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Approach to Hypoglycemia

Benny Negalur

DEFINITION

Normally blood glucose levels are tightly regulated between 70 to 150 mg/dl in healthy persons. Hypoglycemia, defined as blood glucose levels of less than 70 mg/dl, occurs as a consequence of fasting for longer than 24 hours or in disease conditions including insulinomas, Addison's disease, pituitary failure, diabetes, etc.

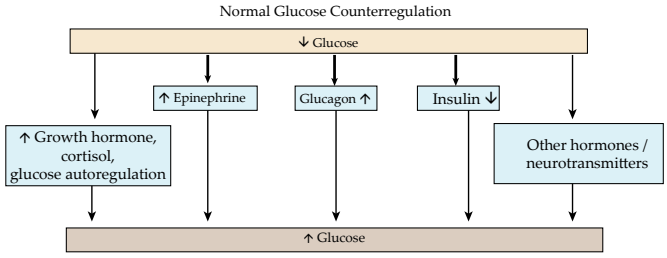
Allen Whipple first described the clinical diagnosis of hypoglycemia which includes the symptoms of hypoglycemia, low circulating plasma glucose and prompt relief of symptoms after glucose administration called Whipple's triad.

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have both clearly demonstrated that intensive control of type 1 diabetes mellitus (T_1DM) and type 2 diabetes mellitus (T_2DM) delays the onset and slows the progression of long-term microvascular complications. However, in both T_1DM and T_2DM, intensive versus conventional glucose control also contributes to a significant increase in severe hypoglycemia. In fact, the DCCT found a three-fold increase in severe hypoglycemia (blood sugar less than 50 mg/dl where the patient needed external resuscitative assistance) when hemoglobin A_1c (HbA_1c) was 7.2% as compared to 9.0%.

ETIOLOGY

In all diabetic patients, hypoglycemia can be caused by excess exogenous insulin administration (and the use of some oral agents in T_2DM), lack of appropriate food intake and reduced physiologic defenses against falling blood glucose (lack of ability to recognize and treat as well as abnormal counter regulation). Also, insulin clearance is decreased by renal failure which contributes to a relative hyperinsulinemia and subsequently a rapid lowering of blood glucose.

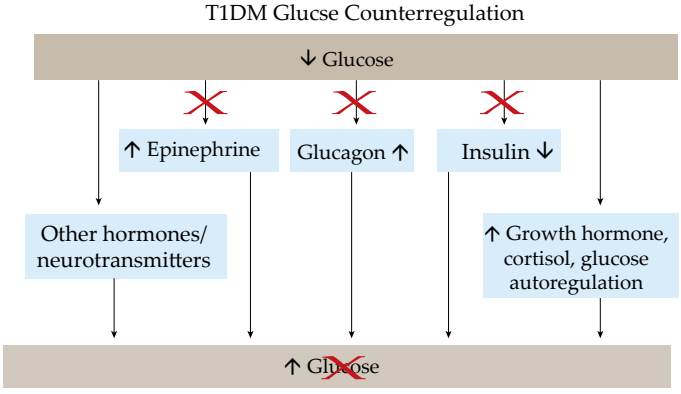
PATHOPHYSIOLOGY

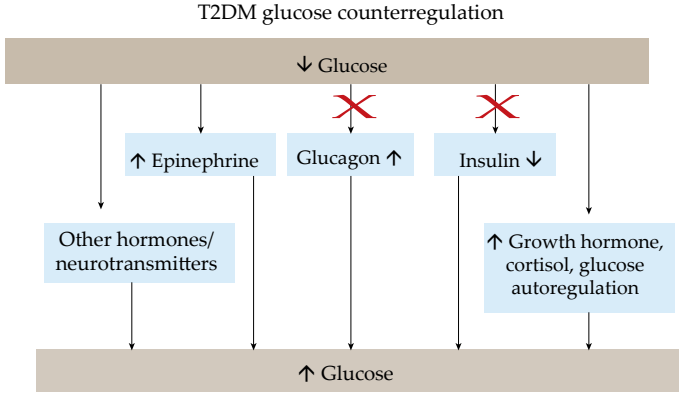


In normal individuals when blood glucose level falls, a variety of autonomic and neuroendocrine hormonal defense mechanisms are initiated by glucose sensors in the hypothalamus. There is also stimulation of the alpha cell sensors to release glucagon and β cells to suppress endogenous insulin. Glucagon increases glucose output by the liver via glycogenolysis and gluconeogenesis and reduces glucose uptake by the periphery, thus providing adequate glucose to the brain. Epinephrine also stimulates lipolysis and skeletal muscle glycogenolysis, providing substrates (alanine, lactate, and glycerol) for gluconeogenesis in the liver. Other hormones, like cortisol and growth hormone, play a role in prolonged hypoglycemia (longer than 2 hours).

In T_1DM patients, loss of endogenous insulin removes one of the many defenses.

They also have impaired glucagon response which results in reduction of glucose recovery. T_2DM patients do have endogenous insulin and so incidence of hypoglycemia is small as these people have binge eating responses. However, in advanced T_2DM, the counter regulatory mechanism does get compromised and hypoglycemia can be prolonged.





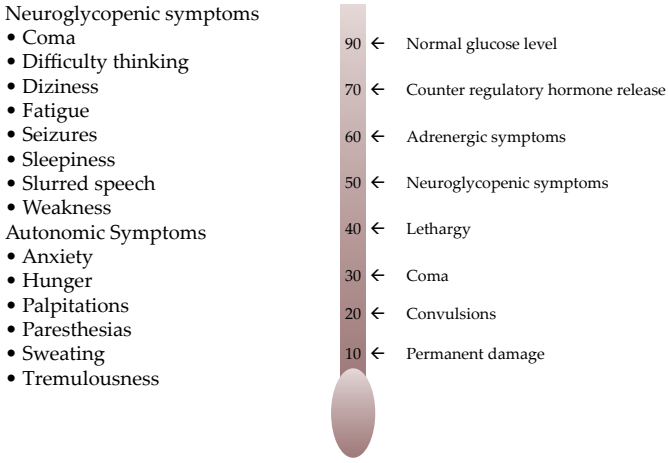


Fig. 1: Symptoms of Hypoglycemia

HYPOGLYCEMIA ASSOCIATED AUTONOMIC FAILURE - HAAF

In recurrent hypoglycemic attacks, prior episodes blunt the autonomic nervous system (norepinephine + epinephrine), neuro endocrine (glucagon, cortisol and growth hormone) and metabolic (endogenous glucose production) counter regulatory responses to subsequent episodes. This can occur within hours with sugars as little as 70 mg/dl known as hypoglycemia associated autonomic failure. HAAF produces a vicious cycle making the patient susceptible to both deeper and more frequent episodes of hypoglycemia. Inability to recognize the symptoms of hypoglycemia due to blunting of the above systems is known as hypoglycemia unawareness.

HYPOGLYCEMIA IN INSULIN TREATED PATIENTS

The goal of insulin treatment is to reproduce the normal physiologic insulin secretion of healthy persons. Regular insulin has a time of onset of 30 minutes, a peak of 2 hours and duration of action of 4 to 6 hours in most patients. This was inconvenient for patients, requiring them to wait 30 minutes after an injection to consume their meal. This regimen can also create a problem for glucose control because blood glucose could peak before insulin action, resulting in postprandial hyperglycemia and later pre-prandial hypoglycemia.

Shorter-acting insulin analogs (aspart and lispro) are used either as multiple-dose injections (MDIs) or in a continuous subcutaneous infusion (CSII; insulin pump). The molecular structure of lispro and aspart allow for rapid onset of action, within 10 minutes, peak is at 90 minutes, and duration of action is 2 to 4 hours in most patients. In fact, several studies have reported that lispro and aspart produce similar or even better glucose control and reduce hypoglycemia compared to regular insulin, probably because they better match the timing of insulin peak and action with food absorption. This unique property allows patients to calculate their actual food intake and dose their insulin much like the normal pancreatic insulin response in non-diabetic persons. In addition, the fast action of these analogs allows patients to inject immediately after a meal if they were unsure how much food was going to be consumed. This will also reduce postprandial hypoglycemia and may be useful in treating gastroparesis.

Traditional long-acting insulin's (NPH, Ultralente, glargine) can contribute to an increased rate of hypoglycemia. This is due to their pharmacokinetics, with a rapid onset of action (1 to 2 hours and a broader peak at about 4 hours) that may rapidly decline within 8 to 16 hours. Bedtime injections can lead to nocturnal hypoglycemia because action peaks at about 2.00 am, when patients are more insulin sensitive. Conversely, NPH action wanes in the early morning hours when patients are more insulin resistant (dawn phenomenon), making hyperglycemia a problem. Glargine, a new basal insulin analogue, produces very little, if any, peak due to its lower solubility at the injection site. Glargine action lasts up to 24 hours and provides the closest to physiologic basal insulin coverage of the long-acting insulin's. The newer long acting insulin basal analogue degludac produces less hypoglycemia like glargine.

HYPOGLYCEMIA WITH ORAL AGENTS

Oral agents have lower reported rates of hypoglycemia compared with multiple doses of traditional insulin's. Oral insulin secretagogues such as sulfonylurea agents or meglitinides bind to the sulfonylurea receptor in the pancreatic beta cell, which causes insulin secretion. The onset and duration of action might not coincide with the ambient blood sugar either due to an inaccurate dose or a lack of carbohydrate intake, or both. This in turn leads to over-secretion of insulin in relation to the blood glucose, which causes relative hyperinsulinemia.

Reported rates of hypoglycemia in patients with T2DM are reported to be 7-fold to 10-fold lower with glimepiride 2nd generation as compared with glyburide which is a 1st generation SU. The newer agents like DPP4 inhibitors, GLP receptor agonists and SGLT2 are higher than inhibitors generally do not cause hypoglycemia, but they may induce it when combined with insulin or sulphonylureas. The hypoglycemia induced by oral agents tends to be of longer duration and most of the times require parenteral treatment with glucose.

HYPOGLYCEMIC SYMPTOMS

The onset of hypoglycemic symptoms in healthy subjects occurs at plasma glucose levels between 49 and 58 mg/dl. Symptoms are categorized as neuroglycopenic or autonomic. Neuroglycopenic symptoms are caused by low cerebral glucose levels there is a gradual order of symptoms as the blood glucose decline as shown below:

The threshold of absolute plasma glucose that triggers these symptoms may be higher (conventional control) or lower (intensive control) depending upon the overall glycemia control of the patient. In other words, patients who tend to have a higher HbA_1c percentage (overall higher ambient blood sugars) can perceive symptoms of hypoglycemia at a higher plasma glucose level than patients whose glycemia is more intensively controlled. This is particularly true for patients with T_2DM, who can perceive hypoglycemia symptoms at blood glucose levels greater than 100 mg/dl, which is termed relative

hypoglycemia. The converse is true in those patients whose glycemia is intensively controlled might not recognize low blood sugar until their plasma glucose is much lower. Hypoglycemia that requires assistance from another person to treat it is severe hypoglycemia.

TREATMENT

The "rule of 15" is a helpful treatment regimen when patients are able to self treat. Typically 15 gms of carbohydrate (rapidly absorbing forms of glucose such as glucose gel, sugar containing soda or sugar tablets should raise the blood glucose by 50 mg/dl glycemia in 15 minutes. The response to oral glucose is transient; therefore ingestion of a small complex carbohydrate snack shortly after the plasma glucose concentration rises is generally advisable, especially if the next meal is larger than 1 hour away.

Hypoglycemic patients who are unconscious or unable because of hypoglycemia to take in oral carbohydrates can be treated with a parenteral glucagon injection if available.

Intravenous glucose is the preferable treatment of severe iatrogenic hypoglycemia, particularly that caused by a sulfonylurea. These reactions are more likely to occur in elderly patients in whom hypoglycemia is often prolonged and require continuous glucose infusion and frequent feeding.

At other times, patients should be instructed to carry with them any form of rapidly available source of glucose at the first sign of hypoglycemia. .

COMPLICATIONS

Other factors influencing incidence of Hypoglycemia are age, exercise, gender and ethanol. Hypoglycemia can increase the QT interval and give rise to various arrthymias which can be detrimental causing sudden death. Increase in inflammatory markers & oxidants stress is known in hypoglycemia.

CONCLUSIONS

Hypoglycemia in a major limiting factor in intensive glycemic control of diabetes. Hypoglycemia is problematic in T_1DM and in advanced T_2DM because of compromised glucose counter regulatory systems. Therefore, patients should be educated in self-monitoring of blood glucose, diet and exercise effectively.

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