

NON-DIABETIC HYPOGLYCEMIA

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ABSTRACT

Objective: To review the diagnosis, evaluation, and management of non-diabetic hypoglycemia in adults.

Methods: A literature review using PubMed and Google Scholar was performed. In absence of data, clinical expert opinion was provided. **Results:**

Hypoglycemia in an individual without diabetes is uncommon mainly because of a tightly regulated counterregulatory physiological response. A detailed medical history, review of medications and physical exam findings are critical first steps in providing guidance for further investigation in a non-diabetic person with documented hypoglycemia based on Whipple's triad (presence of symptoms when plasma glucose concentrations are low and absence of symptoms with normalized glycemia). In this review, we highlight strategies to diagnose and treat hypoglycemic disorders in non-diabetic individuals based on underlying mechanisms. **Conclusion:** Evaluation and management of non-diabetic hypoglycemia should be individualized based on clinical presentation and suspected diagnoses.

INTRODUCTION

In healthy humans, glucose concentrations are efficiently maintained within a narrow range by the physiological mechanisms that respond to intermittent exogenous nutrient ingestion by enhancing glucose utilization and respond to intervals of nutrient deprivation by enhancing glucose production.

Deviation of glucose from the normal range in both hyper or hypoglycemia only occurs when physiological mechanisms involved in maintaining the balance between the glucose utilization and the glucose production fail. As such, hypoglycemia is a manifestation of a heterogeneous group of underlying disorders that increase glucose utilization or reduce glucose production or a combination of both.

While hypoglycemia in persons without diabetes is relatively rare (1), the clinical relevance of this condition regarding patient safety, cognitive function, and quality of life is undeniable. Depending on severity and duration, hypoglycemia also can be fatal (2). Furthermore, hypoglycemia blunts defense against subsequent hypoglycemia leading to a vicious cycle of recurrent hypoglycemia (3), which in turn not only exaggerates related morbidities but also makes the diagnosis more complex.

Here, we review the current recommendations regarding diagnosis, pathophysiology, and management of hypoglycemia in non-diabetic individuals. Hypoglycemia in the pediatric population, hypoglycemia caused by anti-diabetic medications, and a comprehensive review of insulinomas can be found in the Endotext chapters entitled "Hypoglycemia in Neonates, Infants, and Children" (4), "Hypoglycemia During Therapy of Diabetes" (5) and "Insulinoma" (6), respectively.

PHYSIOLOGY / PATHOPHYSIOLOGY

Glucose is the main fuel for the brain since it cannot store glycogen or synthesize glucose (7,8). To minimize any disturbance in glucose supplies to the brain and cerebral function, therefore, redundant but very efficient physiological counter-regulatory responses are in place to prevent or correct hypoglycemia (8-10).

Prandial

In the *prandial* condition, the extent of glycemic excursion (difference between glycemic peak and nadir concentrations) is determined by the pace of food transition from the stomach into the gut (gastric emptying) as well as the net hepatic and extrahepatic glucose uptake (11). In healthy subjects, during the first 30-60 min of an oral glucose or mixed tolerance meal test, plasma glucose and insulin concentrations rise, shifting the hepatic net glucose output during fasting condition to net glucose uptake during the prandial state (12). As a result of changes in glucose kinetics in the early absorptive phase of glucose/mixed meal ingestion, plasma glucose concentrations start to decline in the latter absorptive phase falling below premeal levels in parallel with reduction in ingested glucose delivery to the gut. The regulatory mechanisms that are responsible for preventing hypoglycemia and restoring euglycemia during the transition of glucose flux from the ingested glucose delivery to the hepatic glucose production are not fully characterized, but both hormonal and non-hormonal factors play a role (13).

Fasting

In the *fasting or postabsorptive* state (4-6 hours after nutrient ingestion), plasma glucose concentrations range from 80-90 mg/dl and rates of glucose utilization and production are equal (2mg/kg/min) (14). Glucose homeostasis during fasting is tightly regulated by a reciprocal bihormonal response, in which reduction in glucose concentrations below baseline reduces β -cell

insulin secretion and stimulates α -cell glucagon release (15). While the full range of glucoregulatory effects of glucagon in the prandial state is unclear, the main function of glucagon in the fasting state is to counterbalance the action of insulin on hepatic glucose production (15-17). Glucose production is mainly (~80%) attributed to hepatic glycogenolysis with a smaller contribution (~20%) from hepatic gluconeogenesis primarily from amino acids and lactate (11). After an overnight fast, the liver contains ~ 50 g of glycogen storage, which can supply glucose for 24 hours after complete depletion. With prolonged fasting, hyperglucagonemia enhances gluconeogenesis and hypoinsulinemia promotes lipolysis. Lipolysis releases glycerol, a gluconeogenic substrate, and free fatty acids that are converted to ketones, mainly beta hydroxybutyrate (BOHB) and acetoacetate, in the liver to be used as an alternate fuel by the brain.

Using a hyperinsulinemic hypoglycemic clamp in the fasting condition in normal humans, a decrement in plasma glucose concentration from the physiological range, in a hierarchical manner: (1) suppresses endogenous insulin secretion to lower glucose utilization, (2) increases glucagon response to increase glucose production, and (3) enhances epinephrine secretion (more relevant in absence of glucagon secretion) as well as cortisol and growth hormone release (more relevant during prolonged hypoglycemia) (8). Under physiological conditions during the fasting state, this counterregulatory response can reestablish euglycemia and prevent symptoms. A greater decline in plasma glucose concentration, though, would result in a symptomatic autonomic response to warn of low glucose and prompt the person to correct it by eating. However, if the individual did not (or could not) intervene, such as in the presence of overwhelming hyperinsulinemia) or blunted glucose counterregulatory responses, plasma glucose concentrations would drop further and neuroglycopenic symptoms and cognitive dysfunction would occur (Table 1) (18).

Table 1. Symptoms of Hypoglycemia

Autonomic (neurogenic)	Neuroglycopenic
Sweating	Warmth
Anxiety	Behavioral changes
Tremor	Blurred vision
Palpitation	Confusion/difficulty speaking
Hunger	Dizziness/lightheadedness
Tingling	Lethargy and weakness
Ill-defined symptoms	Seizure
	Loss of consciousness/coma

It is unclear whether this hierarchy in hormonal responses or glycemic thresholds described during the fasting state would also apply to the prandial state. Here, we classify the hypoglycemic disorders based on timing from meal ingestion (fasting versus prandial) given the differences in the regulatory factors involved in glucose metabolism between the two conditions.

DIAGNOSIS AND EVALUATION

Diagnosis of hypoglycemia should be made when symptoms accompany low plasma glucose concentrations (chemical hypoglycemia) but symptoms are absent when plasma glucose levels are normalized (Whipple's triad (19)).

Chemical hypoglycemia has been defined based on a glucose threshold that can evoke a counterregulatory response. In the fasting state, a decline in glucose below 55 mg/dl causes neurogenic symptoms while insulin secretion is maximally suppressed (insulin < 3 uU/ml and C-peptide < 0.6 ng/ml) and glucagon response is maximized (9).

Awareness of hypoglycemia alerting individuals to correct hypoglycemia is mainly because of increased autonomic nervous system activity triggered by hypoglycemia. The autonomic (neurogenic) hypoglycemic symptoms can be adrenergic (such as palpitation, tremor, and anxiety) or cholinergic (such as sweating, hunger, and paresthesia) (18). As

glucose concentrations drop below 48-50 mg/dl during the fasting state, the neuroglycopenic symptoms (caused by brain glucose deprivation) manifest; these symptoms range from behavioral changes, fatigue, and confusion to loss of consciousness or seizure (18,20-22).

Diagnosis of hypoglycemia in the prandial state is much more complex since the glycemic threshold to define hypoglycemia in the prandial state has not been well characterized. Using an oral glucose challenge in 650 healthy individuals in a previous study (23), 10% of subjects developed postprandial nadir glucose concentrations below 47 mg/dl without associated symptoms, suggesting that asymptomatic low glucose events are relatively common following an oral glucose load in normal humans. Hence, the mixed meal test (described below) is the preferred provocative test to diagnose prandial hypoglycemia. Furthermore, recurrent postprandial symptoms suggestive of hypoglycemia but not associated with low glucose concentrations have also been observed in normal individuals (24), indicating that other factors beyond hypoglycemia play a role in provoking autonomic symptoms.

Therefore, after obtaining a detailed medical history and physical exam, diagnosis of hypoglycemia should be confirmed by verification of low glucose concentration associated with symptoms or signs that

are relieved by raising glucose values (Whipple's triad).

A careful history of nutritional status, current medication use, and concurrent multisystem illnesses such as liver, heart, kidney failure, or sepsis, as well as a thorough physical exam and laboratory data, can point to existing primary conditions that predispose to hypoglycemia. This is especially crucial in patients who are often too ill to be subjected to extensive evaluation. For healthy subjects who lack any background predisposing illnesses, the details about timing (relationship to food ingestion, physical activities, day versus nocturnal time), severity (frequency, presence of neuroglycopenia, and requiring assistance to treat), and time of onset of hypoglycemic episodes are critical in differential diagnosis. To understand the pattern of hypoglycemic episodes, reviewing the records of symptoms, activity, food intake along with capillary blood or interstitial glucose levels measured by glucometer or continuous glucose monitoring (CGM), respectively, may be helpful. However, the accuracy of glucometer and CGM is low in the hypoglycemic range, and they should not be used for diagnostic purposes. On the other hand, masked (blinded) monitoring by CGM can provide insights into patterns of hypoglycemic episodes and triggering factors during patients' daily routine (25).

The flowchart in Figure 1 demonstrates the suggested approach for evaluation in healthy appearing patients after a careful medical history, physical exam, and

laboratory data excludes an underlying illness that can predispose to hypoglycemia. Disorders that may cause hypoglycemia are listed in Table 2.

To confirm the diagnosis and explore etiology, it is necessary to collect blood samples during hypoglycemia, whether it occurs spontaneously or by provoked testing that can be selected based on clues from the medical history.

In asymptomatic patients with documented chemical hypoglycemia, artifactual hypoglycemia due to conditions such as reticulocytosis (polycythemia, sickle cell anemia), leukocytosis (leukemia), and thrombocytosis that increase in vitro glycolysis in the blood sample while awaiting laboratory analysis should be considered (26). Also, nadir glucose levels in the prandial state can be low without any associated symptoms, particularly in persons with a history of upper gastrointestinal (GI) surgery (25). A potential diagnostic challenge in using clinical criteria remains in patients who are adapted to recurrent hypoglycemia by blunted autonomic response, so called hypoglycemic unawareness (27). It has been well recognized that antecedent insulin-induced hypoglycemia impairs counterregulatory glucose responses and blunts hypoglycemia symptoms (mainly autonomic symptoms) in normal humans (28). Therefore, in patients with a high index of clinical suspicion, monitoring of symptoms and signs of neuroglycopenia, which is less likely to be affected by recurrent hypoglycemia, and reevaluation over time should be considered.

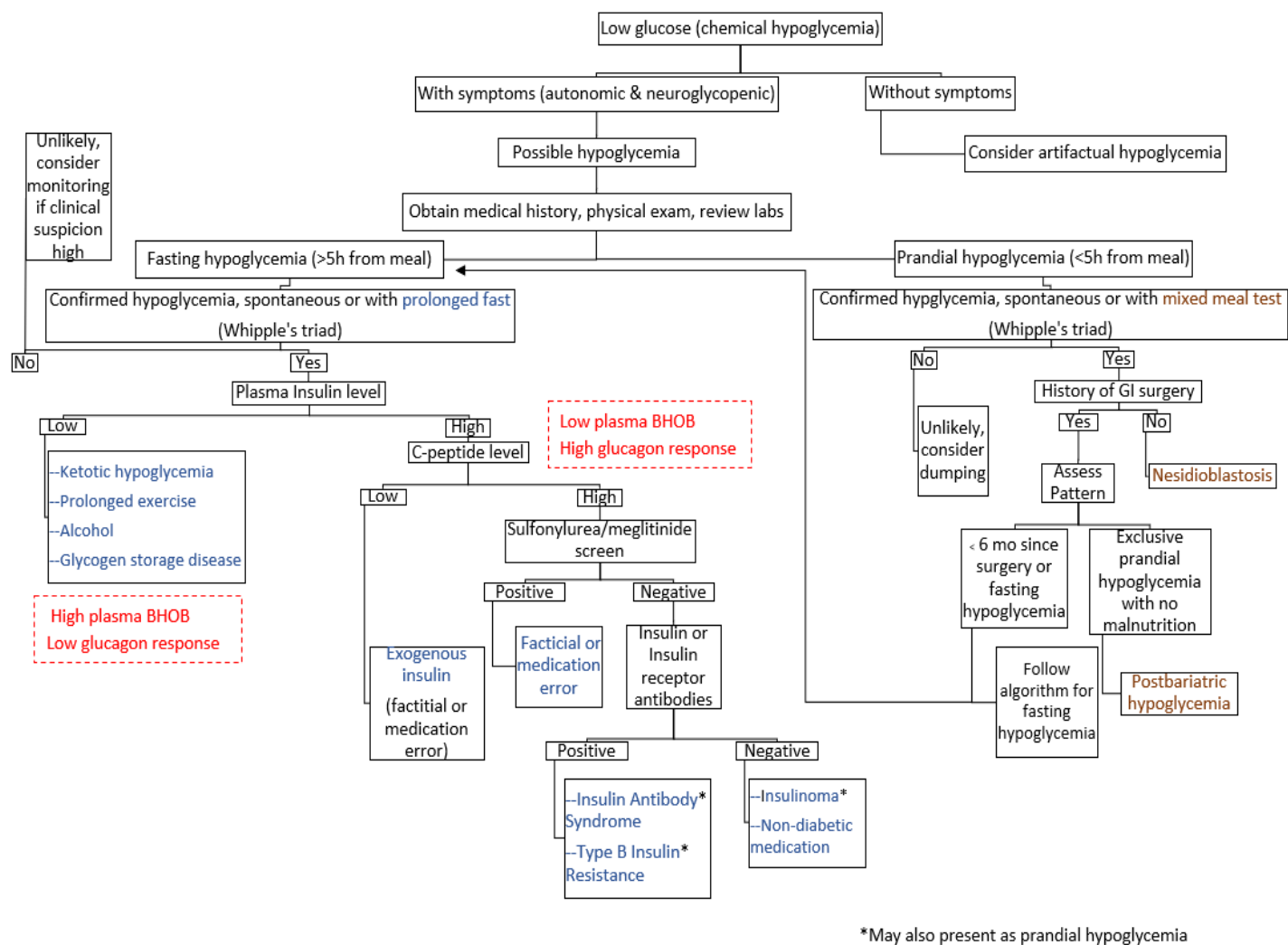


Figure 1. Evaluation of non-diabetic hypoglycemia in healthy appearing adults.

Table 2. Causes of Hypoglycemia
Artifactual Hypoglycemia (without symptoms)
Reticulocytosis (polycythemia, sickle cell anemia)
Leukocytosis (leukemia)
Thrombocytosis
Fasting Hypoglycemia (> 5 hour from the last meal)
High Insulin, Low beta-hydroxy butyrate, High glucagon response
Insulinoma
Auto immune syndrome (antibodies to insulin or the insulin receptor)
Factitial due to exogenous insulin
Factitial due to insulin secretagogues
Induced by non-diabetic medications
Low Insulin, High beta-hydroxy butyrate, Low glucagon response
Ketotic hypoglycemia
Prolonged exercise
Alcohol induced
Glycogen storage diseases
Post Prandial Hypoglycemia (within 5 hours from the last meal)
Bariatric surgery
Nesidioblastosis
Hereditary fructose intolerance
Associated with Other Disorder
Critical illness (liver failure, congestive heart failure, sepsis, renal failure, etc.)
Malnutrition
Adrenal insufficiency
Non-islet cell tumors

Fasting Hypoglycemia

In patients with concern for fasting hypoglycemia, confirmation of Whipple's triad and exploration of the cause is recommended during an episode of spontaneous hypoglycemia or with a supervised fast of up to 72 hours (9) (Figure.1). During the fast, patients can consume non-caloric caffeine-free beverages with all non-essential medications discontinued. Plasma glucose, insulin, c-peptide, and BOHB are collected every 6 hours until plasma glucose is < 60 mg/dL; at that time, frequency of blood collection should be increased to every 1-2 hours. The fast is terminated after collecting the last blood sample when the plasma glucose is < 45 mg/dL and the patient has signs and/or symptoms of hypoglycemia or if the patient has not exhibited symptoms after 72

hours have elapsed. Alternatively, the fast can be terminated when plasma glucose is < 55 mg/dL in men and < 35 mg/dl in women, given the sex differences in abnormal fasting glycemic concentrations (29), without signs/symptoms if Whipple's triad was documented previously but blood samples were not collected (9). At the end of the fast, glucose response to 1 mg of glucagon IV bolus injection will be measured every 10 minutes for a 30-minute period and then the patient is fed. Insulin antibodies from baseline blood samples as well as hypoglycemic anti-diabetic medications (sulfonylureas and meglitinides) screening from baseline blood and urine samples are also collected. After confirmation of diagnosis, the results of the fasting test will help to differentiate hypoglycemia mediated by insulin- versus non-insulin factors.

INSULIN-DEPENDENT HYPOGLYCEMIA (HIGH PLASMA INSULIN CONCENTRATION)

C-peptide is secreted from β -cells at an equimolar ratio to insulin (30). Approximately half of the insulin which is secreted into the portal vein is removed by the liver (31). Therefore, plasma insulin concentration reflects not only insulin secretion or exogenous insulin administration, but also hepatic insulin degradation. In contrast to insulin, c-peptide undergoes minimal extraction by the liver and other organs (32), therefore c-peptide concentration represents endogenous insulin secretion (32,33). It has been well documented that exogenous insulin administration during euglycemia or hypoglycemia inhibits endogenous insulin secretion (34,35). In fact, this physiological phenomenon has been used to support the diagnosis of insulinoma using hyperinsulinemic hypoglycemic or euglycemic clamp (36,37).

Therefore, low plasma concentration of c-peptide in presence of elevated insulin values during hypoglycemia indicates factitious hypoglycemia due to exogenous insulin administration, whereas elevated c-peptide and insulin represents inappropriately greater endogenous insulin secretion due to insulin secretagogues (sulfonylurea or meglitinides), autoimmune syndromes (insulin antibody syndrome or type B insulin resistance) or an insulin-producing tumor (insulinoma).

Further, hypoglycemia induced by hyperinsulinemia is associated with low BOHB and glycemic response >25 mg/dl to glucagon injection. Insulin increases fatty acid synthesis and esterification and decreases fatty acid oxidation and ketogenesis in the liver, leading to lower plasma concentrations of BOHB. Enhanced insulin signaling in the liver activated by hyperinsulinemia or any non-insulin ligands, such as insulin-like growth factor—2 (IGF-2), also results in higher glycogen storage, hence a larger glycemic response to glucagon injection.

Factitious Hypoglycemia

Factitious hypoglycemia due to exogenous insulin (high insulin and low c-peptide) or insulin secretagogues medications (high insulin and c-peptide) remains a diagnostic challenge and often leads to extensive and costly investigation to rule out other causes because of limitations in biochemical assays (38), as well as patients' denial of medication misuse. Factitious hypoglycemia is observed more often in patients who work in the medical health care system, have relatives with diabetes living in the same household, and those with underlying mental illness such as major depression. Therefore, obtaining detailed information regarding the patient's medication list including herbal preparations that can be contaminated with sulfonylurea as well as family history is essential (39).

Hypoglycemia due to exogenous insulin is characterized by elevated plasma insulin, suppressed c-peptide and low BOHB, as well as an increase in plasma glucose >25 mg/dL after glucagon challenge (9). Insulin antibodies may also be positive (40).

Insulin-induced hypoglycemia due to insulin secretagogues (sulfonylurea or meglitinide) has a similar biochemical profile except that the c-peptide is elevated. Therefore, the only way to differentiate anti-diabetic factitious hypoglycemia from insulinoma is by detecting the drug in blood or urine.

In a single-center retrospective study, factitious hypoglycemia accounted for 11 of 70 (16%) of admissions for evaluation of hypoglycemia. (41). Prognosis is poor based on a small-size study, in which only 30% of affected patients during several years of follow-up recovered (42). Treatment requires a multisystemic treatment team led by a psychiatrist (42).

Autoimmune Syndromes

Autoimmune syndromes are a rare cause of hypoglycemia characterized by high concentrations of

insulin autoantibodies (insulin autoimmune syndrome [IAS]) or anti-insulin receptor antibodies (type B insulin resistance) (43,44). While IAS is the third leading cause of hypoglycemia in Japan, it is very uncommon in the non-Asian population; type B insulin resistance is even less common (43).

Insulin autoantibodies (IAAs) are mainly immunoglobulins (Ig) directed against endogenously released insulin in response to nutrient ingestion with a high binding capacity but low affinity to insulin. As a result, patients may manifest hyperglycemia in the early absorptive phase of meal or oral glucose intake, when exogenous glucose appearance into circulation is maximal, followed by hypoglycemia in a few hours during the late prandial condition or postabsorptive state. Hypoglycemia, in IAS, is caused by the binding and release of insulin from the antigen-antibody complex independently of changes in glucose concentrations. Therefore, insulin and c-peptide are both elevated at the time of low plasma glucose concentrations. IAAs are different from insulin antibodies produced against exogenous insulin that are generally low binding and high affinity, thus, unable to cause hypoglycemia.

In non-Asian patients, IAS is mainly reported in individuals with autoimmune (lupus, rheumatoid arthritis) /hematological diseases (multiple myeloma, benign monoclonal gammopathy), who are exposed to triggering factors, such as medications (captopril, propylthiouracil, penicillin G) and viral infections (measles, mumps, rubella, varicella zoster, coxsackie B, and hepatitis C) (43,44). In Japanese patients, IAS is commonly associated with exposure to medications with a sulphhydryl group (methimazole) (43). The prognosis is relatively good with self-remission reported in 82% of patients (44). Treatment is often dietary modification (small, frequent low-carbohydrate meals and uncooked cornstarch) and occasionally requires medications to decrease insulin secretion (somatostatin analogues, diazoxide) or immunosuppressants (high -dose corticosteroids, azathioprine, rituximab) (43,44).

Type B insulin resistance is caused by anti-insulin receptor antibodies. Affected patients tend to be middle-aged women of Black race with obesity, acanthosis nigricans, and hyperandrogenism. Co-occurrence of systemic autoimmune disease (i.e., lupus) is common (43). Patients typically present with hyperglycemia; however, a subset of patients (8 of 34 patients in an NIH cohort) experience fasting or postprandial hypoglycemia after period of hyperglycemia or without a history of hyperglycemia (43). The autoantibodies are believed to be partial agonists for the insulin receptor. Hyperglycemia or hypoglycemia ensues depending on the antibody titer: high titers antagonize the receptor, resulting in hyperglycemia and high insulin and c-peptide levels to compensate for the resistance; low titers activate the receptor, leading to hypoglycemia. There are diagnostic challenges as immunoprecipitation, the gold standard method to detect insulin receptor autoantibodies, is generally not commercially available (45). Unlike IAS, prognosis of type B insulin resistance is poor with high mortality especially in patients that transition from a hyperglycemic to hypoglycemic phase. Deaths are related to hypoglycemia and other causes (lupus, renal failure, cancer, cardiovascular events). Therapy can include immunosuppressants, but response is variable or poor (43).

Insulinoma

Neuroendocrine insulin-producing tumors (insulinoma) are relatively rare with an estimated incidence of ~ 1 – 4 new cases per million people/year (46). Less than 10% of insulinomas are malignant, 10% multiple, and 4% associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome (47). They primarily manifest in the 5th decade of life and are slightly more common in females (48). Typically, patients experience episodes of hypoglycemia fasting or after exercise, but some individuals may experience fasting and prandial hypoglycemia (49). Less frequently (6% of 237 patients in a Mayo Clinic cohort), patients present solely with prandial hypoglycemia

(50). Diagnosis relies on biochemical testing. The 72-hour fast is usually successful in capturing hypoglycemia in patients with insulinoma, as 65% of patients will experience hypoglycemia within 24 hours, 93% within 48 hours, and 99% within 72-hours (51).

Individuals with confirmed fasting (or postprandial) hyperinsulinemic hypoglycemia, negative screening for oral hypoglycemic medications, and negative insulin autoantibody testing should undergo diagnostic tests to locate the insulinoma prior to surgery (9). Non-invasive imaging can include transabdominal and endoscopic ultrasonography, abdominal computed tomography (CT), and magnetic resonance imaging (MRI) (52). CT has been shown to detect ~70-80% of tumors and MRI 85% (47). Given that insulinomas tend to be small in size (< 1 cm in diameter in 40% of diagnosed cases) (47), negative imaging does not rule out the diagnosis (9). If non-invasive imaging cannot determine preoperative localization, selective arterial calcium stimulation with hepatic venous sampling can be utilized (53). Calcium is injected into arteries supplying the pancreas, which stimulates insulin secretion from insulinomas; a ≥ 2 -fold increase in insulin concentrations from baseline localizes the site of an insulinoma with a > 90% sensitivity (54,55).

Treatment is surgical enucleation of the tumor, performed more commonly via open surgery than laparoscopic (48). If not localized prior to surgery, intraoperative palpation by an experienced surgeon coupled with intraoperative ultrasound detects > 80% of tumors (48). Pancreatectomy (distal or central depending on location of tumor) is preferred over enucleation if the insulinoma is large or there is concern for malignancy or metastases. Pancreatic fistula is the most common complication in both open and laparoscopic surgeries. As noted earlier, the hyperinsulinemic hypoglycemic or euglycemic clamp has also be utilized to differentiate insulinoma from other causes when conventional evaluation (prolonged fasting, imaging) were equivocal (37) or when surgery failed to detect an insulinoma but clinical suspicion was high (56).

Benign insulinomas have a high 5yr survival rate of 95-100% post-resection with relapse frequency 6% at 10yr and 8% at 20 yrs (48). Malignant insulinomas carry a poor prognosis with median life expectancy of 2 years (48). Inoperable cases may benefit from medical management such as diazoxide, streptozocin, verapamil, and phenytoin by reducing insulin secretion and corticosteroids by diminishing insulin action (48,57-59). Non-surgical procedures such as CT guided radiofrequency ablation, US-guided ablation with ethanol, peptide receptor radionuclide therapy, and robotic radiosurgery have also been utilized (48).

Non-Diabetic Medications

Non-diabetic medications such as quinolones, non-steroidal anti-inflammatory drugs, antipsychotics, and α and β blockers have been implicated in inducing hypoglycemia by stimulating insulin secretion (60). Other medications, such as pentamidine, damage the β cells, resulting in transient hypoglycemia induced by cytolytic insulin release (60). Risk factors related to hypoglycemia include higher medication doses, concomitant renal failure, older age, and poor nutrition (60). Treatment may include discontinuation of the medication and supportive care (60).

INSULIN-INDEPENDENT HYPOGLYCEMIA (LOW PLASMA INSULIN CONCENTRATION)

In this group, plasma BOHB is elevated and glucose response to glucagon is small. In patients who *appear healthy* the following conditions should be considered and ruled out:

Ketotic Hypoglycemia

Ketotic hypoglycemia is a relatively rare condition that can occur during extended periods of carbohydrate deprivation, as during fasting or starvation. Prolonged adherence to a ketogenic diet, which severely restricts carbohydrate intake to 20-50g/day to promote weight loss and increase plasma ketone bodies (61), combined with other factors interfering with

counterregulatory response, such as alcohol intake, also can result in ketotic hypoglycemia (62). Hypoglycemia in this condition is mainly caused by reduction in hepatic glucose production by hyperketonemia, which outweighs the diminished glucose utilization (63). Management is largely supportive depending on the severity of the presentation.

Prolonged Exercise

Prolonged exercise can result in plasma glucose to decline to the hypoglycemic range in 30-40% of healthy subjects, but these events are not associated with symptoms (Whipple's triad) nor incompatible with continued exercise (64). While the mechanisms for lack of symptoms is not completely understood, studies in non-diabetic dogs using a hypoglycemic clamp with and without exercise have shown that (a) counterregulatory hormonal responses to exercise and hypoglycemia combined are greater than the response to either conditions alone, and (b) larger insulin action during exercise are negated by the counterregulatory response during hypoglycemia (both enhanced endogenous glucose production and reduced glucose utilization) (65). Thus, disturbed counterregulatory response in prolonged exercise combined with inadequate carbohydrate ingestion may result in clinical hypoglycemia (66). Management is supportive.

Alcohol-Induced Hypoglycemia

Hypoglycemia due to alcohol has been attributed to inhibition of gluconeogenesis and blunting of growth hormone response to hypoglycemia (67). Management is mainly supportive depending on the severity and length of hypoglycemia.

Glycogen Storage Diseases

Glycogen storage diseases (GSD) are rare genetic disorders that impair the breakdown of glycogen. Although these diseases are commonly diagnosed in

infancy, GSDs Type I (deficiency in glucose-6-phosphatase), III (deficiency in amylo-1,6-glucosidase), and 0 (lack of glycogen synthase) can present in adulthood or continue to persist in adulthood (68). Adults with Type 1 GSD (most common form, annual incidence 1/100,000) may present with hypoglycemia, lactic acidosis, hyperuricemia, hypertriglyceridemia, and hepatomegaly (68). Patients with glycogen storage disease are generally managed by frequent feeding with complex carbohydrates and cornstarch to prevent hypoglycemia. Patients need to be followed long-term by a metabolic specialist.

Fatty Acid Oxidation (FAO) Disorders

FAO disorders are a rare group of autosomal recessive conditions characterized by impaired breakdown of fatty acids, leading to hypoketotic hypoglycemia and myopathy. FAO disorders also typically manifest in childhood but can continue through adulthood. Prognosis depends on the specific condition and severity. Treatment typically includes avoidance of fasting and high carbohydrate/low fat diets (68). Patients are managed by metabolic specialists.

ASSOCIATED WITH OTHER DISORDERS

In ill-appearing patients with hypoglycemia but low insulin concentrations the following conditions should be considered:

Critical Illness

Critical illness including organ failure such as acute liver failure and congestive heart failure with hepatic congestion have been associated with hypoglycemia, likely due to impaired gluconeogenesis and depletion of hepatic glycogen stores (69,70). Sepsis-induced hypoglycemia has been appreciated in humans and animal models with depleted glycogen stores, impaired gluconeogenesis, and increased peripheral glucose utilization implicated as contributing factors

(71,72). Hypoglycemia in non-diabetic people with end stage renal disease is attributed to concomitant adrenal insufficiency, certain medications, malnutrition, and infection (73,74). Management of ill-appearing individuals due to sepsis or organ failure is mainly treatment of underlying disorders and treatment of severe hypoglycemia by intravenous glucose administration.

Addison's Disease

Addison's disease is a rare disease that results in primary adrenal insufficiency characterized by glucocorticoid deficiency with or without mineralocorticoid deficiency. Most cases are caused by autoimmune damage to the adrenal cortex by 21-hydroxylase antibodies (75). Hypoglycemia, although rare, is likely due to cortisol deficiency that interferes with counterregulatory response during times of stress (76). Addison's disease should be considered in a hypoglycemic individual with hyperpigmentation, hyponatremia, hyperkalemia and acidosis (75). Further testing, such as ACTH stimulation test, may be warranted to confirm diagnosis (77). Treatment for patients with primary adrenal insufficiency in adrenal crisis should be initiated by volume replacement and immediate treatment with intravenous or intramuscular hydrocortisone 100 mg followed by 100 mg every 6-8 hours until clinically stable. Etiology of the precipitating adrenal crisis should be identified and treated (i.e., infection, hemorrhage, etc.) (75).

Non-Islet Cell Tumors

Nonislet cell tumors are rare mesenchymal and epithelial tumors that can be benign or malignant, are often large (> 10 cm), and clinically apparent. Hypoglycemia results when the tumor overproduces incompletely processed IGF-2 (9,78-80). Tumors can secrete IGF-2 or its posttranslational precursor "big IGF" (81). IGF-2 structurally is similar to insulin; high levels of IGF-2 can bind to the insulin receptor and mimic the action of insulin, resulting in hypoglycemia (82). Insulin and c-peptide levels are appropriately

suppressed in response to the hypoglycemia. Management of non-islet cell tumors may include surgery, radiotherapy, chemotherapy and medical therapy with glucocorticoids, GH, or octreotide (9).

Prandial Hypoglycemia

The glycemic threshold to define hypoglycemia after meal ingestion is unknown. However, symptoms associated with plasma glucose less than 50-55 mg/dL during mixed meal test that is relieved by normalization of glucose has been used to confirm meal-induced hypoglycemia (11,25). In the prandial state, provocative testing should use a mixed meal containing protein, carbohydrates, and fat and not oral glucose. This is mainly because the oral glucose challenge has low specificity for detecting clinical hypoglycemia by causing asymptomatic low glucose nadirs as well as hypoglycemia symptoms (mainly autonomic) that do not correlate with low glucose concentrations (23,24).

Currently meal tests are not standardized as both solid and liquid mixed meals as well as variable carbohydrate content from 45 to 105 grams have been used (83). Regardless of approach, meal studies can increase the risk of inducing hypoglycemia, thus, these tests need to be done under supervision by personnel trained in a safe environment.

HYPOGLYCEMIA AFTER BARIATRIC SURGERY

Meal-induced hypoglycemia after upper GI tract (gastrectomy and pyloroplasty) (84) or bariatric surgery (85-87) (Roux-en y gastric bypass surgery [RYGB] and sleeve gastrectomy [SG]) are well documented. One in 10 bariatric subjects develop a late-complication of hypoglycemia (88,89), and one in 150 suffer from severe hypoglycemia requiring an emergency room visit or hospitalization (88). Hypoglycemia in this population is postprandial, progressive, often associated with cognitive impairment and occasionally with loss of consciousness or seizures and is only partially

responsive to diet modification or available therapeutic options (25,86,90-92). Despite sporadic case reports of postprandial hypoglycemia after SG (85), this condition, in our experience, is less prevalent, and likely to be of lesser severity than RYGB. Severe hypoglycemia after bariatric surgery is debilitating as it compromises patient safety, cognition, and quality of life (both professional and personal). The long-term health outcomes of this debilitating complication are largely unknown. A recent study (93) using a driver simulator has demonstrated that driving performance and cognitive function is impaired following RYGB during prandial hypoglycemia without any changes in perception of symptoms (94,95).

Differentiating true hypoglycemia from those with prandial asymptomatic low glucose concentration or prandial symptoms without low glucose levels is more challenging in patients after GI surgery than non-operated individuals because of higher frequency of both conditions after bariatric surgery. Using CGM for 5 days has demonstrated that 70% of non-diabetic subjects after RYGB (n=40) had at least one episode of low interstitial glucose concentration (<55 mg/dl) (94). However, 80% of these low glucose events have been shown to be asymptomatic. Furthermore, it is well documented that a large proportion of bariatric patients experience dumping symptoms (91), which are almost identical with autonomic symptoms of hypoglycemia, but not associated with low glucose concentrations. Therefore, it is critical to document Whipple's triad (neuroglycopenic rather than autonomic symptoms associated with low glucose) during free-living conditions or using mixed meal test to confirm hypoglycemia in this population.

Additional testing should be considered in ill-appearing patients after bariatric surgery to exclude adrenal insufficiency, other critical illnesses, and

malnutrition (25). Post bariatric patients who experience fasting hypoglycemia (beyond 5 hours from previous meal ingestion) or hypoglycemia within 6-12 months from surgery should be evaluated for other causes of hypoglycemia such as insulinoma (25).

Underlying mechanisms by which rerouted gut after GI surgeries cause hypoglycemia is not completely understood. However, it is well documented that following RYGB, and to a smaller extent after SG, meal ingestion enhances glucose excursion leading to higher glucose peaks and lower nadir glucose concentrations mainly due to faster nutrient emptying from the stomach pouch/stomach to the gut (96) (Figure 2). Increased glucose delivery from the stomach pouch/ tube-like stomach to the gut after bariatric surgery is associated with hyperinsulinemia, which is exaggerated in RYGB patients with hypoglycemia compared to asymptomatic RYGB subjects (92) (Figure 2). Enhanced meal-induced beta-cell secretion in patients with hypoglycemia after RYGB has been attributed to not only a greater beta-cell sensitivity to increasing glycemia in the first absorptive phase, but also a lower insulin suppression during glycemic decline from peak to glucose nadir (87).

Prandial hyperinsulinemia after RYGB, particularly in patients with hypoglycemia, has been shown to be associated with greater prandial plasma concentration of glucagon-like peptide 1 (GLP-1), an insulinotropic gut hormone (87,90,97) (Figure 2). These observations hinted towards a key role for GLP-1 signaling beyond glycemic stimuli in meal-stimulated hyperinsulinemia after RYGB. In fact, we and others have shown that blocking the GLP-1 receptor (GLP-1R) corrects post-RYGB hypoglycemia (87,98).

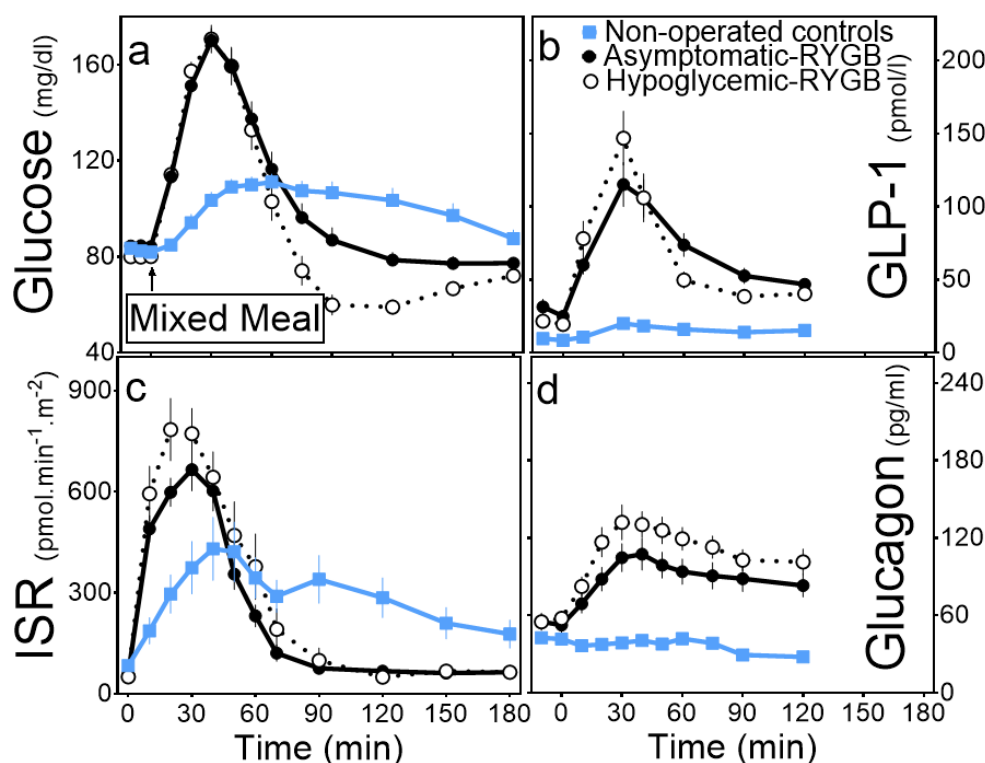


Figure 2. The prandial glycemic effects of RYGB are exaggerated in patients with late-complication of hypoglycemia. RYGB enhances prandial glycemic excursion and increases insulin secretion rate (ISR) along with plasma GLP-1 concentrations. Patients with documented hypoglycemia after RYGB have greater insulin and GLP-1 secretin compared to those without. Following RYGB, glucagon response to meal ingestion is enhanced but there is no further increase in response to hypoglycemia. Adapted with permission from Salehi, JCEM, 2014.

Despite a larger meal-induced glucagon response after RYGB compared to non-operated individuals, there is no further increase in plasma glucagon concentration during prandial hyperglycemia (Figure 2), suggestive of dysregulated pancreatic α -cell response. In fact, we have shown that patients with RYGB and SG, glucagon response to insulin-induced hypoglycemia is smaller than healthy individuals without GI surgery (99,100). This data is aligned with a report demonstrating that counterregulatory hormonal response (glucagon, cortisol, and catecholamines) to hypoglycemia is significantly reduced after RYGB compared with before surgery (101). In prandial state using tracer technique, we also have shown that despite a larger prandial plasma glucagon concentration, endogenous glucose production response to hypoglycemia is smaller after

RYGB compared to non-operated controls (102), suggestive of diminished liver sensitivity to glucagon. However, we have demonstrated that blocking the GLP-1R increases the prandial hepatic glucose production response to insulin-induced hypoglycemia in RYGB subjects but not in non-operated controls, suggesting that enhanced GLP-1 signal due to rerouted gut can potentially contribute to the impaired counterregulatory response to hypoglycemia (103).

Based on current pathophysiologic understanding treatment strategies that selectively reduce the pace of nutrient delivery to the gut and prandial insulin secretion or improve counterregulatory response are the most effective options. Because of limited therapeutic options at this point, dietary modification remains the cornerstone of management. The goal of

dietary modification is to lower prandial glucose spikes while increasing glucose nadirs by (a) lowering the amount of carbohydrates for every meal (<30g) or snacks (<15 g), (b) avoiding simple carbohydrates with high-glycemic index, (c) adding fats and proteins to every meal and snack, and (d) changing the composition of carbohydrate from glucose to fructose (25). Uncooked starch has also been used in this population based on effectiveness in reducing hypoglycemic episodes in patients with diabetes mellitus (104).

The current medical interventions rely on drugs that had previously been used for treatment of other hypoglycemic conditions. Acarbose, an antidiabetic medication, has been utilized as the first drug started with dietary modification. The effect of this intestinal alpha-glucosidase blocker is to block carbohydrate absorption and reduce prandial glycemic excursion after RYGB {Valderas, 2012 #6617}. Adverse effects include flatulence and bloating, especially if the dose is not gradually titrated. Other medications such as somatostatin analogues, diazoxide, and GLP-1R agonists also are used based on sporadic case reports (25). Unblinded CGM in a small size study of patients with post-RYGB hypoglycemia has also been shown to reduce hypoglycemic episodes, likely due to better self-assessment of glycemic excursion and the need for treatments (105). The investigational drugs that are in various phases of development include exendin-(9-30) (Eiger Biopharmaceutical, Paol Alto, CA, USA), a potent GLP-1R antagonist (87,106), glucagon-based drugs (107,108), somatostatin analogues (109) and sodium-glucose cotransporter-1 inhibitor (110).

OTHER PRANDIAL HYPOGLYCEMIC CONDITIONS (RARE)

Nesidioblastosis

Non-insulinoma pancreatogenous hypoglycemia is a rare condition that typically causes hypoglycemia in the postprandial state due to diffuse nesidioblastosis (β cell hypertrophy, islet hyperplasia, increase in β cell

mass) (111). The pathogenesis in adults is largely unknown, but likely differs from nesidioblastosis that occurs in congenital hyperinsulinism that is caused by a genetic mutation (112,113). This etiology should be considered in a hypoglycemia patient with a negative 72 hour fast, positive mixed meal test concerning for endogenous hyperinsulinism without a history of GI surgery, and negative imaging for insulinoma. Selective arterial calcium stimulation demonstrates diffuse insulin secretion. Histopathology reveals nesidioblastosis (114-116). Ideal management is difficult to determine as the condition is rare; a majority of the publications are from case reports or case-series, and there is a lack of long-term follow up (82,117). Management can include dietary interventions (low-carbohydrate frequent meals) or medical interventions with diazoxide, acarbose, verapamil or octreotide (82). When these interventions fail, partial pancreatectomy can be performed in patients with severe neuroglycopenic symptoms (118).

Hereditary Fructose Intolerance

Hereditary fructose intolerance is a rare autosomal recessive disorder (<1-9/100,000 annual incidence) caused by fructose-1-phosphate deficiency that results in postprandial hypoglycemia after ingestion of fructose (fruits) or sucrose (sweet foods) that is usually diagnosed in childhood. The diagnosis should be suspected in ill-appearing adults with hypoglycemia associated with GI symptoms (nausea, vomiting, diffuse abdominal pain) after eating fruits or sugar. Clinical symptom resolution within days of elimination suggests hereditary fructose intolerance and can be confirmed by molecular diagnosis on DNA obtained from peripheral leukocytes (68).

CONCLUSION

Non-diabetic hypoglycemia is a rare phenomenon since in healthy individuals counterregulatory mechanisms prevent and correct hypoglycemia by reducing glucose uptake and by enhancing hepatic

glucose production. These mechanisms are less well characterized in the prandial state compared to the fasting state. Nonetheless, hypoglycemia only occurs when impaired physiological responses offset the balance between glucose utilization and production. Evaluation of hypoglycemia starts with a detailed history, comprehensive review of medications and clinical presentation, and a thorough physical exam that guides the diagnostic approach in patients with documented hypoglycemia based on Whipple's triad.

In absence of confirmation of hypoglycemia during free living condition provoked testing, prolonged fast or mixed meal test for hypoglycemic conditions reported during fasting or prandial state, respectively, are indicated. Diagnostic and management strategies for non-diabetic hypoglycemia is individualized depending on specific pathophysiology and can include interventions that are dietary, medical, or surgical.

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