Approach to Reactive Hypoglycemia

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Abstract

Hypoglycemia episodes are a real nightmare for physicians and as well as patients. If clinician comes across non-diabetic patients visiting their clinic with symptoms of an episode of hypoglycemia like tachycardia, cold sweats, hunger, tremor, and other autonomic nervous symptoms after 3 to 4 hours of their meal, and during the event, their random blood sugar is <70mg/dl with all adrenergic and neuroglycopenic symptoms usually following a carbohydrate-rich meal diet. This kind of hypoglycemia is known as Reactive Hypoglycemia (RH) or Postprandial hypoglycemia (PPH). This article will help physicians to better understand reactive hypoglycemia diagnosis, differential diagnosis, and management. The categorization of the patient with hypoglycemia is the key to treating and avoiding future hypoglycemic episodes.

Introduction

In nondiabetic patients, reactive hypoglycemia or postprandial hypoglycemia is defined by low blood sugar occurring within 3 to 4 hours post high carbohydrate meal. Patients present with autonomic and neuroglycopenic symptoms due to low blood sugar levels which is <70mg/dl.

Autonomic symptoms that result from epinephrine secretion include tremors, palpitations, anxiety, hunger, paresthesia, and diaphoresis. Neuroglycopenic symptoms that result from glucose deprivation in the brain include dizziness, fatigue, confusion, behavioral changes, blurred vision, diplopia, amnesia, seizure, and loss of consciousness [1].

As per recommendation the term reactive hypoglycemia be reserved for the pattern of postprandial hypoglycemia which meets the ‘Whipple criteria’ (which consist of symptoms of hypoglycemia, low blood glucose concentration, relief of symptoms post increase in blood glucose levels), and that the term idiopathic postprandial syndrome to be used when the patient suffers from the symptoms of hypoglycemia.
without documented low blood glucose levels [2]. The prevalence of reactive hypoglycemia is not fully known. One Scandinavian study showed reactive glucose pattern following intake of a high glycemic load is relatively prevalent and could be modulated by dietary fiber intake [3].

Figure 1 depicts the mechanism during such episode. It’s a vicious cycle of carbohydrate and insulin secretion.

![Figure 1: Representing the mechanism during an acute attack](image)

Reactive hypoglycemia can be categorized into three different forms clinically

1. Alimentary RH (at 120 min)
2. Idiopathic RH (at 180 min)
3. Late RH (240-300 min)

**Types of reactive hypoglycemia**

**Alimentary**

In patients who have gone under vagotomy, gastrectomy, pyeloplasty or esophageal resection, peptic ulcer disease, renal glycosuria, and in patients with altered gastric motility. The disequilibrium between excessive insulin secretion and decreased plasma glucose post 3 to 4 hours due to quick absorption results in postprandial hypoglycemia in patients. Following gastric bypass surgery increase in severe postprandial hypoglycemia is seen. This condition can develop months or even years after bypass surgery. It occurs due to accelerated gastric emptying and may be attributed to the exaggerated incretin effect [4]. An increase in glucagon-like peptides (GLP-1) and gastrointestinal peptides (GIP) which ultimately increases insulin release from beta cells along with suppressing glucagon secretion results in early hypoglycemia.
Pre-diabetes

This kind of reactive hypoglycemia is seen in cases of impaired glucose tolerance (IGT). The physiology of insulin secretion can explain the cause of late reactive hypoglycemia. The disequilibrium between insulin level and glucose level is responsible for hypoglycemia. In patients with prediabetes, the first phase of insulin secretion which lasts about 10 minutes is impaired resulting in increased blood glucose level post-meal, following which there during the second phase which is slow and lasts about 24 hours excess insulin secretion occurs which leads to late reactive hypoglycemia. This may be attributed to insulin resistance syndrome, where the first phase of insulin secretion is impaired along with delayed or decreased second phase insulin release [5].

The episodes of hypoglycemia are usually mild and asymptomatic. The main reason behind hypoglycemia in such cases is delayed secretion of insulin which results in a state of late hyperinsulinemia in response to hyperglycemia. How often this leads to different results in symptomatic hypoglycemia post-meal is not known [6].

Incretins (GLP-1 and GIP) also play a major role in reactive hypoglycemia prediabetes. There is a decreased response of GLP-1 to oral glucose in patients with prediabetes. Incretins help in insulin release from beta cells post-meal. Incretins have a dual function, it increases insulin secretion following a meal and at the same time it suppresses glucagon secretion at 2 to 3 hours, resulting in a decrease in blood glucose levels at 4 hours.

Idiopathic/ Functional (Non-hypoglycemic)

This kind of reactive hypoglycemia is not so common. For this diagnosis to be made patient must have arterial hypoglycemia after everyday meals, which is associated with symptoms of hypoglycemia that are relieved by carbohydrate ingestion, and the patient does not have any other causes associated with reactive hypoglycemia. No exact cause has been identified for such episodes of hypoglycemia [7].

Some of these patients may have an adult form of nesidioblastosis also referred to as noninsulinoma pancreatogenous hypoglycemia which is characterized by symptomatic hypoglycemia occurring post-meal associated with hyperinsulinemia along with increased plasma C-peptide level.

In such kind of cases, patients elicit symptoms of hypoglycemia when mixed meals are administered, but hypoglycemia is rarely observed. In such patients’ days, today blood glucose level rarely falls below 50mg/dl, however during OGTT the decrease of blood glucose <30mg/dl can be seen. OGTT should never be used to assess the presence of reactive hypoglycemia. This is the diagnosis of exclusion, if possible, Whipple’s triad should be established. If the diagnosis is confirmed one should exclude other causes of reactive hypoglycemia. If the diagnosis is not confirmed the treatment for such patients includes restriction of the large carbohydrate-containing meal, psychological counseling, and the use of beta-adrenergic antagonists.

The pathophysiology of functional reactive hypoglycemia is not known to date, probable etiology for this could be due to gastrointestinal insufficiency or dysfunction which leads to relatively increased insulin secretion or increased insulin sensitivity, including some idiopathic functional hypoglycemia. It usually occurs after 2–5 hours post-meal and does not easily attract attention due to the paradoxical nature of hypoglycemia post-carbohydrate-rich meal [8].

Reactive hypoglycemia diagnosis needs clinical acumen due to the similarity of symptoms seen with Insulinoma (rarest tumor of beta cells of the pancreas) and other diseases which causes hypoglycemia and
presents with similar presentation. Repeated episodes of untreated hypoglycemia can result in complications like cognitive dysfunction, anxiety, depression, seizures, falls, arrhythmias, and cardiac arrest [9].

**Diagnosis**

Patients who are evaluated for reactive hypoglycemia need special care, and attention and need proper evaluation. At times they require hospitalization and observation for at least 3 or 4 hours. Diagnosis is often based on mixed meal evaluation.

In absence of diabetes, a thorough evaluation of hypoglycemia is recommended only for patients in whom Whipple’s triad can be demonstrated, in absence of such documentation the evaluation of hypoglycemia saves patients from unnecessary evaluation. Plasma glucose concentration used for documenting Whipple’s triad must be measured from an arterial blood sample [10].

Patients are to be given mixed meals during admission, which should include the reported macronutrient (carbohydrate, protein, or fat) as mixed meals likely produce symptoms in such patients. A mixed-meal tolerance test is considered positive if symptoms like dizziness, fatigue, confusion, behavioral changes, blurred vision, diplopia, amnesia, seizure, and loss of consciousness are present while the patient is hypoglycemic [11]. Protocol for mixed meal test, the patient is asked to do overnight fasting. A mixed meal with a similar component that causes symptoms of hypoglycemia is given to the patient, followed by a collection of blood samples every 30 minutes till 300 minutes. During this period symptoms and signs of hypoglycemia are observed, once the blood sugar is < 60mg/dl, a blood sample analysis of C-peptide, insulin, and proinsulin is performed to document hyperinsulinemia-induced hypoglycemia. Unfortunately, a high percentage of symptomatic patients test negative when using this approach [12].

The measurement of plasma glucose, insulin, proinsulin, C peptide levels, and β-hydroxybutyrate should be ordered during the hypoglycemic episode as defined earlier. Subsequently, administer 1mg intravenous glucagon to the patient, and measure plasma glucose to detect a response [13]. At the time of a hypoglycemic event levels of proinsulin, insulin, and C-peptide are out of proportion for the degree of hypoglycemia in cases of endogenous hyperinsulinism [14,15]. The cut-off values for diagnosis of reactive hypoglycemia are as follows:

- Glucose< 55mg/dl,
- C-peptide >0.6ng/ml,
- Insulin >3microunits/ml,
- Proinsulin > 5mol/L,
- Beta-hydroxybutyrate < 2.7 mmol/L.

Newer technology like continuous glucose monitoring (CGM) has shown promising results in diagnosing such patients, as CGM gives precise values and monitors blood glucose levels every 5 to 15 minutes depending upon the type of sensor. Diagnostic accuracy is improved with the use of CGM which helps in depicting glycemic excursions following a carbohydrate-rich diet. In individuals, without diabetes mellitus, CGM can help diagnose reactive hypoglycemia earlier, which can facilitate early intervention like diet modification, assessment of treatment efficacy, and identification of individuals requiring further evaluation to know the type of reactive hypoglycemia [16].
Treatment

Acute Management

Management of acute episodes of hypoglycemia depends on the clinical status of the patient. Patients presenting with neuroglycopenic symptoms with altered sensorium should be administered Dextrose 25g of through an intravenous route followed by continuous infusion of 5% or 10 % dextrose. In case of no Intravenous access injection glucagon, 1mg is administered intramuscularly and can be repeated after 15 minutes. Patients presenting with autonomic symptoms who are awake can be given 15-20gram glucose orally and the same can be repeated to maintain euglycemia.

The first choice of treatment to treat Reactive hypoglycemia is a dietary modification that consists of a low carbohydrate diet along with high fiber and/or frequent small meals. The patient should be counseled regarding avoiding fast-absorbing sugar drinks and alcohol. Whole-grain carbohydrates should be incorporated into the diet. Diet should include increased consumption of high-fiber fruits and vegetables along with restricting starchy carbohydrates to small portions [17]. Obese patients should be counseled about weight loss as it reduces insulin resistance, which helps in reducing episodes of reactive hypoglycemia.

The patient failing to respond to the same may be considered for a medical treatment which includes: acarbose, metformin, GLP-1 receptor agonists, and Calcium channel blockers. Patients with alimentary hypoglycemia may be benefited from acarbose and metformin. Reactive hypoglycemia with prediabetes type whether with impaired fasting glucose (IFG) or/and Impaired glucose tolerance (IGT) should be started on oral antidiabetic medications along with lifestyle modification.

There is no specific medication available to treat reactive hypoglycemia as of today. Although pharmacologic attempts in treating Reactive hypoglycemia involve diazoxide, α-glucosidase inhibitor, glitazones, metformin, and somatostatin, however, none of these treatments are specifically indicated for the condition. Acarbose is often used for the treatment of postprandial syndrome, but the evidence for its effectiveness is sparse and not definitive [18]. In reactive hypoglycemia cases, few studies have been reported to treat the symptoms with the sustained or extended-release formulation of metformin [19].

Acarbose (Intestinal alpha-glucosidase inhibitors)

Acarbose is an alpha-glucosidase inhibitor that prevents post-prandial surge in glucose level and insulin by competitively inhibiting pancreatic alpha-amylase, which results in a reduction of absorption of carbohydrates and fats from the gut by decreasing the release of gastrointestinal peptide (GIP) from the duodenum. The dose ranges from 6.35-300mg/day in 2-3 divided doses. Adverse effects reported are flatulence, diarrhea, elevated liver enzymes, and intestinal discomfort.

As per the case series published in endocrine practice in 2013, the patient with gastric bypass was reported to have resolved symptomatic postprandial hypoglycemia with acarbose. In this case series, 4 patients (mean age of 43 years) with a post gastric bypass that had postprandial hypoglycemia, unresponsive with a low carbohydrate diet were started on pre-meal acarbose. Out of 4 patients, 1 patient discontinued treatment due to rash, and in the other 3 patients, symptomatic postprandial hypoglycemia resolved with acarbose treatment. During the follow-up of 5-48 months, these patients remained asymptomatic. AGI therapy is effective in the long-term treatment of post-Roux-en-Y hypoglycemia in patients unresponsive to a low-carbohydrate diet. This is the first report documenting the long-term usefulness of acarbose therapy in a series of patients [20].
Calcium channel blockers

The use of nifedipine (Calcium channel blockers) can be useful in treating postprandial hypoglycemia; the secretion of insulin post-meal from pancreatic beta cells can be inhibited by blocking the influx of calcium into beta cells by calcium channel blockers. Nifedipine dosing is 0.25-2.5mg/kg/day in 2-3 divided doses. Hypotension is the primary adverse effect associated with it. As per a Study published in endocrine practice in 2015, 6 patients were treated with dietary modification along with nifedipine (dose >10mg/day) or acarbose (25-100mg three times daily) or both. Patients were followed for 2-64 months. Patients with nifedipine (30mg/day or 90 mg/day) showed complete resolution of symptoms of postprandial hypoglycemia [21].

Incretins

Dipeptidyl peptidase -4 inhibitors (DDP4i): It acts by improving insulin secretion and reducing glucagon secretion thereby reducing hyperglycemia. The incretin effect of DDP4i is glucose-dependent because of the impaired phase of insulin secretion causing hyperglycemia which causes late reactive hypoglycemia, that can be prevented by using incretin-based drugs.

GLP-1 receptor agonist: Liraglutide was reported to resolve symptomatic postprandial hypoglycemia in patients with post-gastric bypass hypoglycemia. Based on case series published in the European journal of endocrinology in 2013, 5 patients (with a mean age of 44 years) with late postprandial hypoglycemia post-gastric bypass surgery were treated with liraglutide 1.2-1.8 mg/day subcutaneously. All 5 patients showed symptomatic resolution of postprandial hypoglycemia with liraglutide treatment. As the treatment was reduced or discontinued symptoms returned in 4 patients [22].

Glitazones

A low dose of 15 mg pioglitazone is effective in patients with IGT along with reactive hypoglycemia [23].

Gut microbiome

Gut microbiota plays an essential role in metabolic disorders, correction of gut microbiota dysbioses may be considered a potential treatment. A high-fiber load diet like Ma-Pi 2 diet has been associated with the production of metabolites that can counterbalance the metabolic deregulation in a person with glucose impairment disorders like reactive hypoglycemia and diabetes.

Discussion

Reactive Hypoglycemia is an emergency condition that needs to be addressed to prevent repeated episodes in the future. The treating physician must try to categorize the patients as per Whipple’s criteria and refer such patients to endocrinologists for further evaluation. (24) The use of CGM sensors or more frequent self-blood glucose monitoring should be encouraged for such patients as this can help in early diagnosis and appropriate management accordingly. The patients along with their families should be counseled about the symptoms associated with hypoglycemia to prevent devastating outcomes associated with the event. Dietitians should counsel patients regarding dietary modifications to avoid future hypoglycemia episodes.

Conclusion

The nondiabetic patients presenting with signs and symptoms of hypoglycemia must be categorized as per Whipple’s criteria to make a diagnosis of reactive or postprandial hypoglycemia. Once the diagnosis of reactive hypoglycemia is suspected patient can be evaluated with a mixed meal test to confirm the same.
The first choice of treatment for patients remains dietary modification, patients failing to respond to the same can be started on anti-diabetic medications and calcium channel blockers. With advancements in medical science, we can expect a proper treatment for reactive hypoglycemia in the future.

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