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Glucose Counterregulatory Responses to Hypoglycemia

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Abstract

The brain relies almost exclusively on glucose for fuel. Therefore, adequate uptake of glucose from the plasma is key for normal brain function and survival. Despite wide variations in glucose flux (i.e. fed state, fasting state, etc), blood glucose is maintained in a very narrow range. This is accomplished by a series of hormonal and physiologic responses. As a result, hypoglycemia is a rare occurrence in normal individuals. However, glucose counterregulatory responses are altered in patients with diabetes treated with insulin especially after repeated hypoglycemia or antecedent exercise.

Keywords

Hypoglycemia; Counterregulation

Glucose is an essential fuel for the brain. Therefore, adequate uptake of glucose from the plasma is key for normal brain function and survival. For this reason, glucose homeostasis is tightly regulated by a series of hormones and physiologic responses. As a result, hypoglycemia is a rare occurrence in normal individuals, but occurs commonly in patients with diabetes mellitus treated with insulin. Severe hypoglycemia results in cognitive dysfunction including obtundation and seizures; if prolonged it can lead to coma and death. In healthy subjects, the thresholds for counterregulatory hormone production are highly reproducible. However, in diabetic patients, many of these responses are blunted and thresholds may vary depending on their glycemic control. The severe consequences of hypoglycemia and the blunting of counterregulatory and symptom responses make hypoglycemia the limiting factor in the glycemic management of diabetes (1).

DEFINITION OF HYPOGLYCEMIA

Under normal circumstances plasma glucose concentration is maintained in a relative narrow range, 4.0–8.0 mmol/L (72–144 mg/dl) in healthy subjects. This results from a fine balance between glucose influx (exogenous glucose delivery and endogenous glucose production) and glucose efflux (glucose utilization by insulin sensitive tissues such as the skeletal muscle and insulin insensitive tissues, particularly the brain) (2). A series of hormones, neurotransmitters and substrate factors are involved in the regulation of glucose metabolism, and the levels of most of these factors change in response to falling plasma glucose levels (3–5). Hypoglycemia results from an imbalance between glucose influx and glucose efflux due to either excessive glucose removal from the circulation, deficient glucose delivery into the circulation, or both. During conditions of increased glucose

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utilization such as exercise, pregnancy, and sepsis, blood glucose levels are sustained in the normal range by the capacity of the normal liver (and kidneys) to increase glucose production by gluconeogenesis and glycogenolysis. Therefore, hypoglycemia occurs in instances of defective counterregulatory hormone regulation, elevated circulating insulin levels due to excessive secretion of insulin or iatrogenic hyperinsulinemia; deficiency of counterregulatory hormones; gluconeogenic enzymatic defects or failure to mobilize or utilize gluconeogenic substrates.

The diagnosis of a hypoglycemic disorder or an iatrogenic hypoglycemic episode is more convincing when the Whipple's triad is documented: (6) a measured low plasma glucose level, symptoms compatible with hypoglycemia, and the recovery of symptoms when the plasma glucose level is raised to normal. The plasma glucose level that defines hypoglycemia has been controversial in children (7). Among term neonates, the plasma glucose level to define hypoglycemia has ranged from <1.0 mmol/L (18mg/dL) to <4.0 mmol/L (70mg/dL), with a modal value of 2.0 mmol/L (36mg/dL) according to a survey of pediatricians in the United Kingdom (8). Lower levels (<1.1 mmol/L [20 mg/dL]) were used in low-birth weight infants. Aynsley-Green suggested that the use of a lower plasma glucose levels in low-birth weight infants stems from studies in the 1960s which demonstrated a fall in plasma glucose level immediately after birth in all neonates which was more pronounced and prolonged in those weighing <2.5 kg; this would include both pre-term and small for gestational age infants. At that time feeding or intravenous glucose support was often delayed for hours (9). However, Lucas et al. followed more than 600 preterm infants and demonstrated that although plasma glucose levels <2.6 mmol/L (46 mg/dL) were common in the newborn period, if those plasma glucose levels persisted for 5 or more days there was an increase in cerebral palsy and developmental delay (10).

Current data suggest a cutoff of plasma glucose level ≤2.5 mmol/L (45 mg/dL) in infants <24 h of life and a plasma glucose level ≤2.8 mmol/L (50 mg/dL) after 24h of life as operational thresholds for hypoglycemia (7) (11). Venous plasma glucose concentrations greater than 3.9 mmol/L (70 mg/dL) after an overnight fast are clearly normal in healthy children and adults. Those between 3.0 and 3.9 mmol/L (54–70 mg/dL) are borderline, and those less than 3.0 mmol/L (54 mg/dL) indicate postabsorptive hypoglycemia in older children and adult subjects without diabetes mellitus. However, in patients with diabetes, glycemic control is limited by hypoglycemia and its associated risks including altered mental status, seizure, coma and even death. Thus, a plasma glucose level of less than 3.9 mmol/L (70 mg/dL) has been recommended as an alert and intervention value for hypoglycemia in patients with diabetes(12). Repeated episodes of hypoglycemia result in hypoglycemia unawareness, impaired glucose counterregulation and predisposition to severe hypoglycemia (12).

GLYCEMIC THRESHOLDS FOR HYPOGLYCEMIC RESPONSES

Progressively declining plasma glucose concentrations elicit a sequence of physiological and behavioral responses, with defined glycemic thresholds, in healthy individuals (Fig. 1) (13–15). As plasma glucose fall within the physiologic range (4.4–4.7 mmol/L [80–85 mg/dL]), insulin secretion by the pancreatic β-cells decreases, favoring increased glucose production and decreasing glucose utilization by tissues other than the brain. If plasma glucose levels continue to fall just below the physiologic range (3.6–3.9 mmol/L [65–70 mg/dL]), counterregulatory hormones are secreted. These include glucagon, which is secreted by the pancreatic α-cells and stimulates hepatic glycogenolysis and favors gluconeogenesis, and epinephrine that stimulates hepatic glycogenolysis, mobilizes precursors for hepatic and renal gluconeogenesis and limits glucose utilization by insulin-sensitive tissues. Lower plasma glucose concentrations (2.8–3.0 mmol/L [50–55mg/dL]) cause neurogenic and

neuroglycopenic hypoglycemic symptoms, and ultimately, brain dysfunction at levels ~<2.8 mmol/L (50 mg/dL). These thresholds shift to higher plasma glucose concentrations in people with poorly controlled diabetes and to lower plasma glucose concentrations in people who suffer recurrent hypoglycemia, such as those with well-controlled diabetes or with endogenous hyperinsulinism (16–18).

GLUCOSE METABOLISM

Plasma glucose is derived from intestinal absorption of dietary carbohydrates or endogenous glucose production by either glycogenolysis, or gluconeogenesis (Figure 2). Glucose is transported into the cellular compartment by different glucose transporters. It enters down a concentration gradient across cellular plasma membranes of myocytes, adipocytes and across the blood brain barrier by GLUT-1; and into hepatocytes and pancreatic β cells by GLUT-2. Myocytes and adipocytes also express GLUT-4 in their cytoplasm, which translocates to the cell membrane in response to insulin. Once glucose enters the cell, it is phosphorylated by a hexokinase (glucokinase in hepatocytes and β cells) and then either stored as glycogen or metabolized through glycolysis. Glycolysis is the conversion of glucose-6-phosphate to pyruvate and generation of adenosine triphosphate (ATP). The pyruvate that is produced can be reduced to lactate under anaerobic conditions or it can be oxidized via the tricarboxylic acid (Krebs) cycle, resulting in greater amounts of ATP.

Gluconeogenesis is the conversion of pyruvate derived from precursors including lactate and amino acids (especially alanine and glutamine) to glucose. Most tissues express the enzymes required for glycogenolysis (phosphorylase) and gluconeogenesis (including the critical gluconeogenic enzymes pyruvate carboxylase, phosphoenolpyruvate carboxykinase, and fructose-1,6-bisphosphatase), but only the liver and kidneys express the enzyme necessary for the release of glucose into the circulation (glucose-6-phosphatase) to contribute to the systemic glucose pool (19). The liver is the major source of net endogenous glucose production (20,21).

Insulin, glucagon and epinephrine regulate the rates of transcription of the key enzymes and regulatory steps involved in endogenous glucose production (gluconeogenesis and glycogen synthesis), and glucose utilization (glycolysis and glycogenolysis). Insulin, which is secreted by pancreatic β cells in response to increases in plasma glucose levels, suppresses glucose production and increases glucose utilization by sensitive tissues such as muscle, fat and liver. Glucagon, which is stimulated by low plasma glucose levels, increases hepatic glucose production primarily by stimulating glycogenolysis. Epinephrine increases glucose production directly by mobilizing the gluconeogenic precursors such as alanine and lactate from muscle and glycerol from fat. It also decreases glucose clearance by insulin-sensitive tissues and limits insulin secretion.

PHYSIOLOGICAL RESPONSES IN THE FED STATE

After a meal the blood glucose concentration increases depending on the amount of carbohydrate ingested, its rate of transit through and absorption from the GI tract, and release of insulin. In the β-cell, glucose is taken up via GLUT2 and phosphorylated to glucose-6-phosphate via an islet-specific glucokinase. Glucose-6-phosphate is then metabolized to produce ATP. Increased levels of ATP result in closure of the ATP-dependent potassium channels (KATP), depolarization of the cell, calcium influx, and release of insulin from secretory granules into the circulation. Basal insulin secretion is pulsatile occurring every 9–14 minutes. There is also a cephalic insulin secretion phase that occurs in response to the sight, smell and taste of food and is mediated by parasympathetic cholinergic innervation (22). Rapid increases in serum glucose, such as following an intravenous bolus of glucose, result in an early (first-phase) burst of insulin secretion that

peaks in 3–5 minutes and subsides within 10 minutes. If elevated glucose concentrations are sustained, a second phase of insulin secretion occurs with release of both stored and newly-synthesized insulin. Insulin decreases serum glucose concentrations by three mechanisms: a) inhibition of hepatic glucose production b) suppression of glucagon production by alpha cells in the pancreatic islets and c) stimulation of glucose uptake by myocytes and adipocytes by inducing translocation of GLUT4 to the cell surface. The rate of glucose uptake and utilization by the peripheral tissues subsequently exceeds the appearance of exogenous glucose, resulting in a fall of glucose levels close to the preprandial level. This decline in plasma glucose level results in a decrease in insulin secretion and a resumption of glucagon secretion. Thus, systematic glucose balance is maintained, hypoglycemia does not occur and glucose delivery to the brain is preserved.

PHYSIOLOGICAL RESPONSES IN THE POSTABSORPTIVE STATE

The postabsorptive state begins 4–6 hours after a meal when nutrient absorption from the proceeding meal has subseeded. In this condition plasma glucose levels are maintained in the normal physiologic range and rates of glucose production and utilization average about 2.2 mg/kg/minute in adults(23). This is higher in children and even higher in infants, presumably due to their larger brain mass as a proportion of their body weight. Low insulin levels favor hepatic glycogenolysis and hepatic and renal gluconeogenesis during an overnight fast. As fasting period is prolonged, glycogen stores are depleted and plasma glucose levels decline. This stimulates the secretion of glucagon, epinephrine, growth hormone, and cortisol, which promote hepatic gluconeogenesis, lipolysis and ketogenesis. If fasting is prolonged 24–48 hours, glucose utilization by fat and muscle decreases significantly; insulin levels are suppressed and lipolysis and ketogenesis increase and ketones become the significant fuel source for the brain.

PHYSIOLOGICAL RESPONSES TO HYPOGLYCEMIA

With intact counterregulatory factors, a drop in plasma glucose results in the key physiological defenses against falling plasma glucose concentrations: 1) a decrease in pancreatic β-cell insulin secretion, 2) an increase in pancreatic α-cell glucagon secretion and 3) an increase in adrenomedullary epinephrine secretion. It also results in the perception of hypoglycemic symptoms that are largely sympathetic neural and which prompt carbohydrate ingestion.

Insulin and Glucagon

The first response to falling glucose levels is decreased insulin secretion. As plasma glucose continues to fall (3.6–3.9 mmol/L [65–70 mg/dL]), glucagon is released (13,24) through incompletely understood mechanisms. Studies of isolated rat α-cells, isolated islets, the perfused pancreas and rodents in vivo suggest that it is regulated by intrinsic, paracrine and neuronal mechanisms on both β-cells and α-cells. Alpha cells, like beta cells, express glucokinase and KATP channels so they can sense low glucose concentrations directly. One paracrine effect is insulin inhibition of glucagon secretion from alpha cells(25). Another is somatostatin-mediated inhibition. There is evidence that gut incretin and CNS factors are also involved.

Sympathoadrenal Response

In normal subjects, plasma glucose level of 3.6–3.9 mmol/L [65–70 mg/dL] increases catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system (specifically the sympathoadrenal system) and in the CNS (13,24). The glucose level at which activation of catecholamine responses occur in children has been shown to be higher than in adults and it

varies with the level of glycemic control (26). The sympathoadrenal response includes activation of the adrenal medulla to secrete epinephrine and norepinephrine as well as activation of the sympathetic nervous system to release norepinephrine and acetylcholine. DeRosa and Cryer demonstrated lack of increase in plasma epinephrine in response to hypoglycemia in adrenalectomized compared to control subjects, thus implicating the adrenal gland as the primary source of these counterregulatory hormones during hypoglycemia. In contrast, neurogenic symptoms (nervous, sweaty, and hungry) were similar in hypoglycemic control and adrenalectomized subjects suggesting that these are mediated by the sympathetic and parasympathetic neural system rather than adrenomedullary activation (27).

Epinephrine and norepinephrine act on the liver via beta-2 adrenergic receptors to increase hepatic glycogenolysis and gluconeogenesis (28). Several studies in fasted dogs demonstrate only an indirect effect of epinephrine on gluconeogenesis by increasing gluconeogenic substrate release in peripheral tissues (29,30). Increased gluconeogenesis in humans in response to epinephrine also appears to reflect increased lipolysis with generation of gluconeogenic precursors, glycerol and free fatty acids (31). As both glucagon and epinephrine are secreted at similar levels of hypoglycemia, it is important to consider the effect of these hormones in concert. Studies in dogs show an additive effect of epinephrine and glucagon on glucose production (32). Co-infusion of gluconeogenic precursors with glucagon and epinephrine further augmented this increase in hepatic glucose production by increasing gluconeogenesis after 60 minutes suggesting that peripheral production of gluconeogenic precursors is the limiting factor in hepatic gluconeogenesis induced by glucagon and epinephrine.

Growth Hormone and Cortisol

In contrast to the rapid effects of glucagon and epinephrine on glucose regulation, the effects of growth hormone and cortisol during hypoglycemia are delayed. In pharmacologically-induced suppression of all the glucose counterregulatory hormones in humans, and selective replacement by a pancreatic-adrenocortical-pituitary clamp with subcutaneous insulin infusion, lack of cortisol rise resulted in lower rates of glucose production and higher rates of glucose utilization after 6 hours when glucagon, insulin, and growth hormone were infused to maintain similar plasma concentrations in the two groups (33). Plasma glucose levels were also lower in the low cortisol group after 9.5 hours. In a similar study, the effect of growth hormone replacements on glucose utilization and production appeared to have a similar delay (34). Comparison of adult control subjects and untreated hypopituitarism patients with documented growth hormone and cortisol deficiency showed lower plasma glucose levels in the GH and cortisol deficient patients beginning at 2.5 hours after initiation of an insulin infusion which become statistically significant by 12 hours (35). Hypoglycemia corrected rapidly in both groups after stopping the insulin infusion suggesting no critical effect of GH or cortisol on correction of hypoglycemia.

Symptoms

Hypoglycemic symptoms commonly occur with plasma glucose levels < 3.0 mm/L (54 mg/dL). However, the absolute BG level at which signs and symptoms occur may vary among individuals and within the same individual at different times or situations. Particularly in patients with diabetes, it may vary depending on their glycemic control, or prior hypoglycemic episodes (36,37). Symptoms of hypoglycemia can be divided into neurogenic (autonomic) and neuroglycopenic categories (38–40). Neurogenic symptoms result from the sympathoadrenal discharge triggered by hypoglycemia. Adrenergic symptoms such as palpitations, tremor, and anxiety are mediated by norepinephrine from sympathetic postganglionic neurons, the adrenal medullae, or both, and epinephrine from the adrenal

medullae. Cholinergic symptoms such as sweating, hunger and paresthesias are mediated by acetylcholine from sympathetic postganglionic neurons. Both are largely mediated by sympathetic neural, rather than adrenomedullary, activation (27). Neuroglycopenic symptoms result from CNS neuronal glucose deprivation and include behavioral changes, confusion, fatigue or weakness, visual changes, seizure, loss of consciousness, and, even death if hypoglycemia is severe and prolonged (38).

CENTRAL INTEGRATION OF GLUCOSE COUNTERREGULATION

Neuronal circuits both peripherally and centrally play an important role in integration of the response to glycemic stimuli. Glucose in the mouth activates taste receptors with projections to the brainstem, resulting in activation of the vagus nerve and induction of the cephalic phase of insulin secretion (22,41). Intestinal glucose stimulates the secretion of various intestinal hormones (glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) and activates enteric and autonomic neurons (42,43). Portal venous glucose activates afferents projecting to the hypothalamus and nucleus of the tractus solitarius among others resulting in simulation of glucose storage in the liver, muscle and fat as well as inhibition of counterregulation, cessation of eating and first phase insulin secretion (44–47).

Glucose sensing in CNS, particularly in the hypothalamus, plays an important roll in modulating counterregulatory hormones. In the central nervous system, both glucose-excited (activated by increased glucose concentrations) and glucose-inhibited (inhibited by increased glucose concentrations) neurons have been identified widely throughout the brain but are increased in the hypothalamus and brain stem (48). Intracarotid glucose infusion reduces secretion of counterregulatory hormones in response to systemic hypoglycemia (49,50). Similarly, intraventricular injection of 2-deoxyglucose, which competes with glucose for cellular uptake but is not metabolized (phosphorylated), increases secretion of glucagon resulting in systemic hyperglycemia (51). Similar to beta cells, glucose excited cells express GLUT2, which transports glucose into the cells. Metabolism of glucose increases the ATP: ADP ratio resulting in closure of the KATP channel, membrane depolarization, and neuronal activity (52). Activation of the hypothalamus and brainstem results in release of the appetite stimulating peptides NPY and AgRP as well as the appetite suppressing peptides POMC and CART (53,54). In addition glucose plays a direct role in regulation of feeding. A drop in glucose precedes initiation of feeding, and feeding is suppressed by an increase in plasma glucose levels (55,56). Although the ventral medial hypothalamus (VMH) has been considered the central integrator of the sympathoadrenal response to hypoglycemia, recent findings by Teves et al. (57), Arbelaez et al. (58) and the Amiel laboratory have shifted the focus to other brain regions (premedial frontal cortex, orbitoprefrontal cortex, thalamus and amygdala) as possible integrated cerebral networks that regulate physiologic responses to hypoglycemia (59).

DIAGNOSIS AND MANAGEMENT OF HYPOGLYCEMIA IN NONDIABETIC INFANTS AND CHILDREN

Diagnosis of hypoglycemia must be based on a laboratory glucose level due to variability of glucose meter readings. A critical sample should be obtained during a hypoglycemic episode or if the blood glucose level is ≤ 2.8 mmol/L (≤ 50 mg/dL) during a prolonged fast to evaluate the etiology of hypoglycemia. This critical sample includes blood glucose, serum bicarbonate (HCO_3) to assess for acidosis, insulin, c-peptide, β-hydroxybutyrate, lactate, cortisol, growth hormone, free fatty acids and ammonia as well as urine ketones during the hypoglycemic episode. During a normal response to a blood glucose level below 50 mg/dL, the insulin level should be undetectable (≤ 2 μU/mL), β-hydroxybutyrate increased (≥ 2–5

mmol/L), lactate reduced (≤ 1.5 mmol/L), free fatty acids increased (≥ 1.5 mmol/L), and all the counterregulatory hormones increased (60). A glucagon challenge test (0.03 mg/kg to a maximum of 1 mg IV) is also useful to determine hyperinsulinism when blood glucose is ≤ 2.8 mmol/L and critical samples have already been obtained; an increase in glucose of >30 mg/dL within 15–30 minutes of the injection is highly suggestive, if not diagnostic of hyperinsulinism. Additional laboratory studies that may be useful include plasma free and total carnitine, urine organic acids, and acylcarnitine profile. These can be obtained at any time but are most sensitive during a hypoglycemic episode. An Acylcarnitine profile is suggested prior to a scheduled diagnostic fast, as disorders of fatty acid oxidation are not uncommon and can result in hypoglycemia, lethargy, seizures and SIDS associated with fasting.

Particular attention in the clinical history should be placed to the timing of hypoglycemic symptoms or signs in relation to the duration of fasting or time since last meal before hypoglycemia occurred. Hypoglycemia that occurs after a short fasting period (within 4 to 6 hours of fasting) is caused by either hyperinsulinemia or a glycogen storage disease. In contrast, fasting that takes 8 to 12 hours to provoke hypoglycemia usually implies a defect in gluconeogenesis, or counterregulatory hormone deficiencies, as occurs in hypopituitarism, growth hormone, or cortisol deficiency. Other entities that take more than 10 hours of fasting to manifest hypoglycemia include defects in gluconeogenesis, glycogen metabolism, and fatty acid oxidation and are unlikely to manifest in the newborn period (11).

In non-diabetic pediatric patients, hypoglycemia can be classified based on the presence or absence of acidosis (HCO_3 ≤ 15–17). (Figure 3). The acidosis is due to either lactic acidosis or ketosis. Hypoglycemia with lactic acidosis can be attributed to glycogen storage disease type 1 (glucose-6-phosphatase deficiency), defects in hepatic gluconeogenesis (fructose-1,6-bisphosphatase deficiency, pyruvate carboxylase or phosphoenolpyruvate deficiency), galactosemia, alcohol ingestion or it can be seen in normal newborns in the first 24 hours of life. Hypoglycemia with ketotic acidosis occurs in patients with glycogen storage disease types 3, 6, and 9 (debrancher, liver phosphorylase, and phosphorylase kinase deficiencies), cortisol deficiency, growth hormone deficiency, and ketotic hypoglycemia. Ketotic hypoglycemia occurs commonly in the toddler/preschool age group during periods of poor oral intake (intercurrent illness) or prolonged fast (10–12 hours); this entity is common, but should be a diagnosis of exclusion. Hypoglycemia without acidosis or ketosis is caused by conditions with elevated insulin levels, hypopiuitarism or disorders of fatty acid oxidation, the latter of which presents with elevated free fatty acids. Transient neonatal hyperinsulinism is found in infants of diabetic mothers, those with intrauterine growth retardation, perinatal stress such as hypoxic-ischemic injury and infants taking beta-blockers. Congenital hyperinsulinism is caused by mutations in potassium channel genes (SUR1 and KIR6.2), glutamate dehydrogenase, glucokinase and short-chain acyl CoA dehydrogenase (SCHAD) (61). Exogenous insulin or insulin secretagogues should also be considered (62).

The initial treatment of hypoglycemia should be with feeding, IV dextrose or glucagon (if due to hyperinsulinism) to raise and maintain the plasma glucose ≥ 3.8 mmol/L (70 mg/dL) (63). Treatment and prevention of further hypoglycemia depends on the etiology. Patients are managed with frequent feedings, avoidance of fast, and, in older children, uncooked cornstarch can be used to facilitate an overnight fast. Patients with congenital hyperinsulinism may require high rates of glucose infusion (GIR 10–30 mg/kg/min) until definitive management can be initiated. Many of these patients respond to treatment with diazoxide. However, patients with mutations in potassium channel genes (SUR 1, Kir6.2) often do not respond to diazoxide and may require additional treatment, such as octreotide,

until definitive surgical management either with focal or subtotal pancreatectomy can be done depending on the presence of focal or diffuse disease (64).

The major long-term effects of severe, prolonged hypoglycemia are cognitive impairment, recurrent seizure activity, or both (65,66). Subtle effects on personality are also possible but have been less clearly defined. Permanent neurologic sequelae are present in 25–50% of patients with severe recurrent symptomatic hypoglycemia who were hypoglycemic at younger than 6 mo of age (64). These sequelae may be reflected in pathologic changes characterized by atrophic gyri, reduced myelination in cerebral white matter, and atrophy in the cerebral cortex (10,67–69).

HYPOGLYCEMIA AND DIABETES

Hypoglycemia is the limiting factor in the glycemic management of insulin-treated diabetes (1). Absolute therapeutic insulin excess of sufficient magnitude can cause isolated episodes of iatrogenic hypoglycemia and in its extreme manifestations, hypoglycemia, can lead to permanent sequelae and even death (70–74). Most episodes in diabetic patients are the result of the interplay of relative or mild to moderate absolute therapeutic insulin excess and compromised physiologic defenses against falling blood glucose concentrations. The pathogenesis of hypoglycemia in insulin-treated diabetes typically involves no decrease in circulating insulin (which has been given exogenously), lack of glucagon secretion, and an attenuated increase in sympathoadrenal (both adrenomedullary and sympathetic neural) activity. In this setting, prior hypoglycemia, exercise and sleep result in the clinical syndromes of defective glucose counterregulation and hypoglycemia unawareness. These constitute the concept of hypoglycemia-associated autonomic failure (1). Defective glucose counterregulation is associated with a 25-fold (75) or greater (76) increased risk of severe iatrogenic hypoglycemia and hypoglycemia unawareness is associated with a 6-fold increased risk of severe hypoglycemia (77). Severe hypoglycemia has been defined as a blood sugar resulting in altered mental status resulting in the patient being unable to assist in their own care; this includes episodes associated with loss of consciousness or seizure requiring glucagon or parenteral glucose therapy (78). Severe hypoglycemia is more common among infants and adolescents and in those patients with lower glycosylated hemoglobin (HbA1c) and longer duration of the disease (79–81).

There is no consistent value of blood glucose used to define hypoglycemia for children with diabetes. Nevertheless, the ADA Workgroup suggested using a self-monitored glucose concentration of 3.9 mmol/L (70 mg/dL) as the definition in all age groups for research purposes in evaluating therapies designed to alter frequency of hypoglycemia (12). This level represents a glucose concentration near the lower limit of the post-absorptive range (3.9–6.1 mmol/L; (70–110 mg/dL)) and the threshold for activation of counterregulatory hormones (3.6–3.9 mmol/L; (65–70 mg/dL)) in non-diabetic patients, but is higher than the level of hypoglycemia required to produce symptoms and cognitive dysfunction in non-diabetic and well-controlled diabetic patients (78,82,83).

Although hypoglycemia is a rare disorder for healthy subjects it is a fact of life for people with T1DM or T2DM on insulin secretagogue or insulin therapy. They suffer untold numbers of episodes of asymptomatic hypoglycemia, an average of two episodes of symptomatic hypoglycemia per week, and one episode of severe hypoglycemia, often with seizure or coma, per year. Although the risk is low early in the course of T2DM, hypoglycemia becomes progressively more frequent, approaching the frequency in T1DM, as people with T2DM develop absolute endogenous insulin deficiency (1,84,85). With the new intensive insulin regimens and the use of insulin analogs, data suggest that despite continuously declining mean HbA1C levels the rate of severe hypoglycemia of

hypoglycemia has decreased to 8–30 episodes per 100 patient-years of diabetes exposure and more recently plateau (79) (80,86–88). Hypoglycemia can interfere with school and social activities. It can be disabling presenting with recurrent seizures, cognitive dysfunction, particularly in those diagnosed before the age of 5 years (89) and can cause changes in the white and gray matter of developing brains (90). Hypoglycemia can be fatal. Recent reports suggest that 6 to 10% of people with T1DM die from hypoglycemia (91–93). Multiple cases of previously well patients with type 1 diabetes experiencing sudden, unexpected death, have occurred while the patient sleeps during the evening. This is known as the “dead in bed” syndrome. It has been thought to be due to cardiac arrhythmias, particularly prolonged QT (94). Mortality rates in T2DM are as yet unknown, but deaths due to hypoglycemia have been documented (1).

Hypoglycemia may be precipitated by missed snack/meal, wrong dose of insulin, exercise (during and several hours after), alcohol ingestion and sleep (95). The effect of exercise has been demonstrated in the Diabetes Research in Children Network study (DirecNet), which reported hypoglycemia during exercise in 22% of subjects and overnight following exercise in 42% compared to only 16% in patients after a sedentary day (96). The goal of treatment in hypoglycemia is to restore the blood glucose level to euglycemia (4.4–5.6 mmol/L (80–100 mg/dL)) and prevent recurrent hypoglycemia. During non severe hypoglycemic episodes patients require immediate treatment with oral, rapidly absorbed, simple carbohydrates and in severe hypoglycemia, patients can be treated with intravenous dextrose or intramuscular glucagon (0.5 mg for age <12 yr, 1.0 mg for ages >12 yr,). It is of key importance to determine the precipitating factors of the hypoglycemic episodes to prevent these from happening again. Comorbidities such as celiac disease or Addison’s disease may also increase the risk for hypoglycemia. Appropriate treatment of these may reduce the frequency of hypoglycemia (97,98). Short-term scrupulous avoidance of hypoglycemia reverses hypoglycemia unawareness and improves defective glucose counterregulation (99–102). Evidence from research studies of the use of continuous glucose monitoring (103) and potential pharmacologic interventions with KATP agonists, beta-adrenergic agonists, SSRIs, opioid agonists, may be shown to be effective in the prevention of hypoglycemia and HAAF (104–110)

Once the mechanism causing hypoglycemia is determined, it should be aimed to either correction of that disorder or if that is not possible, to attain measures to reduce the likelihood of recurrent hypoglycemia with its attendant morbidity and potential mortality.

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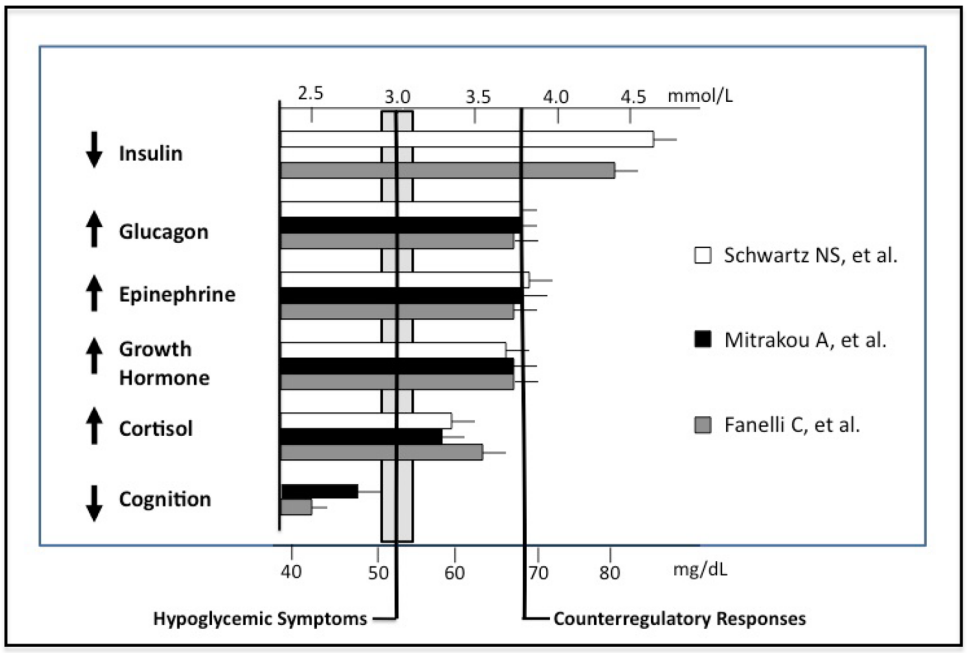

Figure 1.
Glycemic thresholds for physiological responses to hypoglycemia. Adapted from Cryer PE. Hypoglycemia. Pathophysiology, Diagnosis and Treatment. New York: Oxford University Press, 1997, pp. 184, with permission from the author and publisher.

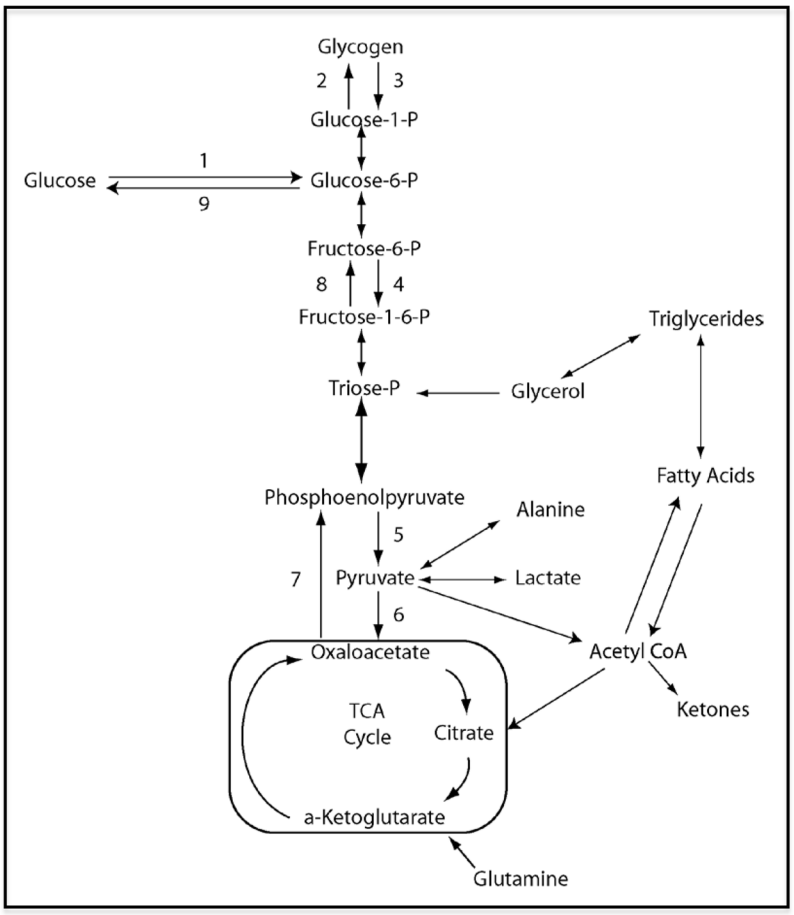

Figure 2.

Schematic representation of glucose metabolism. 1: Hexokinase/glucokinase, 2: Glycogen synthase, 3: Phosphorylase, 4: Phosphofructokinase, 5: Pyruvate kinase, 6: Pyruvate carboxylase, 7: Phosphoenolpyruvate carboxykinase, 8: Fructose-1,6-biphosphatase, 9: Glucose-6-phosphatase.

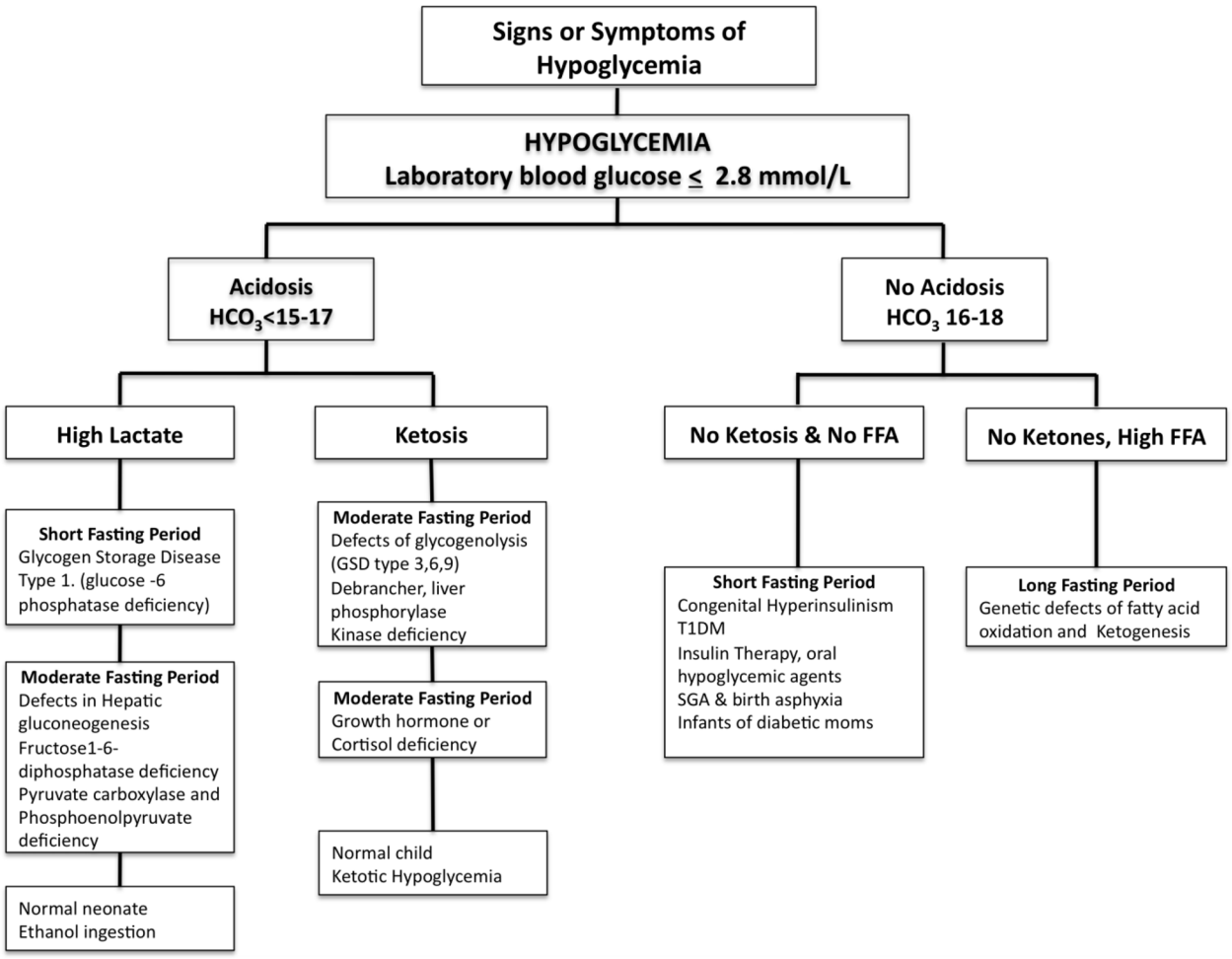

Figure 3.

Diagnostic approach to hypoglycemia in infants and children. Adapted from Shepherd SP, Kalla A, Arbelaez AM. Endocrine Diseases, Chapter 14. In: Dusenbery SM, White A, eds. The Washington Manual of Pediatrics. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins, 2009;198–222. Adapted from the original with permission from the publisher.