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Hypoglycemia: Mechanisms and possibilities of prevention

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Introduction

Intensive glucose control reduces the risk for the development of the microvascular complications of diabetes[1,2]. There is also evidence that suggests that intensive glycose control for 6.5 years reduces the risk of macrovascular complications in type 1 diabetes, 30 years later[3]. Therefore tight glycemic control is recommended in patients with diabetes. One of the limiting factors in achieving tight glycemic goals in patients treated with insulin and insulin secretagogues is hypoglycemia[4].

Episodes of severe hypoglycemia,where a person with diabetes requires the assistance of another person for treatment, are relatively easy to track. However it is rather common that the persons with diabetes who do not have severe neuroglycopenia do not always confirm that their blood glucose is low when they have symptoms associated with hypoglycemia or, because episodes are asymptomatic. The International Hypoglycemia Study Group (IHSG) recently published a position statement on the glucose levels that should be used to define hypoglycemia[5]. The statement has been adapted by the American Diabetes Association and the European Association for the Study of Diabetes (Table 1).

Table 1.

GLUCOSE VALUE	
<70mg/dl	Alert value to take action to prevent further fall in plasma glucose
<54 mg/dl	Sufficient low to indicate serious clinically importan thypoglycemia
Any low value	Severe cognitive impairement requiring external assistance for recovery

Prediction of Hypoglycemia

Intensive glucose control has been linked with increased risk of severe hypoglycemia. The incidence of severe hypoglycemia in the

DCCT trial the incidence of severe hypoglycemia was three times higher in the intensive treatment group than in the conventional[2]. Like wise in studies with type 2 diabetes like ACCORD, VADT[6,7], the rate of hypoglycemia requiring medical assistance was three times higher in the intensive therapy group compared tothe standard therapy. Both in type 1 and type 2 diabetes patient those with an A1c <6,5% and >9% have the same risk of hypoglycemia[8].

In patients with type 2 diabetes, hypoglycemia is associated with several risk factors including older age, diabetes duration, co-morbidities, intensified treatment, current insulin treatment and duration of insulin treatment. Moreover in theACCORD study severe hypoglycemia was associated with sex, race, serum creatinine, age, duration of diabetes, body mass index, albuminuria, educational level, Insulin use and higher HbA1c[9]. Recent analysis of the ACCORD indicated that c-peptide or GAD antibodies may predict severe hypoglycemia and mortality in type 2 diabetes[10].

Consequencies of Hypoglycemia

1. Cardiovascular disease and mortality

Severe hypoglycemia has been associated with increased risk of cardiovascular death both in the ACCORD and the ADVANCE trial. The mechanisms of increased mortality among patients with severe hypoglycemia is under current investigation but there is evidence to support that cardiac ischemia or arrythmias may play a role especially in patients with cardiac autonomic neuropathy[11]. The catecholamine release induced by hypoglycemia have been described to cause cardiac arrythmia, increased thrombogenesis, inflammation and vasoconstriction leading to cardiovascular disease and death.

2. Cognition

In the DCCT trial there was no evidence of long term declines in cognitive function in patients with type 1 diabetes who were followed for an average of 18 years despite high rates of recurrent severe hypoglycemia[12]. In the ACCORD study, subjects in the lowest tertile of performance on a cognitive test at baseline had a significantly higher risk of experiencing hypoglycemia during the subsequent twenty months compared to the subjects who performed better on the same cognitive test[13].

From the available trials it is not clear if severe hypoglycemia causes dementia or if pre-clinical forms of cognitive dysfunction increase the risk of severe hypoglycemia.

3. Health Economics and Quality of Life

Hypoglycemia has significant health care economic burden on the society through frequent emergency room visits, ambulance utilization and hospitalization costs. Hypoglycemia also affects the economic wellbeing of the individual. Recurrent hypoglycemic episodes result in lost work-time and reduced work productivity[14].

The fear of hypoglycemia also has a significant impact on the quality of life of patients and their families. The fear often limits adherence to treatment regimens leading to persistent hyperglycemia both in type 1 and type 2 diabetes[15].

Physiology and Pathophysiology

In normal individuals plasma glucose is kept within a narrow range (70-100 mg/dl). When the plasma glucose fall below this threshold the body initiates physiologic responses in order to raise the plasma glucose level. Plasma glucose <80 mg/dl reduces the secretion of insulin from the pancreas which ensures maintenance of normoglycemia. If blood glucose continues to fall, glucagon is released at a blood glucose level of 65 mg/dl. At this glucose level the sympathetic nervous system gets activated resulting in epinephrine and norepinephrine release. These responses increase hepatic glucose production and reduce glucose uptake into muscle and fat to achieve return to normoglycemia. In addition, the activation of the sympathetic nervous system leads to the appearance of adrenergic symptoms[16].

In patients with type 1 diabetes or advanced type 2 diabetes where pancreatic beta cell function is absent, the first defense mechanism preventing hypoglycemia is lost. These patients are unable to reduce the secretion of insulin since insulin is injected. They also lose the ability to release glucagon in response to hypoglycemia and they depend only in the activation of the sympathoadrenal system to prevent hypoglycemia which is also diminished after almost 15 year duration of the disease (17 gerich). Consequently they get exposed to repeated hypo-

glycemias which reduces the glucose level at which the sympathetic response is elicited and reduce the magnitude of the response. As a result patients may not trigger the counterregulatory response until the blood glucose level is below the level associated with neuroglycopenia[18]. This situation is called hypoglycemia unawareness and is associated with 6-fold increase of the risk of iatrogenic hypoglycemia[19].

Prevention of Hypoglycemia

The ADA working group on hypoglycemia recommends that persons with diabetes become concerned about the possibility of developing hypoglycemia when self-monitoring concentration is falling rapidly or equal or below 70 mg/dl[20]. This concentration should be taken as an alert value to take action to prevent further fall in plasma glucose.

1. Education

Patients need to be educated in understanding the risk for developing hypoglycemia so they are able to prevent it. The greatest risk is excessive insulin on board for their physiological needs (insulin or secretagogues), especially when exogenous glucose delivery is decreased (missed meals, fasting, gastroparesis or celiac disease), when glucose utilization is increased (shortly after exercise), when endogenous glucose production is decreased (alcohol ingestion), when insulin sensitivity is increased (middle of the night, weight loss) or when insulin clearance is decreased (renal failure). Education should be provided in individual sessions or group classes (21 Amiel). Programs like DAFNE and BGAT (Blood Glucose Awareness training) have been shown to be effective in reducing the risk of hypoglycemia[22].

2. Technology

Continuous glucose monitoring (CGM) with real time glucose readings, is an important tool in assessing glucose trends while displaying the direction and rate of change of interstitial blood glucose. The recently published DIAMOND trial showed that CGM use, decreased the time spent with glucose values less than 70 mg/dl during the day and night in patients with type 1 diabetes[23].

Recent advances in technology, include continuous glucose monitors coupled to an insulin pump. In one system, insulin infusion is suspends for up to two hours if glucose falls into hypoglycemic range[24]. In the latest sensor augmented pumps insulin infusion is suspended if the if user is below 140 mg/dL and is predicted to be below 70 mg/dl in 30 min and resumes if user is above 80 mg/dL and is predicted to be at or above 110 mg/dl in 30 min and insulin has been suspended for at least 30 min[25].

Data on the Artificial Pancreas show consistent reduction in overnight low blood glucose index and a shortening of time below 70 mg/dl over a 24 hr period by about 20 minutes compared with control treatment. Incidence of severe hypoglycaemia is very low[26].

3. Transplantation

Pancreas and, now, islet transplants can effectively prevent hypoglycemia and restore normoglycemia and may stabilize the complications of T1D. Patients with T1D who undergo an islet or a pancreas transplant exhibit recovery of physiologicislet cell hormonal responses to insulin-induced hypoglycemia whereby endogenous insulin secretion is suppressed and glucagon secretion restored, although in islet transplant recipients, the glucagon response remains partial likely due to lower islet mass compared to organ transplantation. Both islet and pancreas transplant recipients also have improved epinephrine and normalized autonomic symptom responses to hypoglycemia, providing evidence of amelioration of hypoglycemia-unwareness[27-29].

In type 2 diabetes hypoglycemia can be prevented with avoidance of secretagogue antidiabetic drugs and use of premixed insulin regimens. The use of metformin, DPP-4 inhibitors, SGLT-2 agonists and their combinations are preferred for the prevention of hypoglycemia[30].

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