Review Article

Postprandial hypoglycaemia in adults: pathogenesis, diagnosis and management

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Abstract: Postprandial hypoglycaemia (PPH) develops due to the dysregulated insulin release from pancreatic β-cells in the presence of low blood glucose levels. It is the presenting feature of some rare disorders such as non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS), insulinoma, insulin autoimmunity and hereditary fructose intolerance. It is also a known complication of upper gastrointestinal tract surgery and is increasingly encountered by the physicians following a worldwide rise in bariatric surgery cases. Fasting blood glucose is typically normal in these patients except in those with insulinoma. Hypoglycaemia symptoms are nonspecific; therefore, the fulfilment of Whipple's triad is required to confirm hypoglycaemia. Further evaluation is carried out during an episode of hypoglycaemia which can be provoked by a mixed meal test. The diagnosis of PPH may prove challenging, and the establishment of its underlying aetiology often requires extensive investigations. This includes measurement of blood insulin, proinsulin, C-peptide, free fatty acids, ketones and a wide range of imaging studies. The treatment options are limited. Patients with severe life-threatening hypoglycaemia, unresponsive to dietary modifications and medical therapy, may require surgical intervention. This review provides an overview of various disorders which present with PPH and a systematic approach to its diagnosis and treatment based on the underlying pathophysiology.

Keywords: Endogenous hyperinsulinemia; neuroglycopenia; bariatric surgery; nesidioblastosis

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Introduction

Development of hypoglycaemia in a nondiabetic individual within a few hours of food ingestion is termed as postprandial hypoglycaemia (PPH). It represents a heterogeneous group of disorders characterised by inappropriate insulin secretion from the pancreatic β-cells following a meal, resulting in hypoglycaemia (*Table 1*).

Under physiological condition, insulin secretion from the pancreatic β-cells is precisely regulated in response to changes in plasma glucose concentrations (1). A postprandial rise in blood glucose and release of glucagon-like peptide-1 (GLP-1), an incretin hormone from the small intestine, stimulate insulin synthesis and secretion from pancreatic β-cells (2). As blood glucose falls, the first defence against hypoglycaemia is a reduction in insulin secretion (3,4). When blood glucose falls below 3.8 mmol/L, there is a rapid rise in glucagon and epinephrine secretion to prevent hypoglycaemia. If hypoglycaemia continues, cortisol and growth hormone secretion increase as a delayed counter-regulatory response (3-5). Insulin secretion is completely suppressed at plasma glucose of approximately 3.0 mmol/L or lower (6-8). PPH develops when insulin secretion fails to suppress, in response to falling blood glucose concentrations and normal counter-regulatory response of glucagon and epinephrine is blunted. Excessive insulin suppresses glycogenolysis, gluconeogenesis. Therefore, hypoglycaemia results from reduced glucose production rather than its

Table 1 Causes of PPH

Causes	Disorders
Endogenous hyperinsulinaemia	Insulinoma
	Non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS)
	Upper gastrointestinal surgery
	Insulin autoimmunity syndrome
	Hereditary disorders: congenital hyperinsulinism, hereditary fructose intolerance
Factitious hypoglycaemia	Administration of insulin, sulfonylurea

PPH, postprandial hypoglycaemia.

increased utilisation (4,9). Suppression of lipolysis leads to reduced ketogenesis with no alternative fuel available for cerebral metabolism. Severe hypoglycaemia with a lack of alternative fuels can cause irreversible cerebral damage. Prompt diagnosis and appropriate management of PPH is, therefore, crucial. I present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jlpm-20-102).

Search methodology

An electronic literature search using PubMed for articles published from January 1980 till June 2020, was performed using the keywords—postprandial hypoglycaemia, reactive hypoglycaemia, hyperinsulinemic hypoglycaemia and dumping syndrome. Available publications were reviewed including their reference lists and clinically relevant articles were included.

Causes of endogenous hyperinsulinaemia

Insulinoma

Insulinoma is a rare tumour which causes endogenous hyperinsulinism and typically presents as fasting hypoglycaemia, though occasionally patients develop hypoglycaemia exclusively after meals (10). Rarely it may be associated with familial multiple endocrine neoplasia type 1 (MEN1) syndrome (11). Insulinoma will not be discussed here.

Non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS)

This rare disorder in adults is characterised by endogenous hyperinsulinemia and diffuse nesidioblastosis. Hypoglycaemic symptoms develop within 3–4 hours after a meal while fasting blood glucose is normal (12-15). Imaging studies are negative for insulinoma, and the diagnosis is confirmed by diffuse calcium stimulated hyperinsulinemic response from multiple pancreatic vascular territories.

Its aetiology is unknown. There is no previous history of gastrointestinal tract surgery. It was first described in a group of five patients who had PPH, endogenous hyperinsulinism, normal fasting glucose, negative screening for *SUR1*, *Kir6.2* mutation and pancreatic islet hypertrophy with nesidioblastosis (13). Diffuse nesidioblastosis has been reported in 3% of adults who underwent partial pancreatectomy to treat hyperinsulinemic hypoglycaemia (16). However, it is not clear that hyperinsulinism is solely due to the structural changes in the β-cells, as a previous study demonstrated nesidioblastosis in 36% of autopsy specimens with no history of hypoglycaemia (17).

Post-bariatric surgery hypoglycaemia

PPH is a well-known late complication of upper gastrointestinal surgery (18-22). Although it is seen more often after Roux-en-Y gastric bypass (RYGB) surgery, it may present after gastric sleeve surgery (23). It was first reported in six post-bariatric patients who underwent partial pancreatectomy to treat the symptoms. In these patients, PPH was thought to be due to nesidioblastosis, which was suggested in the pancreatic pathology (24). However, subsequent studies on the same specimens did not confirm nesidioblastosis (25).

Its exact incidence is unknown; one study reported 9.1% and 7.9% incidence at 1 and 5 years, respectively, post-RYGB surgery (20) while another study reported 2.7% and 13.3% incidence at 1 and 5 years (22). Following surgery, rapid transition of food to small intestine causes early and higher glycaemic peak and increased GLP-1 secretion, triggering larger insulin synthesis, leading to a rapid drop in blood glucose, with a nadir in 90 to 180 minutes after meals (26,27). A blunted glucagon response to insulin-induced hypoglycaemia is well documented in patients post-RYGB

compared to the same patients before surgery (28). It is unclear why individual patients who develop hypoglycaemia show much enhanced pancreatic β-cell stimulation and exaggerated GLP-1 response, compared to those who do not develop hypoglycaemia after surgery (29-31). There is also reduced postprandial insulin clearance compared to asymptomatic subjects after this surgery (26,29). Recently bile acids were suggested as a metabolic regulator when postprandial unconjugated bile acids were shown to be high during hypoglycaemia in two patients with RYGB while these were normal in asymptomatic post-RYGB patients (32).

Post-bariatric hypoglycaemia mostly presents at least 6 to 12 months after surgery (10,19) and is associated with neuroglycopenic symptoms which usually appear 1 to 3 hours after meals. Plasma glucose is <2.7 mmol/L and symptoms are relieved with improved blood glucose concentration (10,19). There is no fasting hypoglycaemia. Many patients may develop symptoms of dumping syndrome in the first 6 months of post-bariatric period related to adrenergic stimulation such as perspiration, palpitations, tremor and irritability (33-35).

Insulin autoimmunity

In this extremely rare condition, insulin antibodies or anti-insulin receptor antibodies develop and patient presents with hypoglycaemia which may be in late postprandial state (42%), fasting state (31%) or both (24%) (36-40). Plasma insulin levels are typically high, and antibodies are detected in the plasma. This disorder is discussed in detail in another review.

Congenital endogenous hyperinsulinemia

This disorder is due to dysregulated insulin secretion, secondary to a mutation in specific genes (*ABCC8*, *KCNJ11*, *GLUD1*, *HADH*) which regulate insulin secretion from pancreatic β-cells. It is mainly seen in infants and children (41,42). However, a few milder late-onset forms have been reported in adults (43,44). Patients usually show sensitivity to specific proteins in the meal and develop postprandial hyperinsulinemic hypoglycaemia (42-44). A mutation in *INSR* (insulin receptor kinase) gene leading to impaired insulin clearance and insulin resistance, results in PPH with onset in adolescence to adulthood (45).

Hereditary fructose intolerance

This disorder develops due to aldolase B deficiency. It manifests as PPH following fructose or sucrose ingestion, which leads to accumulation of fructose-1-phosphate, inhibiting glycogenolysis and gluconeogenesis. Several cases have been diagnosed late in adulthood (46,47).

Factitious hypoglycaemia (exogenous hyperinsulinemia)

Exogenous hyperinsulinemia causing PPH, due to surreptitious administration of insulin or insulin secretagogues such as sulfonylureas and meglitinides, is usually seen in people who have access to these medications.

Hypoglycaemia symptoms

Symptoms of hypoglycaemia are categorised as autonomic and neuroglycopenic symptoms. Autonomic symptoms such as tremors, anxiety, palpitation, sweating are due to adrenergic and partly cholinergic stimulation, triggered by hypoglycaemia and develop at a plasma glucose concentration of approximately 3.3 mmol/L (48,49). Perception of these symptoms provides awareness of hypoglycaemia (49). Neuroglycopenic symptoms such as dizziness, light headedness, blurred vision, diplopia, cognitive impairment, behavioural changes, slurred speech, seizures and coma are typically seen in PPH. These are due to cerebral glucose deprivation, and develop at plasma glucose levels of approximately 2.7 mmol/L and lower (6,49). Patients may experience symptoms at different glycaemic thresholds, and with recurrent episodes of hypoglycaemia, they may lose hypoglycaemic awareness (10).

Patient evaluation

These patients are mostly healthy-looking individuals who present with nonspecific symptoms suggestive of hypoglycaemia, after a meal. It is crucial to confirm the presence of hypoglycaemia associated with symptoms or signs that are relieved after raising blood glucose concentration (Whipple's triad) (10,50). This may be challenging as the patient may not be able to go to the lab during symptoms, and the use of glucometer during symptoms may give false reading due to

inadequate technique, and the method may not give accurate result at low glucose concentrations (10,51). Hypoglycaemia is confirmed by detecting blood glucose <2.7 mmol/L and plasma glucose <3.0 mmol/L measured from a venous blood sample with a precise laboratory method. Preanalytical errors such as a collection of the blood sample in a tube without a glycolysis inhibitor (sodium fluoride or ethylenediaminetetraacetic acid-citrate: EDTA) and delayed separation of the plasma from the formed elements in blood, may result in continued glucose metabolism giving false low glucose concentration-pseudo-hypoglycaemia particularly in the presence of erythrocytosis, leucocytosis, or thrombocytosis (10). Postprandial hypoglycaemic symptoms without Whipple's triad, previously termed as "reactive hypoglycaemia" is a functional disorder now known as a postprandial syndrome, in which symptoms are not due to hypoglycaemia (52).

Once Whipple's triad is established, a comprehensive medical history should include the details of symptoms; timing in relation to meals; duration; provoking and alleviating factors; any prescribed or over the counter drug intake; any surgery on upper gastrointestinal tract including bariatric surgery; any known critical illness or hormonal deficiency and any similar family history. These patients' physical examination is usually unremarkable with no evidence of critical illness, hormone deficiency, or non-islet cell tumour.

Further evaluation of hypoglycaemia should be carried out during an episode of spontaneous hypoglycaemia when blood samples are collected to measure glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate (β-OHB), insulin antibodies and for oral hypoglycaemic agents screen, to confirm different causes of PPH (*Figure 1*). Diagnosis of endogenous hyperinsulinemia is confirmed when in the presence of plasma glucose of <3.0 mmol/L, there is detectable plasma insulin (3 μU/mL; 18 pmol/L) with high C-peptide (0.2 nmol/L), proinsulin of 5.0 pmol/L, suppressed plasma free fatty acid (<1.5 mmol/L) and β-OHB (≤2.7 mmol/L) (8,10,53).

Provocative test

If further investigation is not possible during a spontaneous episode of hypoglycaemia, a mixed meal test is recommended to recreate PPH settings (10). Oral glucose tolerance test has no role in the evaluation of PPH (10,54). A mixed-meal test should be performed under the supervision of trained personnel who can promptly intervene to manage severe hypoglycaemia. After an overnight fast, the patient is given a meal containing protein, carbohydrates, and fat that provokes symptoms. Blood samples are taken for baseline plasma glucose, insulin, C peptide, proinsulin, β-OHB, and then every 30 minutes for 5 hours. Fasting blood glucose is typically normal in these patients except in those with insulinoma. Neuroglycopenic symptoms develop at a blood glucose concentration of <2.7 mmol/L and plasma glucose <3.0 mmol/L. Blood samples are also taken for measuring any circulating oral hypoglycaemic agents (sulfonylureas, glinides) during hypoglycaemia and insulin antibodies to differentiate between various causes of PPH (*Figure 1*).

Imaging

Imaging studies such as abdominal computed tomography, MRI, and endoscopic pancreatic ultrasonography with fine-needle aspiration are required to detect insulinoma as a cause of PPH (55,56). Selective pancreatic arterial calcium stimulation test, confirms the diagnosis of NIPHS by demonstrating diffuse calcium-stimulated hyperinsulinism from multiple segments of pancreatic vascular supply. It also helps differentiate NIPHS from a solitary tiny insulinoma that is not apparent on standard imaging procedures (56,57). New imaging modalities like fluorine-18-L-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET) and PET/CT with 68Ga-DOTA-exendin-4 are helpful in precisely localising insulinoma (58-60).

Management of PPH

General measures

Patient education is crucial in managing hypoglycaemia as they are at risk of accidents and injuries due to neuroglycopenic symptoms. They should learn to monitor their capillary blood glucose by a glucose meter, when symptomatic. Family members should be educated to be aware of hypoglycaemic symptoms and the use of glucagon injection in an emergency.

Emergency management

Severe symptoms are treated with glucose tablet/gel or intramuscular glucagon injection, which raises blood glucose concentration by inducing glycogenolysis and gluconeogenesis. Those who require attendance at the

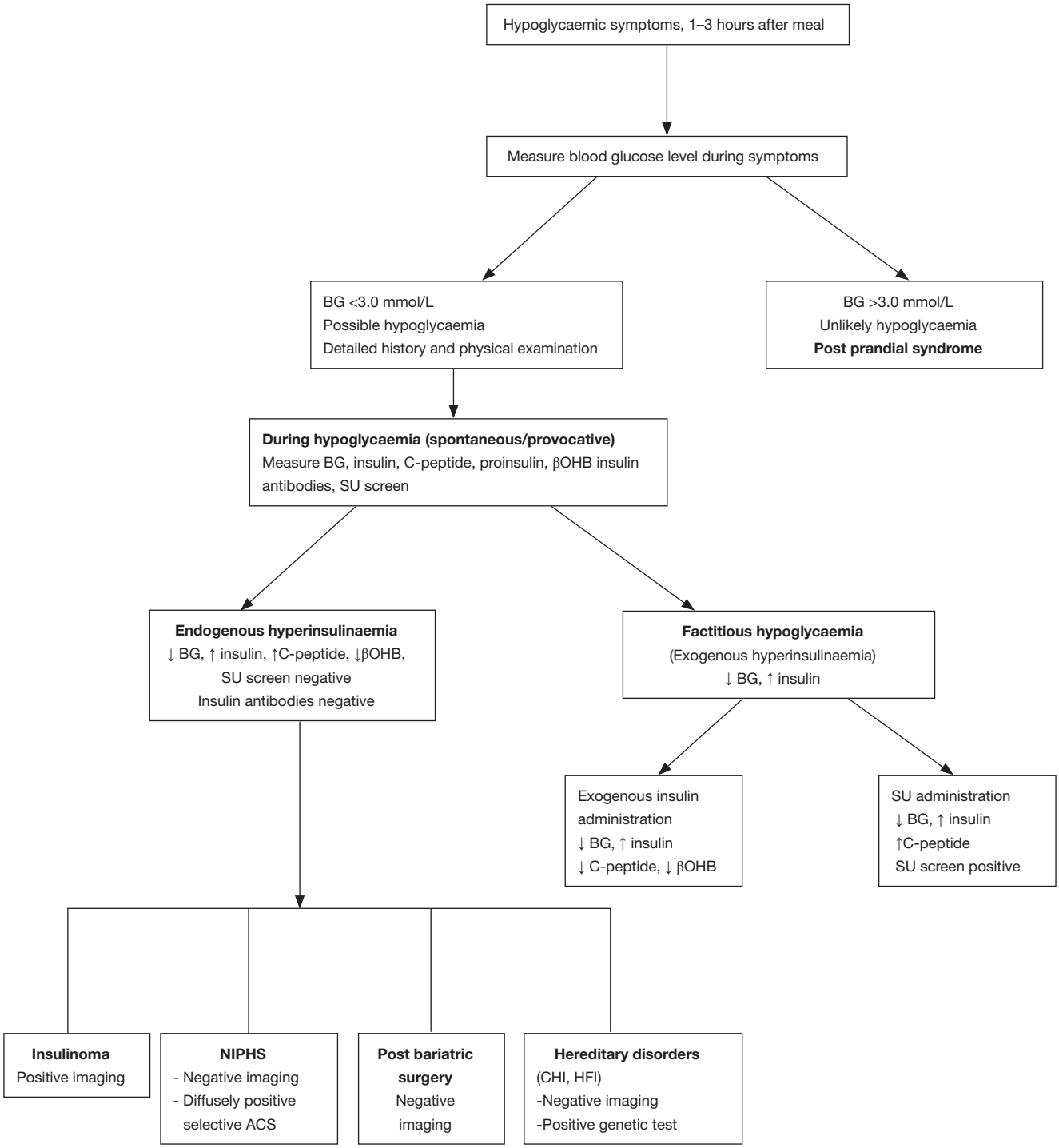

Figure 1 Evaluation of a patient with PPH. PPH, postprandial hypoglycaemia; BG, blood glucose; βOHB, β-hydroxybutyrate; SU, sulfonylurea; CHI, congenital hyperinsulinism; HFI, hereditary fructose intolerance; selective ACS, selective arterial calcium stimulation.

hospital with loss of consciousness and seizures are treated with 50% dextrose or glucagon followed by dextrose infusion.

Long term management

Dietary modifications

This is the first step in the management of PPH. The patient is advised to maintain a food diary to identify provocative food. A diet with low carbohydrate, high protein content with added fibres and fat helps reduce post-meal glycaemic excursions and ameliorate hypoglycaemia (61,62). Use of complex carbohydrate with a low glycaemic index is advised while simple carbohydrate with high glycaemic index should be avoided (62). Uncooked corn starch was used in a study for preventing symptoms hyperinsulinaemic hypoglycaemia of infancy (63); however, it may not work in all cases.

Acarbose

It is an α-glucosidase inhibitor, which delays the intestinal breakdown of complex carbohydrate to glucose, reducing postprandial glucose and insulin surge and subsequent hypoglycaemia (64,65). Although it is the first-line medication for postprandial hyperinsulinemic hypoglycaemia, its use is limited by the side effects like flatulence and diarrhoea.

Diazoxide

It inhibits insulin secretion by inhibition of β-cell ATP-sensitive potassium channels (66). It is used for controlling hyperinsulinemic symptoms in insulinoma and other causes of endogenous hyperinsulinaemic hypoglycaemia.

Somatostatin analogues

Octreotide is used when a dietary modification, acarbose and diazoxide are ineffective. It binds to somatostatin receptor-2 and receptor-5 located on β-pancreatic cells, inhibiting calcium influx and reducing insulin synthesis and secretion (67). Its long-acting preparation, lanreotide, which is given once monthly, may show better results in some patients. However, it loses its efficacy over time because of gradual internalisation of somatostatin receptors, when the patient becomes desensitised to the medication. A combination of somatostatin analogue and diazoxide may prove helpful in some patients (68). Side-effects of octreotide include diarrhoea, risks of cholelithiasis and prolonged QT interval.

Novel therapies

GLP-1 receptor antagonist, exendin-9, has been reported to be effective in preventing PPH and maintaining plasma glucose stability (27,69). Sirolimus, an immunosuppressant, has been successfully used in children with severe hyperinsulinaemic hypoglycaemia, unresponsive to maximum doses of diazoxide and octreotide (70).

Surgery

Surgical resection of insulinoma is the preferred treatment. Nevertheless, surgery is the last option to treat other causes of severe endogenous hyperinsulinism, refractory to dietary modification and medical therapy. A gradient graded or distal pancreatectomy is the treatment of choice in severely affected refractory cases of NIPHS (14,15). Partial pancreatectomy has not been successful in post-bariatric cases, as most patients continue to have symptoms (71). Feeding through gastrostomy tube placed into the remnant stomach has been effectively used in some post-RYGB cases, as the nutrients pass through the duodenum and upper jejunum with normal glucose, insulin and GLP1 response (72,73). Reversal of RYGB may relieve the refractory hypoglycaemic symptoms in cases, unresponsive to other measures (74,75).

Conclusions

PPH in adults is not common; however, with an increasing number of bariatric procedures worldwide, clinicians are encountering more patients with this complication. Its evaluation and management can be arduous and challenging. Further studies are required to explore novel therapies to prevent and treat neuroglycopenia that not only increases morbidity, reduces the quality of life, and it also impairs patient safety as they are more prone to have accidents.

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