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Postprandial Hypoglycemia

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1. Introduction

Postprandial hypoglycemia is a syndrome secondary to disorders in which hypoglycemia is manifested within 5 hours after a meal (1). It is classified into two types depending on the time of occurrence, i.e., 'early,' with onset within 2 hours, and 'late,' occurring between 3 and 5 hours after a meal. The early variety is thought to be secondary to abnormally rapid gastric emptying, whereas late postprandial hypoglycemia is frequently deemed to be a precursor to the onset of type 2 diabetes mellitus (1-14). Causes of late postprandial hypoglycemia also include disorders manifesting as fasting hypoglycemia, such as factitious hypoglycemia due to exogenous insulin administration or surreptitious use of insulin secretogogues, e.g, sulfonylureas, glinides, or other hypoglycemic agents, insulinoma, islet cell hyperplasia, autoimmune hyperinsulinemia, hyperinsulinemia caused by drugs and toxins, excess of circulating IGF2 secreted by non-pancreatic tumors, adrenal or pituitary hypofunction, advanced liver dysfunction, and end-stage renal disease(15-29) Several rare disorders, including some congenital syndromes, e.g., glycogen storage disorders, can also cause late postprandial hypoglycemia(30). In contrast, early postprandial hypoglycemia occurs only postprandially and usually is noted in subjects following upper gastrointestinal surgery, including bariatric procedures, hyperthyroidism, etc (1,21,26,31,32). In some subjects, it occurs without an obvious apparent cause and is therefore termed 'idiopathic reactive hypoglycemia.' Arguably, many endocrinologists approve of this syndrome, whereas others question its existence and call it 'postprandial syndrome,' probably because of the debate over the diagnosis of hypoglycemia itself (8,21,29).

Hypoglycemia presents with manifestations of increased sympathetic activity, i.e., anxiety, jitters, palpitations, dizziness, tremor, weakness, drenching perspiration, hunger, systolic hypertension, mydriasis, etc., attributed to prompt release of catecholamines, which is documented to occur with a fall of blood sugar to lower than 70 mg /dl (29,34,35). Manifestations more seriously detrimental to life, i.e., of a neuroglycopenic nature, include convulsion, confusion, coma, or other altered states of consciousness, and transient CNS manifestations, including hemiparesis. Cardiac manifestations include symptomatic coronary artery disease, i.e., angina pectoris, arrhythmias, or even myocardial infarction following extreme lowering of blood sugars, usually to concentrations below 50 mg/dl (35).

Few authorities still believe that the onset of manifestations of exaggerated sympathetic activity may be dependent on the rapidity of rate of fall in blood glucose irrespective of the exact concentration, although several studies have refuted this hypothesis.

Therefore, in subjects with diabetes, hypoglycemia is deemed to occur with the onset of symptoms even when the blood sugar is between 50 and 70 mg/dl. Moreover, blood sugars lower than 70 mg/dl in the absence of manifestations of sympathetic overactivity are also defined as hypoglycemia and the subject is deemed to manifest hypoglycemia unawareness (36-38). Finally, all efforts are made to prevent 'hypoglycemia' in both these circumstances frequently by altering the treatment plan. In contrast, several authorities promote that the diagnosis of hypoglycemia should be made in the presence of blood sugar <50 mg/dl and that too only if criteria for Whipple's triad are fulfilled (39). The triad consists of documentation of a blood sugar <50 mg/dl accompanied by symptoms of hypoglycemia, and resolution of symptoms by inducing a rise in blood sugar by either ingestion of sugar or a meal, or iv administration of glucose.

Thus, according to these authors, subjects with documentation of a blood sugar < 50 mg/dl, after an overnight fast, postprandially, or randomly, deserve evaluation in the absence of diabetes mellitus only if the low blood sugar is accompanied by symptoms (21,26,29),. The recommendation is totally different in the presence of diabetes. In subjects with diabetes, a thorough assessment of hypoglycemic symptoms and even asymptomatic low blood sugar is recommended. Therefore, in the absence of symptoms, in non-diabetic subjects, a blood sugar < 50 mg/dl is not defined as a syndrome of 'hypoglycemia' by these authors. However, this concept is in stark contrast to the tenet of ethical medical practice to define and treat disorders with definite documentation of metabolic abnormalities despite the absence of symptoms, e.g., hyperglycemia, hypercalcemia, changes in sodium and potassium concentrations, and many other medical disorders, including subclinical hypo and hyperthyroidism. This practice is obviously prudent in the light of clear documentation of increased morbidity and even mortality of subclinical disorders, especially with lack of restoration of the normal state. Furthermore, restoring and preserving the normal state with appropriate treatment is also documented to improve the quality of life in these subjects manifesting subclinical disorders. Therefore, it is difficult to fathom why the same principle is not applied in the management of well documented postprandial hypoglycemia in the absence of typical symptoms or frequently even in the presence of characteristic manifestations.

We firmly believe that postprandial hypoglycemia is a 'true' disorder with a distinct deterioration in quality of life, including attention deficit and loss of productivity (1,9 - 14,40),. Moreover, a cause of the abnormality is easily determined by a detailed history, a thorough physical examination, and simple laboratory testing. A history of upper gastrointestinal surgery for esophageal and gastric diseases, bariatric procedures, symptoms of hyperthyroidism, the timing of the occurrence of symptoms following a meal, i.e., 'early' or 'late' onset, dietary pattern provoking symptoms, i.e., high carbohydrate content or ingestion of simple sugars, changes in body weight, use of certain drugs, history of gestational diabetes; all provide clues to indicate a specific diagnosis. Family history of type 2 diabetes mellitus is important information as well. Similarly, a thorough physical examination may indicate the presence of a specific disorder. Finally, the determination of appropriate laboratory tests after an overnight fast and at frequent (30 minute) intervals, up

to 5 hours or at the onset of symptoms of hypoglycemia following ingestion of a mixed meal or glucose (OGGT) often clinches the diagnosis.

The occurrence of postprandial hypoglycemia within 2 hours is attributed to an exaggerated insulin response to markedly elevated plasma glucose levels within 15-30 minutes caused by a prompt absorption of carbohydrate content, especially the simple variety due to a super fast transit of an ingested meal across the stomach as initially documented in subjects undergoing gastric surgery e.g. partial or total gastrectomy for several decades and more recently in morbidly obese subjects undergoing gastric bypass surgery(1,54,8,20,21,26) In fact ,we believe that persistent occurrence of hypoglycemia irrespective of timing of the meal during the later years following gastric bypass surgery may attributed to repeated frequent postprandial stimulation of pancreatic beta cells ultimately leading to autonomous beta cell hyperplasia requiring excision (26) .Surgery may be prevented by appropriate dietary changes as well as a prompt therapy with medications during the initial period following a bariatric procedure (42-47)

In the absence of documentation of a known disorder, early postprandial hypoglycemia is also termed 'Idiopathic reactive hypoglycemia' by some and 'postprandial syndrome' by others. We firmly believe that 'Idiopathic reactive hypoglycemia' is a genuine disorder, since several pathophysiologic mechanisms have been implicated (2-14).The occurrence of hypoglycemia in this disorder has been attributed to rapid gastric emptying secondary to lack of rise in Gastric Inhibitory Polypeptide following an ingestion of a meal or altered secretion of other gastrointestinal motility factors,e.g.Motilin, Bombesin etc(1-4) Remission of hypoglycemia by inhibition of gastric emptying by use of drugs with ability to induce cholinergic blockade enhances this hypothesis. Alternatively, altered function of both pancreatic alpha and beta cells has also been invoked. We have documented enhanced 1st or early phase insulin secretion within 30-60 minutes in response to glucose ingestion as well as aberrant pancreatic alpha cell function in this syndrome (Table 1). plasma glucagon is elevated after an overnight fast in comparison to normal subjects despite presence of normal glucose concentration indicating glucagon insensitivity (Table1). However, inhibited glucagon decline with initial hyperglycemia and a blunted rise following onset of hypoglycemia documents altered glucagon secretion in this syndrome.(Figure1) Impaired regulation of glucagon in this syndrome is further confirmed by decline in glucagon response following oral administration of a protein meal (figure 2), a well established stimulus for facilitating glucagon secretion and release by pancreatic alpha cells(41).This altered pancreatic alpha and beta cell function is also documented in several other studies (7,9,1,33,40). Finally, the presence of the disorder is further enhanced by documentation of remission of symptoms and hypoglycemia by appropriate intervention with several protocols, including lifestyle changes with use of a diet with tolerated amount of fiber as well as high protein, low carbohydrate contents, avoidance of ingestion of simple or free sugars, and frequent small feedings (1,5,14). Moreover, in the absence of total remission with these lifestyle changes, several drugs have been successfully used. These include agents, e.g. atropine derivatives which delay gastric emptying by cholinergic blockade as mentioned earlier, drugs inhibiting conversion of complex to simple carbohydrates,e.g.alpha-glucosidase inhibitors, medications altering insulin secretion e.g.calcium channel blockers, or drugs possessing all of these properties, e.g. octreotide (3,42-47). In contrast, 'late reactive or postrprandial hypoglycemia'documented in 'impaired glucose tolerance', a prediabetic state is induced by exaggerated 2nd or late phase insulin

secretion occurring between 90 -120 minutes induced by marked elevated plasma glucose concentration at 60-90 minutes due to inhibition of 1`st phase insulin secretion following a meal or oral administration of glucose (48-52)).Moreover, hypoglycemia in this disorder also is remediable by appropriate lifestyle changes and certain drugs (53).

Therefore, A subject manifesting symptoms of hypoglycemia following a meal must be evaluated by a detailed history, a thorough physical examination and appropriate laboratory testing. First and foremost, the presence of low blood sugar level, e.g ≤ 6O mg/dl must be documented with accompanying hypoglycemic symptoms. The diagnosis could be further established by assessment of blood sugars following ingestion of a mixed meal or oral administration of glucose. Once the diagnosis is confirmed, the appropriate treatment should be provided as it distinctly improves quality of life. Early postprandial hypoglycemia with onset within 2 hours may be treated with life style dietary changes initially. The drugs may be used later as an adjunctive therapy if dietary manipulations fail to attain and maintain remission. The documentation of late reactive hypoglycemia indicates a presence of 'Prediabetes' which also may be managed with lifestyle changes, e.g. diet and exercise, to achieve weight loss especially in the obese subjects as well as with drugs, e.g. Metformin in subjects with increased risk for progression to Diabetes as recommended by American Diabetes Association(48),

Therefore, in the final analysis, it is imperative to consider the presence of postprandial hypoglycemia as a disorder and conduct an appropriate evaluation and provide suitable therapeutic strategies.

Group	Age (yr)	Body Weight (kg)	Fasting Plasma Glucose (mmol/L)*	Fasting Plasma Insulin (mU/L)*	Fasting Plasma Glucagon (ng/L)*
IHR	37±6	59±8	4.9±0.2	7±2	347±83†
Normal	34±5	62±7	5.2±0.1	6±1	135±20

* The average of 2 values in individual subjects, 1 during the OGTT and the other during the protein meal study, was used for calculation.

† P< .025, IRH v normal.

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Table 1. Fasting Plasma Glucose, Insulin,and Glucagon Levels in Five Subjects With IRH and Six Normal Subjects.

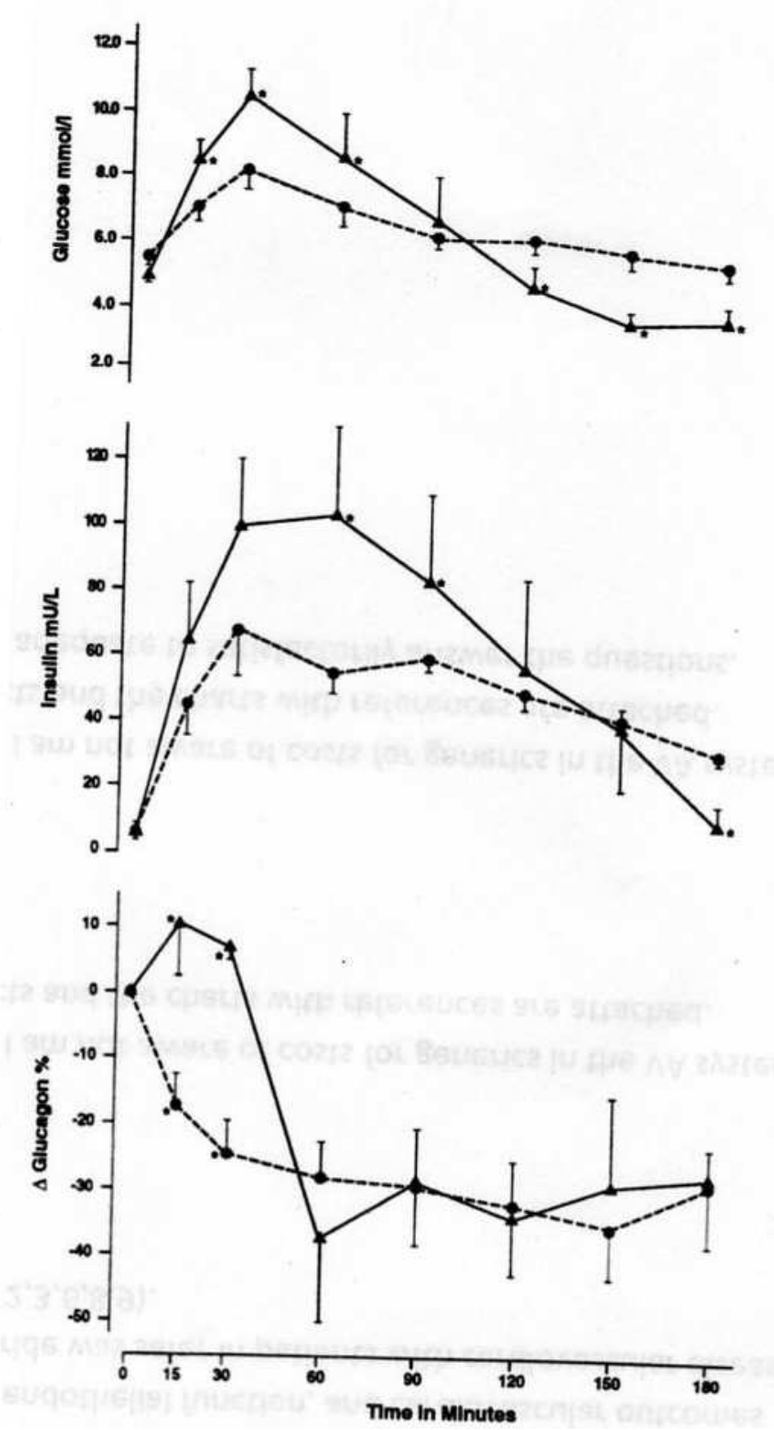

Fig. 1. Glucose, insulin, and glucagon responses to oral ingestion of 100 g glucose(OGTT) in 5 subjects with IRH (▲) and 6 normal subjects (●) * P< .01 v normal. Reprinted from reference 12, with permission

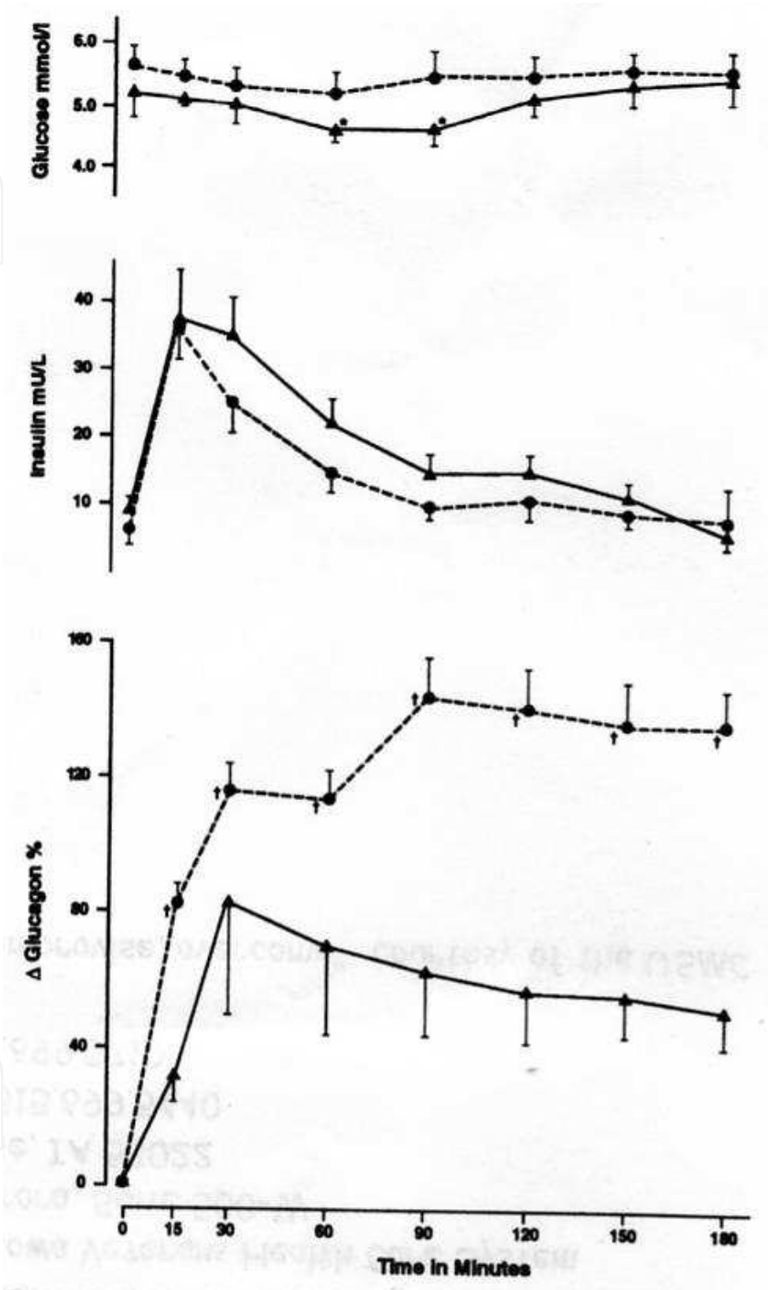

Fig. 2. Glucose, insulin, and glucagon responses to oral ingestion of a protein meal in 5 subjects with IRH (▲) and 6 normal subjects (●). * < .05 v normal. † P< .01 IRH. Reprinted from reference 12, with permission

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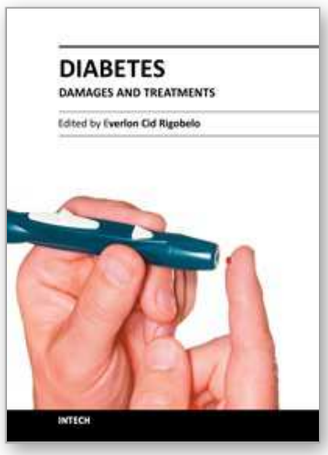

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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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