EDITORIAL (SEE MUSEN ET AL., P. 1933)

Glycemic Control and Hypoglycemia

Is the loser the winner?

Glycemic control remains a delicate balancing act. The diabetic patient is tasked with maintaining euglycemic blood glucose levels, a goal requiring education, decision strategies, volitional control, and the wisdom to avoid hyper- and hypoglycemia, with the latter defined as plasma glucose less than ~60 mg/dl. Glucose levels must be controlled continuously and without holidays. Failure to maintain euglycemia results from biological factors and psychosocial factors including overmedication and/or inappropriate choices regarding food, drink, and, in certain cases, exercise.

Diabetic patients, especially those treated with insulin, are at risk for developing hypoglycemia. Treatment, even with oral agents such as sulfonylureas, increases this risk. Asymptomatic episodes of hypoglycemia may constitute up to 10% of a 24-h period in diabetic patients (1,2). Individuals with type 1 diabetes average 43 symptomatic episodes annually; insulin-treated individuals with type 2 diabetes average 16 episodes (3). As for severe hypoglycemic episodes, patients with type 1 diabetes experience up to two episodes annually, whereas patients with type 2 diabetes experience about one episode over 5 years. The risk increases with a history of hypoglycemia and an increased number of years of insulin treatment (3,4).

Hypoglycemia deprives the brain of the constant supply of glucose needed for energy. Such low levels of blood glucose are sensed by the ventromedial hypothalamus (5). In turn, a counterregulatory hormonal cascade is activated to rapidly restore euglycemia that begins with inhibition of insulin secretion. Thereafter, the release of glucagon and epinephrine elevates endogenous glucose production through increased hepatic glycogenolysis and gluconeogenesis, as well as renal gluconeogenesis. Growth hormone and cortisol are slow-acting adjustments to prolonged hypoglycemia (6). Hypoglycemia may promote oxidative stress and neuronal cell death, primarily as a consequence of neuronal NADPH oxidase activation and extracellular zinc release during glucose reperfusion. Thus, heightened glucose concentrations during reperfusion can lead to cell death (7). Counterregulatory responses also stimulate the sympathetic autonomic nervous system, resulting in symptoms of sweating, trembling, anxiety, hunger, and nervousness. Deprivation of glucose triggers neuroglycopenic symptoms, including confusion and irritability (8).

Severe hypoglycemic episodes often occur during sleep, when the intensity and recognizability of counterregulatory responses tend to be diminished, thereby depriving individuals of the adequate stimulus to counteract hypoglycemia (9). These episodes, termed nocturnal hypoglycemia (NH), may result in part from insufficient food intake and/or inappropriate insulin dosage the previous evening. Asymptomatic NH is a relatively common phenomenon affecting up to 50% of adults and 78% of children and lasting as long as several hours (10). Moreover, NH is suspected to contribute to the "dead-in-bed syndrome" that leads to the mortality of 6% of type 1 diabetic individuals below the age of 40 years (11).

In addition to NH, individuals may also fail to recognize hypoglycemic episodes during the day. Such desensitization is due to decreased neuroendocrine responses to hypoglycemia that dampen symptomatic responses (12). Men are more prone to desensitization, whereas women inherently exhibit decreased counterregulatory responses to hypoglycemia (13). Thus, in both sexes, the warning signs and symptoms of hypoglycemia are typically not exhibited until blood glucose drops to dangerously low levels. Even two episodes of moderate hypoglycemia are sufficient to decrease counterregulatory hormonal responses to hypoglycemia (14). Hence, as has been said, hypoglycemia begets hypoglycemia (15).

Hypoglycemia-associated autonomic failure may also result from intense physical activity. Exercise-induced hypoglycemia occurs up to 17 h after cessation of physical activity and can result from increased insulin sensitivity and glucose utilization. Furthermore, counterregulatory responses may be reduced by 50% during hypoglycemia following moderately intense exercise (16).

From a practical perspective, a 10-s "sprint" of maximal effort immediately before or after moderately intense physical activity may reduce the rapid fall in glucose level associated with exercise. The sprint stabilizes glycemia in the period of early recovery from exercise, possibly by facilitating the release of counterregulatory response hormones (17,18).

Fear of hypoglycemia

While the symptoms of hypoglycemia alert individuals to an impending episode, these warning signs can diminish quality of life and reduce glycemic control. These symptoms may elicit anxiety and fear of future hypoglycemia. In addition, the observation of a hypoglycemic event may elicit even greater fear in family members (19) and in nondiabetic spouses than in the patient (20). Hypoglycemic episodes may provoke marital conflict regarding diabetes management (21), and such experiences of stress and conflict can further raise glucose levels (22). Finally, in an effort to prevent future hypoglycemic episodes, an individual may resort to behaviors (e.g., reducing or eliminating insulin dose and/or consuming high–glycemic index food) that increase glucose levels.

The subjective experience of hypoglycemia is influenced by ambient glucose levels. Higher resting levels of glucose may falsely increase an individual's sensitivity to the symptoms of hypoglycemia. Thus, preventative action may be initiated to increase blood glucose levels that are already above normal, thereby further worsening glycemic control. On the other hand, tight glycemic control can lead to hypoglycemia desensitization and reduced recognition of symptoms, thus risking a more severe drop in blood glucose (23). Hence, good glycemic control may constitute a Pyrrhic victory.

The inconsistent outcomes of tight glycemic control have spawned extensive

literature designed to examine its antecedents and consequences. One such consequence, recurrent hypoglycemia, has been linked to neuronal and retinal cell death, reductions in gray matter, persistent cognitive dysfunction, and even developmental growth deficiencies (24–27). The Diabetes Control and Complications Trial (DCCT) was initiated in 1983 to examine the beneficial effects of tight glycemic control on reducing diabetes comorbidities. The study's principal finding was that intensive therapy selectively reduced diabetes-related complications compared with conventional therapy (28). However, improved glycemic control came with a cost: severe hypoglycemic episodes. Severe hypoglycemic episodes—those requiring assistance of another individual to avoid or respond to seizure or coma—occurred three times more often in the intensive therapy group. Hypoglycemia was a factor in the deaths of at least three individuals participating in the DCCT and was found to contribute to 2–4% of deaths in diabetic patients (28,29).

One important conclusion from these studies was that hypoglycemia was not an equal opportunity outcome. Moderating these outcomes are age, sex, severity of hypoglycemia, number of such events, certain diabetes and hypertension medications, and disease duration (13,14,30–32). When is tight control a form of glycemic hormesis?

The stability of blood glucose levels is complicated by several factors, including circadian rhythms, stress, insulin sensitivity, and time of day (33). In addition, certain genetic factors (e.g., levels of ACE) can predispose diabetic patients to severe hypoglycemia (34). Furthermore, a recent study has shown that current smokers have an increased risk for severe hypoglycemia, which the investigators attributed to the decreased insulin clearance associated with smoking (35).

Short-term consequences

The acute sequela of mild hypoglycemic episodes includes decrements in motor skills, visual acuity, auditory processing, mood, and a variety of cognitive processes (36–40). It is unclear whether age moderates the level of decline exhibited with mild hypoglycemic episodes. However, hypoglycemic criteria can vary by age: healthy children may experience hypoglycemia-induced neurological impairment at 75 mg/dl and healthy young adults at 54 mg/dl (41).

The rate at which glucose decreases in acute hypoglycemia also affects cognition. In a hyperinsulinemic clamp study with type 1 diabetic adults in the postprandial state, a fast decline in blood glucose following rapid-acting insulin injection reduced the counterregulatory response and increased cognitive dysfunction (42).

Long-term consequences

The longitudinal study by Musen et al. (43) featured in this issue of *Diabetes Care* concluded that despite many severe hypoglycemic events, there was no measurable decline in cognition over ~18 years. While their summary is generally accurate, more detailed examinations may be inconsistent with their conclusion. First, potential participants were excluded from the DCCT if they had a history of severe hypoglycemic reactions, thus limiting the generalizability of the study. Second, 74 individuals chose to discontinue their participation in the Musen et al. study (43), and only 18 of these individuals were accounted for, leaving 56 potential participants unaccounted for. Perhaps these 56 people suffered from more severe hypoglycemic events and/or related cognitive deterioration and terminated their participation. Thus, this discontinuance may be an instance of nonrandom dropout. To further address this possible source of bias, the presentation of complete baseline data for the dropouts would have been useful. Third, it was unclear how old the individuals were when they experienced each severe hypoglycemic episode. Fourth, the statistical support for evaluating the possible synergistic effects of hyperglycemia and hypoglycemia on cognitive function was not reported. The association between elevated A1C and poorer cognitive performance gives more urgency to the possible association of cognition with hypoglycemic and hyperglycemic episodes (28,43,44). Finally, the adolescent sample was of above-average intelligence at the start of the DCCT (IQ ~110) and included relatively few minorities. In summary, despite this study's wealth of data, the relationship between hypoglycemia and cognition remains somewhat difficult to decipher.

Contradictory findings

Studies on the long-term effects of severe hypoglycemia on cognition have produced mixed results. The age at which severe hypoglycemic episodes occur moderates the effects on cognition (27,30,45). Brain developmental stages before adolescence provide a unique resource for evaluating acute and chronic effects of hypoglycemia on cognition. For example, structural abnormalities existed in the occipital lobes of 82% of newborns who experienced severe non–diabetes-related hypoglycemia and led to visual impairment in half of the sample (46). Recurrent moderate hypoglycemia in infants resulted in reduced head circumference and lower psychometric scores at age 5 years (27). Several studies conducted on children (ages 5–18 years) have found that the number of hypoglycemia-induced seizures was a predictor for decreased motor skills, memory, attention, and verbal IQ (47–49). A similar study on the impact of severe hypoglycemic episodes on children found no impairments in full-scale IQ, planning, or attention but did not examine memory or verbal IQ (50).

It has been suggested that the medial temporal lobe, involved in memory, is particularly sensitive to hypoglycemic insult. Declarative memory (factual memory) and spatial memory have been shown to inversely correlate with the number of severe hypoglycemic episodes in children (51,52). Even mild hypoglycemia during sleep impaired consolidation of declarative memory (53). Thus, in children, hypoglycemia may have both an immediate and long-term effect on declarative memory.

Relatively few studies have examined cognitive effects of hypoglycemia in adult diabetic patients. Adults diagnosed with type 1 diabetes after the age of 19 years exhibited lower full-scale IQ scores as the number of severe hypoglycemic episodes increased (45). Moreover, in hyperinsulinemic middle-aged patients free of diabetes, cognition declined as a result of exposure to hypoglycemic events (54).

Mechanisms secondary to hypoglycemia: adults and children

Hypoglycemia appears to be more closely associated with cognitive problems in children than in adults, although the majority of such studies occur in children. Reduced counterregulatory responses in adults may be responsible for this relationship. We propose that a delayed and weaker counterregulatory effect may be protective, i.e., that the gradual reperfusion of cerebral tissue after a hypoglycemic event may reduce cognitive damage resulting from oxidative stress (7,14). Thus, individuals with an impaired coun-

terregulatory response (adults and the elderly) may be spared the immediate and harmful effects of rapid reperfusion on cerebral tissue.

In addition, acute hypoglycemia may temporarily affect the cardiovascular system; however, in those with endothelial dysfunction, these changes can trigger major cardiovascular events, including myocardial and cerebral ischemia (55). Hypoglycemia also induces distinct modifications in cardiac repolarization (decreases in the height and width of the T-wave and/or lengthened corrected QT interval), which may heighten susceptibility to cardiac arrhythmias (56,57).

Anxiety and depression

Hypoglycemia adversely alters mood. Recurrent hypoglycemia elevates anxiety, depression, and anergia (36,39). Such changes in emotion are usually associated with a decreased self-reported energy level and self-efficacy that can degrade cognitive performance. Of particular importance is that in depression, selective serotonin reuptake inhibitors are associated with a progressively increased risk of severe hypoglycemia (58). Other types of antidepressants may be more appropriate for diabetic individuals with high risk of severe hypoglycemia.

Interacting effects of multiple treatment methods

Additionally, several medications have been shown to increase the risk of hypoglycemia. A selective review of the literature indicates that levothyroxine was associated with an increased risk of hypoglycemia in Japanese patients with liver impairment (59). ACE inhibitors may increase the risk of hypoglycemia in diabetic individuals compared with other antihypertensive drugs, possibly by increasing insulin sensitivity (31). Short-acting insulin analogues (lispro, aspart, and glulisine) have better postprandial glycemic control without intensifying the risk of hypoglycemia compared with human insulin (32). Finally, the insulin pump appears to improve glycemic control, reduce episodes of hypoglycemia, and increase quality of life more effectively than multiple-daily-injection therapy (60).

Oral antihyperglycemic agents, especially sulfonylureas, increase the risk of hypoglycemia. However, third-generation sulfonylureas have decreased the risk of hypoglycemia to 0.8 episodes/1,000 patient-years down from the 5.6 episodes/1,000 patient-years rate associated with second-generation sulfonylureas. Combination therapy with sulfonylureas and insulin remains risky (61).

Antidote to hypoglycemia

Recent animal studies have shown that treatment for brain damage incurred during severe hypoglycemic episodes is possible. The same excitotoxic mechanism that destroys neurons following a stroke is thought to destroy neurons during hypoglycemia. *N*-methyl-D-aspartate (NMDA)- and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor antagonists, currently used to treat stroke patients, are being assessed for efficacy in treating severe hypoglycemia. These studies have shown that these drugs reduced hypoglycemia-induced striatal and neocortical damage, as well as hippocampal seizures (62,63).

Conclusion

Hypoglycemia is a vital issue for patients and their families. Diabetes education can provide patients with options that reduce fear and discourage choices that provide a rationale for poor glycemic control. Finally, until stronger evidence is found, it appears that the benefits of good glycemic control still outweigh the risks. Maintaining balance is key.

LAWRENCE C. PERLMUTER, PHD[1,3]
BRIAN P. FLANAGAN[2]
PARINDA H. SHAH[2]
SANT P. SINGH, MD[3]

From the [1]Department of Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois; the [2]Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois; and the [3]Department of Medicine, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois.

Corresponding author: Lawrence C. Perlmuter, lawrence.perlmuter@rosalindfranklin.edu.

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