia, a mixed meal tolerance test is an appropriate option. Non-essential medications should be discontinued. After an overnight fast, patients are given a non-liquid meal that typically triggers symptoms of hypoglycemia, called a "mixed meal". A meal determined according to the total caloric need of the patient and corresponding to 25-30% of the daily caloric intake; 50% of the calories are carbohydrates, 33% fat, and 17% protein, and the person is asked to eat the meal in 10 minutes.[16] It is more rational to use a mixed meal that the patient reports cause symptoms.[15] Blood sample is collected for plasma glucose, insulin, c-peptide, and proinsulin before and at 15, 30, 60, 90, and 120 minutes, and at 3, 4, and finally 5 hours after eating.[17] The patient is observed for the development of symptoms. The samples mentioned above are sent for analysis only if glucose is <60 mg/dl.[11,15] If hypoglycemia develops at the end of the test, 1 mg of IV glucagon is given, and the response in blood glucose can be monitored as recommended in the 72-hour fasting test.[11]

Imaging

When insulinoma is suspected, imaging procedures are meaningful only after biochemical confirmation of hyperinsulinemic hypoglycemia. Contrast-enhanced abdominal computed tomography (CT) and abdominal magnetic resonance imaging (MRI) with pancreatic protocols are appropriate imaging options.[11] However, it is not possible to localize almost 30% of neuroendocrine tumors with conventional imaging modalities such as ultrasound, CT, and MRI. Endoscopic ultrasonography is a more sensitive and successful method of detecting the insulinoma focus.[18] The combination of nuclear imaging methods and positron emission tomography (PET)/CT is also a sensitive method for the identification of most insulinomas. 68Ga-DOTA-TATE-PET/CT can be considered an adjunctive imaging study when all imaging procedures are negative and a minimally invasive surgical approach is planned.[19] If clinical symptoms and findings are clearly suggestive of an insulinoma, intraoperative Doppler ultrasonography at the time of resection seems to be the simplest but most sensitive diagnostic method to localize the mass.[20] In selected cases, selective arterial calcium stimulation (SACST) and hepatic venous sampling are effective and safe minimally invasive methods for insulinoma localization and can be used when noninvasive techniques fail.[21]

NON-DIABETIC HYPOGLYCEMIA IN APPARENTLY HEALTHY INDIVIDUALS

Hypoglycemia is a rare metabolic emergency in non-diabetic individuals. Its incidence rate in individuals admitted to hospitals was found to be 0.26% in one study.[22] The rates of plasma glucose levels below 50 mg/dl and 40 mg/dl were found to be 13 and 8 per 10,000, respectively.[23] While hospital admission was to the emergency department with a rate of more than 90%, the cases with plasma glucose levels below 50 mg/dl were listed as follows from most to least frequent: renal disease 32%, sepsis 30%, alcohol 21%, pneumonia 16%, liver disease 16%, congestive heart failure 16%, factitious hypoglycemia 11%, and cancer 5%. In another prevalence study, adrenal insufficiency (34%) and prediabetes (24%) were found to be the most common causes of non-diabetic hypoglycemia in patients followed up in endocrinology clinics. Factitious hypoglycemia was 16%, iatrogenic hypoglycemia 10%, insulinoma 6%, alcohol 2%, and criminal hypoglycemia 1%.[24]

Insulinoma

Insulinoma is a rare neuroendocrine tumor that leads to excessive insulin release and consequently causes symptoms of hypoglycemia in patients, with an annual incidence of 4 per 1 million people. However, it is the most common neuroendocrine tumor of the pancreas. Most occur sporadically, but they may also be associated with multiple endocrine neoplasia type-1 (MEN-1) syndrome. Sporadic insulinomas are typically smaller than 2 cm (90% of cases), solitary (90% of cases), and benign (90% of cases).[25] The most common cause of hyperinsulinemic hypoglycemia in adults is insulinoma. Neuroglycopenic attacks during food deprivation are a typical clinical feature of patients with insulinoma.[26]

Insulinomas are characterized by episodes of hypoglycemia that are normally associated with fasting but may also occur postprandially. If suspected, early referral to a specialized center for testing and confirmatory diagnosis is appropriate because the cure rate with surgical treatment is quite high in the majority of cases.[27]

Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome (NIPHS) - Nesidioblastosis -

Non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is a rare syndrome characterized by pancreatic beta cell hypertrophy leading to endogenous hyperinsulinism and bouts of neuroglycopenia resulting from increased beta cell function.[11] It manifests itself with increased autonomic insulin secretion and a consequent decrease in blood glucose. It is observed in approximately 0.5% to 7% of patients with hyperinsulinemic hypoglycemia.[28] In adults, nesidioblastosis is extremely rare and is mostly diagnosed in adolescence and middle age.[26] NIPHS in adults was formerly referred to as "nesidioblastosis" and was characterized by an increase in the number and volume of beta cells, as in childhood.[29] However, the incidence of NIPHS has started to increase relatively, especially with the increase in bariatric surgical procedures, and has taken its place among the chronic complications of gastric bypass surgery.[28] The clinical features of adult-onset nesidioblastosis can be predominantly determined by postprandial hyperinsulinemic hypoglycemia, a negative 72-hour fasting test, negative preoperative localization studies for insulinoma, and a positive SACST.[26]

Post-Gastric Bypass Hypoglycemia (PGBH)

The incidence of obesity is increasing day by day, and bariatric surgery is becoming an important treatment option for individuals with obesity. Hypoglycemia after bariatric surgery is one of the possible complications of treatment. This condition may present with symptoms and signs ranging from mild hypoglycemic symptoms and signs to neuroglycopenia. The incidence is higher pos-gastric bypass compared to other procedures.

Postprandial hyperinsulinemic hypoglycemia after bariatric surgery is a rarely reported metabolic complication of bariatric surgery and is most commonly associated with Roux-en-Y gastric bypass (RYGB). A consensus has begun to emerge that the main cause is changes in glucose kinetics and changes in gastrointestinal and pancreatic hormone levels involved in glucose homeostasis due to anatomical changes after bariatric surgery.[30] After RYGB, functional increases in insulin secretion occur as a result of increased glucose sensitivity of the beta cell and increased fasting and postprandial secretion of incretin hormones, especially GLP-1.[31]

Postprandial hyperinsulinemic hypoglycemia seen after RYGB surgery has historically been referred to as "late dumping syndrome". This is distinct from the so-called "early dumping syndrome", which is common after RYGB and usually occurs within minutes to 1 hour after ingestion of high-calorie-dense foods (especially refined sugars and fats).[30] Early dumping, a consequence of rapid emptying of food into the jejunum due to surgically altered anatomy, is characterized by vasomotor symptoms (flushing, tachycardia), abdominal pain, and diarrhea. Late dumping is a form of "reactive hypoglycemia". It occurs 1-3 hours after a meal and is the result of an intense insulin response to hyperglycemia caused by the rapid absorption of simple sugars from the proximal small intestine.[32]

However, animal studies have shown an increase in first-phase insulin secretion, pancreatic hyperplasia, improvement in islet cell structure, a marked increase in beta cell mass, a slight increase in the ratio of beta cell area to total pancreatic area, and an increase in the number of small islet cells closely associated with exocrine ducts post-gastric bypass surgery.[33] However, Meier et al.[34] compared the cellular changes in individuals with PGBH after partial pancreatectomy with the pancreas of obese and lean individuals in an autopsy study and sought an answer to the questions of whether beta cell area and beta cell formation increased and beta cell apoptosis decreased in patients with hypoglycemia after PGBH. At the end of the study, it was observed that beta cell area did not increase in individuals with PGBH compared with obese and even lean control subjects. Consistent with this finding, it was found that there was no increase in beta cell formation (islet neogenesis and beta cell replication) or a decrease in beta cell loss in individuals with PGBH.[34] As a result, the view that beta cell hyperplasia seen in individuals with PGBH is actually a relative concept and is due to beta cell hyperplasia that has already developed over the years to compensate for hyperinsulinemia while obesity develops in individuals has prevailed. This view is supported by the finding that hypoglycemia is not completely resolved in individuals with PGBH, even if beta cell mass is reduced by partial pancreatectomy.[35]

Typically, presentation with post bariatric hypoglycemia first occurs 1 year or more postoperatively, with symptoms usually occurring 1 to 3 hours after a meal. Symptomatic hypoglycemia occurring very early in the postoperative period (<6 to 12 months), in a fasting state, or 4 hours after caloric intake is not typical, and other causes of hypoglycemia should be considered in the presence of these conditions.[35] It should be kept in mind that rare cases of NIPHS and insulinoma may also be seen post-gastric bypass.[36,37]

Dumping Syndrome

Dumping syndrome includes gastrointestinal and vasomotor symptoms that occur after eating a meal. Early dumping syndrome occurs 15 minutes to 1 hour after ingestion of food. The symptoms that follow are mainly related to the gastrointestinal tract and are caused by osmotically driven fluid shifts from the blood into the lumen. Symptoms of late dumping syndrome occur 1 to 3 hours after a meal and include mainly vasomotor symptoms. They are caused by reactive hypoglycemia caused by an increase in insulin secretion that overcompensates for the glucose load delivered to the portal circulation. A number of peptides and vasoactive substances contribute to the pathogenesis of both types of dumping: neurotensin, vasoactive intestinal peptides, catecholamines, serotonin, and substance P.[38]

Both dumping syndromes can be seen after bariatric surgical procedures, and the prevalence is close to 10%. It can occur after both sleeve gastrectomy and gastric bypass surgeries, but is significantly more common post-gastric bypass.[38] Early dumping syndrome may also occur after total or partial gastrectomy, total or partial esophagectomy, fundoplication, gastroesophageal reflux or hiatal hernia operation, vagotomy operation for gastric ulcer treatment, or pyloroplasty operation for pyloric stenosis treatment. In addition, signs and symptoms such as postprandial reactive

hypoglycemia, early satiety, and diarrhea may be observed in patients with normal gastric anatomy due to primary accelerated gastric emptying and have been defined as Middleton syndrome.[39]

In Dumping syndrome, symptoms usually improve with regulation of nutrition. There are publications indicating that alpha-glucosidase inhibitors may also be beneficial.

Autoimmune Hypoglycemia

Autoantibodies against insulin cause hyperinsulinism and ultimately hypoglycemia through the inappropriate dissociation of insulin-antibody complexes. Conversely, autoantibodies directed against the insulin receptor cause hypoinsulinemic hypoglycemia by direct stimulation of insulin receptors. Postprandial hypoglycemia is usually observed.[11]

Insulin Autoimmune Syndrome

Insulin autoimmune syndrome (IAS) is a condition to be kept in mind in patients with very high insulin levels and no evidence of insulinoma. It is characterized by spontaneous hypoglycemia, elevated insulin levels, and increased circulating insulin antibodies, and the imaging modalities used to diagnose insulinoma are completely normal. Compared to insulinoma cases, very high insulin levels are observed and are mostly above 1000 mlU/ml.[40] It is a form of immune-mediated hypoglycemia that develops in the presence of a predisposing genetic predisposition, especially with the effect of a triggering factor such as a drug or viral infection. It is thought that there is a strong association, especially with drugs containing the sulfhydryl group, and methimazole stands out in terms of causing IAS among drugs containing this group.[41] Drugs that may lead to IAS are listed in Table 8. There are also publications showing an association of IAS with some autoimmune diseases and plasma cell dyscrasias.[40]

In approximately 80% of patients with IAS, hypoglycemia resolves spontaneously after less than 3 months without any special treatment other than prevention of drug exposure, but persistent hypoglycemia may also be observed in some patients. In drug-induced cases, treatment consists of discontinuation of the responsible drug, small and frequent feedings six or more times a day, and a low-carbohydrate diet. For hypoglycemia, alpha-glucosidase inhibitors (acarbose, miglitol) may help by reducing glucose uptake in the intestines and preventing postprandial excess insulin secretion by beta cells. If hypoglycemia persists, high-dose steroid therapy (prednisolone 30-60 mg/day), immunosuppressive therapy (azathioprine or 6-mercaptopurine), or plasmapheresis may be considered. In addition, rituximab, an anti-CD20 monoclonal antibody, suppresses insulin autoantibodies by blocking de novo antibody responses and can be used in treatment.[41,42] Somatostatin analogs, diazoxide, and even pancreatectomy have been proposed as strategies to reduce insulin release with variable results.[41]

Insulin Receptor Autoimmune Syndrome

Autoantibodies to the insulin receptor are rare and typically cause severe insulin resistance and hyperglycemia, a condition referred to as type B insulin resistance. Rarely, antibodies against the insulin receptor can also cause hypoglycemia.[43-45]

However, in one quarter of patients with type B insulin resistance, autoimmune-mediated hypoglycemia may develop during the clinical course. In some patients with autoantibodies to the insulin receptor, pure hypoglycemia may occur without any evidence of insulin resistance or hyperglycemia. In such cases, the mechanism of hypoglycemia is insulin receptor agonism.[43] The association with systemic autoimmune diseases, especially systemic lupus erythematosus, is very high and is more common in women.[43,44] Mixed connective tissue disease is another common autoimmune association. The presence of antibodies directed against the insulin receptor has also been shown very rarely in malignant cases such as multiple myeloma and Hodgkin lymphoma.[40] Hypoglycemia cases with only insulin receptor autoantibody positivity in the absence of another disease may also be observed.[45]

In the presence of marked hypoglycemia, low insulin and c-peptide levels and concomitant IGF-2 levels within normal limits or low are decisive in the diagnosis. Attacks may be observed as both fasting hypoglycemia and postprandial hypoglycemia.[43,45] Glucorticoids and rituximab are among the recommended treatments. Plasmapheresis also has a role in treatment success. Treatment with immunosuppressive agents, such as azathioprine and cyclophosphamide, may also be used. In most cases, various combinations of these treatment modalities are the most commonly used treatment modalities.[43-45]

Table 8. Drugs that can cause insulin autoimmune syndrome

-	Methimazole
-	Carbimazole
-	Alpha lipoic acid
-	Pyritinol
-	Glutathione
-	Methionine
-	Captopril
-	Hydralazine
-	Procainamide
-	Diltiazem
-	Clopidogrel
-	D-penicillamine
-	Penicillin G
-	Imipenem
-	Isoniazid
-	Hydralazine
-	Alpha-mercaptopropionyl glycine
-	Pantoprazole
-	Omeprazole
-	Tolbutamide
-	Gliclazide
-	Steroids
-	Diclofenac
-	Loxoprofen-sodium
-	Tolperisone hydrochloride
-	Albumin

Factitious Hypoglycemia

Factitious hypoglycemia results from inappropriate use of hypoglycemic agents, such as insulin or oral insulin secretagogues; it may be accidental, covert, or malicious. It is more common in healthcare workers, relatives of those receiving diabetes treatment in the family, or those with a history of psychiatric comorbidity.[11] In covert drug intake, individuals aim to obtain "patient" status. For this purpose, they may accept invasive procedures, including laparotomies and sometimes even resections of the pancreas.[46] Evaluation of plasma levels of sulfonylureas should be performed in every case of hyperinsulinemic hypoglycemia, especially if the patient is likely to have access to the drug at work or in the family.[47] Accidental hypoglycemia, on the other hand, occurs when there are medical treatment errors or medication errors, especially pharmacy errors, for example, incorrectly administering a sulfonylurea for another drug.

In general, individuals with factious disorders tell their story in a dramatic way but are quite vague and inconsistent when asked to provide more details.[48] Factitious hypoglycemia resulting from the surreptitious self-administration of insulin or a hypoglycemic agent is usually manifested by irregularly occurring neuroglycopenic symptoms. A stepwise approach and psychiatric evaluation are necessary to provide appropriate guidance and supportive follow-up.[23]

Hypoglycemia of Non-islet Cell Tumors

Hypoglycemia due to non-pancreatic tumors is rarely seen. These tumors, also called non-islet cell tumors, are often caused by an increase in IGF-2, a peptide that activates the insulin receptor.[49] Ectopic insulin secretion has been reported in a few cases, but most have not been convincingly proven.[50] Nevertheless, extrapancreatic insulin-secreting neuroendocrine tumors with hyperinsulinemic hypoglycemia have been reported very rarely.[51]

Non-islet cell tumor hypoglycemia (NICTH) is most commonly seen in tumors of mesenchymal or hepatic origin, but a wide variety of tumor types can cause large IGF-2 production.[50,52] It can be seen especially frequently in solitary fibrous tumors.[53] Fibrosarcoma, leiomyosarcoma, hemangiopericytoma, and mesothelioma are the most common tumors in which NICTH is found.[50,52] Other reported tumors include adenocarcinomas such as large-cell lung adenocarcinomas, ovarian adenocarcinomas, gastrointestinal stromal tumors, and renal cell carcinoma. In tumors with abnormal IGF-2 gene transcription and gene expression, the precursor of IGF-2, 'big' IGF-2, is hypersecreted with incomplete translation. High circulating IGF-2 activates the insulin receptor and causes hypoglycemia.[49]

The clinical features of NICTH result from recurrent episodes of fasting hypoglycemia and tumor growth and spread. The diagnosis of NICTH includes low glucose levels (serum glucose <55 mg/dl) with concurrent low insulin/proinsulin/c-peptide/β-hydroxybutyrate levels and the absence of positive results in screening for oral hypoglycemic agents.[51] Even when IGF-2 levels are normal, IGF-I levels are suppressed, and therefore the IGF-2:IGF-1 ratio increases above the normal molar ratio of 3:1 and frequently approaches or exceeds 10:1.50 Especially in benign solitary fibrous tumors, response to treatment is good, and hypoglycemic attacks end after complete resection.[53]

TOXIC HYPOGLYCEMIA

Alcohol-Induced Hypoglycemia

Alcohol is an important cause of fasting hypoglycemia. It is a rare phenomenon in normal, healthy individuals. It is more common in malnourished individuals, binge drinkers, accidental children, diabetics using insulin or oral drugs, Addison's disease, pituitary insufficiency, and hyperthyroidism. Alcohol may especially exacerbate insulin and sulfonylurea-induced hypoglycemia.[54]

The liver is the key to glucose homeostasis. Numerous drugs, including alcohol, can alter intrahepatic pathways vital for normal glucose production by the liver, resulting in hypoglycemia.[55] Hepatic autoregulation and neurohumoral mechanisms play a role as glucose counterregulatory mechanisms to prevent hypoglycemia and during hypoglycemia. Hepatic autoregulation primarily involves glycogenolysis and gluconeogenesis. One of the main factors contributing to the development of hypoglycemia with alcohol consumption is the inhibitory effect of alcohol on gluconeogenesis. This effect depends on the amount of alcohol consumed and the underlying nutritional status of the individual. In a healthy person with normal glycogen reserves, alcohol has rarely been shown to cause hypoglycemia within 8-12 hours (overnight fasting). However, acute alcohol intake after fasting for 3 to 4 days can cause severe and prolonged hypoglycemia in healthy individuals. Individuals with diabetes, impaired liver function, and malnutrition are at higher risk.[54]

Toxic Hypoglycemic Syndrome

Toxic hypoglycemic syndrome is a condition that is more common in tropical regions, occurs especially as a result of ingestion of unripe ake fruit, and may have a mortal course.[56] In this toxic condition, known as "Jamaican vomiting disease", clinical symptoms may include excessive vomiting, altered mental status, and hypoglycemia. Severe cases have been reported to cause seizures, hypothermia, coma, and death.[57]

Hypoglycin A protein found in unripe fruit inhibits gluconeogenesis, causing depletion of glycogen storage and leading to hypoglycemia. Medical treatment is primarily supportive treatment with intravenous fluids and dextrose.[56] Figure 3 shows unripe and ripe ake fruit.

Figure 3. Immature and ripe ake fruit

Postprandial Reactive Hypoglycemia

Postprandial hypoglycemia describes the timing of hypoglycemia (within four hours after meals) and is not a diagnosis in itself.[12] Postprandial hypoglycemia that occurs after food intake is called reactive hypoglycemia.[58] Many conditions may be associated with postprandial hypoglycemia.[12,39]

The term postprandial syndrome is used to describe a disorder observed in individuals with satiety symptoms suggestive of hypoglycemia but without concomitant biochemical evidence of hypoglycemia, usually seen after ingestion of a high-carbohydrate meal, and in whom symptoms disappear after dietary change.[12]

Reactive hypoglycemia is a phenomenon that may be affected by exaggerated insulin release and insulin resistance. The presence or absence of insulin effects in the development of reactive hypoglycemia is related to the duration and

mechanism of hypoglycemia. It is simply divided into late and early reactive hypoglycemia.

Late reactive hypoglycemia usually occurs as part of the insulin resistance syndrome and may be caused by delayed insulin secretion and thus delayed activation of GLUT-4. Inhibition of first-phase insulin secretion may result in late reactive hypoglycemia due to an exaggerated relative increase in second-phase insulin secretion.[58]

Early reactive hypoglycemia occurs in the first 1-2 hours of glucose loading. It may result from accelerated gastric emptying or an exaggerated incretin effect. It is also possible that accelerated gastric emptying leads to an increase in incretin.[39] This is partly mediated by the gut hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and contributes to early hypoglycemia by causing excessive insulin exocytosis and, in addition, an inadequate response to hypoglycemia by suppressing GLP-1 glucagon.[39,58]

The basis of treatment in individuals with reactive hypoglycemia is a reduced glycemic load and a low glycemic index diet. Low-glycemic-index diets provide significantly lower plasma glucose, serum insulin, and plasma GLP-1 levels during the postprandial period. In such individuals with postprandial autonomic symptoms, avoiding foods high in glucose, consuming foods high in fiber, frequent (every three hours) small meals or snacks, and a regular exercise regimen may significantly contribute significantly to symptom relief. If dietary modification is not successful in reducing symptoms, trying alpha-glucosidase inhibitors to delay carbohydrate absorption and thus reduce the insulin response to a meal may be helpful for some individuals.[12]

TREATMENT

There is a relative increase in the mortality rate among individuals with non-diabetic hypoglycemia. More commonly, an increase in the rate of traffic accidents due to cognitive dysfunction and fatal arrhythmias, such as prolonged QT, may be observed and affect morbidity.[22] Therefore, it is important to raise blood glucose rapidly in cases of hypoglycemia. Emergency treatment of hypoglycemia should be performed with carbohydrate intake if possible or with parenteral glucose if not possible.[15]

Acute Treatment of Hypoglycemia

Treatment depends on the severity of symptoms and the patient's ability to tolerate oral intake. Glucose can be given orally to a patient with conscious neuroglycopenic symptoms. 10-20 grams of glucose are given, and symptoms are monitored. Sugar cubes, glucose tablets, and fruit juices such as orange juice are suitable options. One cube of sugar contains 2.5 grams of glucose, and 4-8 cubes of sugar are consumed quickly. Fast-acting glucose tablets contain 4-5 grams of glucose, and 3-5 are consumed. One glass of orange juice is 200 cc and contains 29 grams of glucose. After 15 minutes, the blood glucose measurement is repeated, and if it is below 70 mg/dl, the treatment is repeated. If there is brain fog or loss of consciousness, IV dextrose treatment should be administered. 50 cc (1 ampoule) IV of 50% dextrose, followed by 10% dextrose infusion at a rate of 100 cc/hour to prevent recurrent episodes of hypoglycemia, is the appropriate treatment option. 1 mg IV, intramuscular or subcutaneous glucagon, or a single dose of 3 mg intranasal glucagon are also among the recommended treatments.[11] After hypoglycemia and state of consciousness improve after both oral and parenteral treatment, the patient is given slowly absorbed carbohydrates orally to prevent a recurrence of hypoglycemia.

Patients with severe, prolonged hypoglycemia may develop hypoglycemic coma due to cerebral edema. This is defined as a decreased level of consciousness that persists for >30 minutes despite correction of hypoglycemia. In the presence of such a condition, 40 g IV mannitol in 20% solution, glucocorticoids (e.g., 10 mg IV dexamethasone), or both are administered over 20 minutes.[11] Figure 4 shows the acute treatment of hypoglycemia.

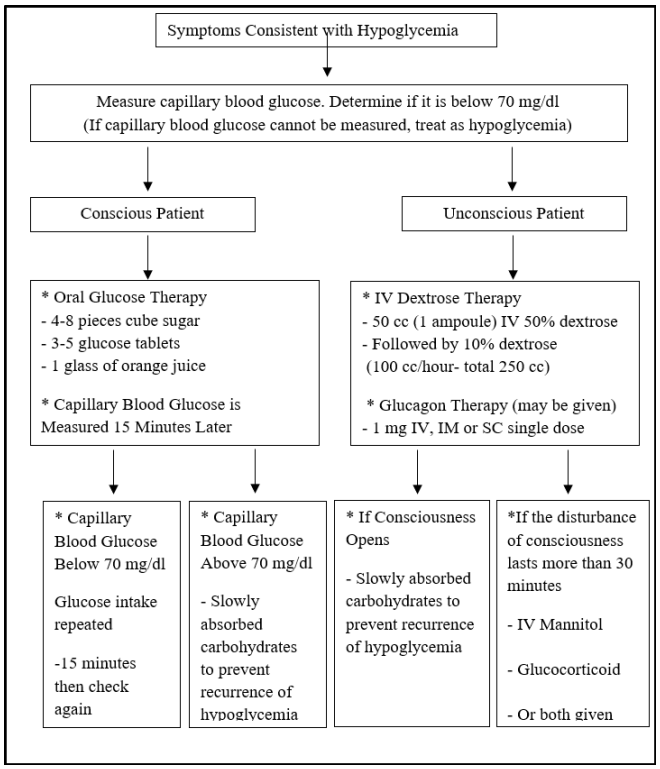

Figure 4. Approach to acute treatment of hypoglycemia

Long-Term Management of Hypoglycemia

The underlying cause should be considered, and the long-term management of hypoglycemia should be tailored accordingly. The management of hypoglycemia should take into account patient well-being and patient preferences and tailor treatment to the specific hypoglycemic disorder. Most hypoglycemic disorders require specialized treatment, such as surgical excision to treat solitary insulinomas. However, in cases such as postprandial reactive hypoglycemia or post-gastric bypass hypoglycemia, appropriate nutritional therapy advice can help manage daily work and activities.[10]

Regulating Diet for Therapeutic Purposes

Dietary interventions may be helpful in non-insulinoma pancreatogenous hypoglycemia, including in patients with Roux-en-Y gastric bypass hypoglycemia. Frequent feeding and a low-carbohydrate diet are common recommendations. In Roux-en-Y gastric bypass hypoglycemia, restricting carbohydrates, avoiding foods with a high glycemic index and simple sugars, and adding protein and fat to every meal are recommended. Gastrostomy tube feeding may be considered in patients with hypoglycemia after the Roux-en-Y gastric

bypass who are resistant to dietary changes.[2]

Medical Treatment

If resection is not possible or as a temporary measure in individuals with hyperinsulinism, medical treatment with alpha-glucosidase inhibitors, calcium channel blockers, diazoxide, or somatostatin analogs may be used.

Alpha-glucosidase inhibitors delay the digestion of ingested carbohydrates, resulting in lower blood glucose concentrations after meals. Acarbose can be used to reduce hyperinsulinism and hypoglycemia after the Roux-en-Y gastric bypass. Calcium channel blockers may help treat hypoglycemia by inhibiting glucose-stimulated insulin secretion from pancreatic beta cells; Verapamil 80 mg twice daily has been reported in the literature, but other agents such as diltiazem and nifedipine have also been used. Diazoxide inhibits insulin secretion by opening ATP-dependent potassium channels in the pancreatic beta cell. Diazoxide is given orally at 3-8 mg/kg/day every 8-12 hours up to 1200 mg/day. Somatostatin analogs (octreotide and lanreotide) inhibit insulin secretion when given in high doses, but may not be as effective as diazoxide. Octreotide is given as a subcutaneous injection, ranging from 100 micrograms twice daily to 1500 micrograms daily, while the longer-acting lanreotide is given monthly. Chemotherapy can be used to treat insulinomas and non-islet cell tumors when necessary. Radiotherapy may also be performed in non-islet cell tumors.[2] Especially in the presence of malignant insulinomas, treatments such as chemoembolization, radiofrequency ablation, radical mass reduction (debulking) surgery, verapamil treatment, octreotide treatment, and chemotherapy can be applied.[59]

CONCLUSION

Non-diabetic hypoglycemia is an important condition that may develop due to a variety of different etiologic factors and should be treated rapidly due to its noisy clinic. Especially untreated fasting, hypoglycemia may lead to severe neuroglycopenia sequelae and even death. Insulinoma is usually a small, solitary, intrapancreatic, benign tumor. It is usually sporadic. However, it may also be associated with MEN-1. The main treatment for insulinoma is surgery. Reactive hypoglycemia is a milder form of hypoglycemia seen in the postprandial period. Untreated reactive hypoglycemia causes discomfort, but leaves no sequelae. Lifestyle changes are recommended and form the basis of treatment. In hypoglycemic conditions that need to be rapidly detected and treated in endocrine emergencies, it is absolutely necessary to investigate the cause after normoglycemia is achieved with emergency treatment.

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