International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 7; Issue 2(J); February 2018; Page No. 10281-10288
DOI: http://dx.doi.org/10.24327/ijcar.2018.10288.1733

Review Article

HYPOGLYCEMIA: A COMPLETE REVIEW

Siva Rami Reddy E*

Faculty of Homoeopathy, Tantia University, Sri Ganganagar, Rajasthan, India – 335002

A R T I C L E I N F O

Article History:
Received 9th November, 2017
Received in revised form 25th December, 2017
Accepted 16th January, 2018
Published online 28th February, 2018

Key words:
Diabetes Mellitus, Hypoglycemia, complications, Treatment.

A B S T R A C T

Hypoglycaemia occurs often in diabetic patients treated with insulin but relatively infrequently in those taking a sulphonylurea drugs. This risk of hypoglycaemia is the most important single factor limiting the attainment of the therapeutic goal, namely near normal glycaemia. However, in certain types of patient (e.g. patients with a long duration of type 1 diabetes), warning symptoms are not always perceived by the patients even when awake so that appropriate action is not taken and neuroglycopenia then unconsciousness ensue.

INTRODUCTION

Hypoglycemia is most commonly the result of taking drugs used to treat diabetes mellitus or other drugs, including alcohol. However, a number of other disorders, including end stage organ failure and sepsis, endocrine deficiencies, large mesenchymal tumors, insulinoma, and inherited metabolic disorders are also associated with hypoglycemia. Hypoglycemia is sometimes defined as a plasma glucose level 2.5 to 2.8 mmol/L (45 to 50 mg/dL)[1-3]. However, glucose thresholds for hypoglycaemia induced symptoms and physiologic responses vary widely, depending on the clinical setting [4, 5]. Therefore, an important framework for making the diagnosis of hypoglycemia is *Whipple's triad*: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration, and (3) relief of symptoms after the plasma glucose level is raised [6-8]. Hypoglycemia can cause significant morbidity and can be lethal, if severe and prolonged; it should be considered in any patient with confusion, altered level of consciousness, or seizures [9].

Causes

Hypoglycemia is traditionally classified as postprandial or fasting (table 1). However, in the clinical setting, hypoglycemia is most commonly a result of diabetes treatment. This topic is therefore addressed before considering the other causes of hypoglycemia[10].

Table 1 Causes of Hypoglycaemia [11]

Causes of Hypoglycaemia

- Missed, delayed or inadequate meal
- Unexpected or unusual exercise
- Alcohol
- Poorly designed insulin regimen, particularly that predisposing to nocturnal hypoglycaemia
- Deficient glucose counter regulation/impaired awareness of hypoglycaemia
- Gastroparesis due to autonomic neuropathy
- Unrecognised other endocrine disorder e.g. Addison's disease
- Malabsorption
- Factitious
- Errors in oral hypoglycaemic agent or insulin dose/schedule/administration

The incidences of most common causes of hypoglycaemia can all be reduced by adequate patient education. Exercise induced hypoglycaemia occurs in treated, well controlled, insulin treated diabetic patients because a key factor in the normal adaptation to exercise, namely decrease secretion of endogenus insulin, does not occur (Fig. 1).

Table 2 The effect of exercise in diabetic patients being treated with insulin

Well controlled: Hyperinsulinaemic	Decompensated: Hypoinsulinaemic
↓	↓
Increased Peripheral glucose uptake	Decreased peripheral glucose uptake
+	+
Decreased hepatic glucose output	Increased hepatic glucose output
+	+
Increase insulin absorption	Increased lipolysis
↓	↓
Hypglycaemia	Hyperglycaemia & ketonaemia

Corresponding author:* **Siva Rami Reddy E
Faculty of Homoeopathy, Tantia University, Sri Ganganagar, Rajasthan, India – 335002

Patients should be taught that if strenuous or protracted exercise is anticipated the preceding dose of insulin should be reduced at all times.

Systemic Glucose Balance and Counterregulation

Glucose is an obligate metabolic fuel for the brain under physiologic conditions. By contrast, other organs can use fatty acids, in addition to glucose, to generate energy. The brain cannot synthesize glucose and stores only a few minutes' supply as glycogen and therefore requires a continuous supply of glucose, which is delivered by facilitated diffusion from arterial blood. As the plasma glucose concentration falls below the physiologic range, blood to brain glucose transport becomes insufficient for adequate brain energy metabolism and functioning. Fortunately, redundant physiologic mechanisms prevent or rapidly correct hypoglycemia. Plasma glucose levels are maintained within a narrow range, usually between 3.3 and 8.3 mmol/L (60 and 150 mg/dL), despite wide variation of food intake and activity level. This delicate balance requires dynamic regulation of glucose influx into the circulation as glucose utilization in various tissues can change rapidly. The diet is normally a major source of glucose. However, between meals or during fasting, plasma glucose levels are maintained primarily by the breakdown of glycogen and by gluconeogenesis. In most persons, hepatic glycogen stores are sufficient to maintain plasma glucose levels for 8 to 12 h, but this time period can be shorter if glucose demand is increased by exercise or if glycogen stores are depleted by illness or starvation. As glycogen stores are depleted, glucose is generated by gluconeogenesis, which occurs mainly in the liver but also in the kidneys. Gluconeogenesis requires a coordinated supply of precursors from liver, muscle, and adipose tissue. Muscle provides lactate, pyruvate, alanine, and other amino acids. Triglycerides in adipose tissue are broken down into glycerol, which is a precursor for gluconeogenesis. Free fatty acids generate acetyl CoA for gluconeogenesis and provide an alternative fuel source to tissues other than the brain. The balance of glucose production and its uptake and utilization in peripheral tissues are exquisitely regulated by a network of hormones, neural pathways, and metabolic signals. Among the factors that control glucose production and utilization, insulin plays a dominant and pivotal role. In the fasting state, insulin is suppressed, allowing increased gluconeogenesis in the liver and the kidneys and enhancing glucose generation by the breakdown of liver glycogen. Low insulin levels also reduce glucose uptake and utilization in peripheral tissues and allow lipolysis and proteolysis to occur, which leads to the release of precursors for gluconeogenesis and provides alternative energy sources. In the fed state, insulin release from the pancreatic cells reverses this process. Glycogenolysis and gluconeogenesis are inhibited, thereby reducing hepatic and renal glucose output;peripheral glucose uptake and utilization are enhanced; lipolysis and proteolysis are restrained; and energy storage is promoted by the conversion of substrates into glycogen, triglycerides, and proteins. Other hormones, such as glucagon, epinephrine, growth hormone, and cortisol, play less important roles in the control of glucose flux during normal physiologic circumstances. However, these hormones are critically important in the response to hypoglycemia [12].

As glucose levels approach, and ultimately enter, the hypoglycaemic range, a characteristic sequence of counter regulatory hormone responses occurs. Glucagon is the first and most important of these responses. It promotes glycogenolysis and gluconeogenesis. Epinephrine can also play an important role in the acute response to hypoglycemia, particularly when glucagon is insufficient. It, too, stimulates glycogenolysis and gluconeogenesis and limits glucose utilization by insulin sensitive tissues. When hypoglycemia is prolonged, growth hormone and cortisol also reduce glucose utilization and support its production. The glucose thresholds at which various counter regulatory hormone responses occur are quite similar in healthy subjects. Nevertheless, these thresholds are dynamic and can be influenced by recent metabolic events. A person with poorly controlled diabetes can have symptoms of hypoglycemia at higher the normal glucose levels. Recurrent hypoglycemia, which may occur in individuals with diabetes or an insulinoma, shifts thresholds for symptoms and counter regulatory responses to lower glucose levels.

Clinical Manifestations

Symptoms of hypoglycemia can be divided into two categories, neuroglycopenic and neurogenic (or autonomic) responses. Neuroglycopenic symptoms are a direct result of central nervous system neuronal glucose deprivation. Symptoms include behavioral changes, confusion, fatigue, seizure, loss of consciousness, and, if hypoglycemia is severe and prolonged, death. Hypoglycemia induced autonomic responses include adrenergic symptoms such as palpitations, tremor, and anxiety as well as cholinergic symptoms such as sweating, hunger, and paresthesia[13-16]. Adrenergic symptoms are mediated by norepinephrine released from sympathetic postganglionic neurons and the release of epinephrine from the adrenal medullae[17]. Increased sweating is mediated by cholinergic sympathetic nerve fibers. Patients with diabetes mellitus learn to recognize the characteristic symptoms of hypoglycemia, but these are less familiar to individuals with other causes of hypoglycemia. Symptoms may be less pronounced with repeated hypoglycaemic episodes. Common signs of hypoglycemia include pallor and diaphoresis[18]. Heart rate and the systolic blood pressure are typically raised, but these findings may not be prominent. The neuroglycopenic manifestations are valuable, albeit nonspecific, signs. Transient focal neurologic deficits occur occasionally [19].

Hypoglycemia in Diabetes

Frequency and Impact: Were it not for hypoglycemia, diabetes would be rather easy to treat by administering enough insulin (or any effective drug) to lower plasma glucose concentrations to, or below, the normal range. But because current insulin replacement regimens are imperfect, individuals with type $_1$ diabetes are at ongoing risk for periods of relative hyperinsulinemia with resultant hypoglycemia. Those attempting to achieve near normal glycemic control may experience several episodes of asymptomatic or symptomatic hypoglycemia each week. Plasma glucose levels may be 2.8 mmol/L (50 mg/dL) as often as 10% of the time. Such patients suffer an average of one episode of severe, temporarily disabling hypoglycemia, often with seizure or coma, in a given year. Although seemingly complete recovery from the latter is the rule, the possibility of persistent cognitive deficits has been raised, but permanent neurologic defects are rare. About 2 to 4% of deaths associated with type$_1$ diabetes are estimated to be a result of hypoglycemia. Fear of hypoglycemia can also lead to disabling psychosocial morbidity Hypoglycemia is a less frequent problem in type 2 diabetes but still occurs in those

treated with insulin or sulfonylureas [20]. Transient, mild hypoglycemia may be seen with the shorter acting sulfonylureas and repaglinide or nateglinide, which also act by enhancing insulin secretion. Patients who take the long acting sulfonylureas, chlorpropamide and glyburide, may experience episodes of severe hypoglycemia that last between 24 and 36 h.

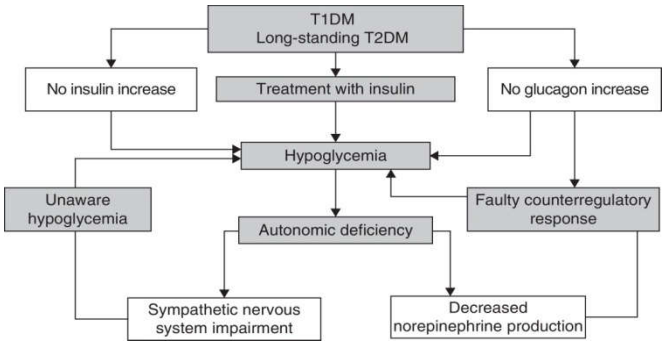

Fig 1 Pathophysiology of Hypoglycemia

Conventional Risk Factors

Insulin excess is the primary determinant of risk from iatrogenic hypoglycemia. Relative or absolute insulin excess occurs when: (1) insulin (or oral agent) doses are excessive, ill timed, or of the wrong type;(2) the influx of exogenous glucose is reduced (e.g., during an overnight fast or following missed meals or snacks);(3) insulin independent glucose utilization is increased (e.g., during exercise);(4) insulin sensitivity is increased (e.g., with effective intensive therapy, in the middle of the night, late after exercise, or with increased fitness or weight loss); (5) endogenous glucose production is reduced (e.g., following alcohol ingestion); and (6) insulin clearance is reduced (e.g., in renal failure). However, analyses of the Diabetes Control and Complications Trial (DCCT) indicate that these conventional risk factors explain only a minority of episodes of severe iatrogenic hypoglycemia; other causes are involved in the majority of episodes [21].

Hypoglycemia Associated Autonomic Failure

It is now clear that inadequate physiologic counter regulatory and behavioural responses greatly compound the problem of hypoglycemia caused by insulin excess. Hypoglycemia associated autonomic failure has two main components: (1) reduced counter regulatory hormone responses, which result in impaired glucose generation; and (2) hypoglycemia unawareness, which precludes appropriate behavioral responses, such as eating [22].

Defective Glucose Counterregulation

The counter regulatory hormone response is fundamentally altered in patients with established (e.g., absent C peptide) type 1 diabetes. As insulin deficiency progresses over the first few months or years of the disease, circulating insulin levels are no longer tightly coordinated with glucose levels and are a passive function of administered insulin. Thus, insulin levels do not decline as glucose levels fall; the first defense against hypoglycemia is lost. Over the same time frame, the glucagon response to falling glucose levels diminishes, and the second defense against hypoglycemia is lost. The cause of defective glucagon production by the pancreatic islet cells is unknown, but it is tightly linked to the loss of insulin production by the cells. It is a functional abnormality rather than an absolute deficiency of glucagon, as responses to stimuli other than hypoglycemia are intact. The third defense against hypoglycemia is compromised when the epinephrine response to hypoglycemia is reduced. In contrast to the absent glucagon response, epinephrine deficiency is a threshold abnormality; an epinephrine response can still be elicited, but a lower plasma glucose concentration is required. This threshold shift is largely a result of recent antecedent hypoglycemia, although an additional anatomic component may also be present in patients affected by classic diabetic autonomic neuropathy. The development of a reduced epinephrine response is a critical pathophysiologic event. Prospective studies have shown that patients with combined deficiencies of glucagon and epinephrine suffer severe hypoglycemia at rates 25 fold or greater than individuals with absent glucagon but intact epinephrine responses [23].

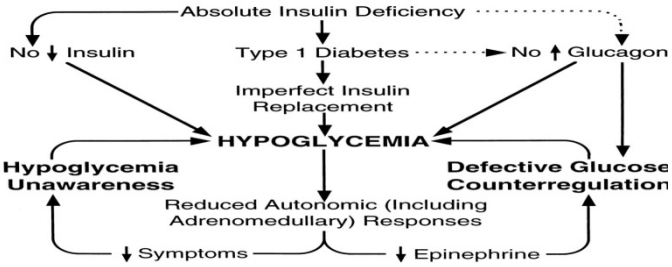

Fig 2 Hypoglycemia in Diabetes Mellitus

Hypoglycemia Unawareness

Hypoglycemia unawareness refers to a loss of the warning symptoms that alert individuals to the presence of hypoglycemia and prompt them to eat and abort the episode [24]. Under these circumstances, the first manifestation of hypoglycemia is neuroglycopenia, when it is often too late for patients to treat themselves. Like defective counter regulation, the presence of hypoglycemia unawareness has been shown in prospective studies to be associated with a high frequency of severe hypoglycemia [25]. The interplay of factors involved in hypoglycemia associated autonomic failure in type 1diabetes, and consequent hypoglycemia unawareness. Periods of relative or absolute therapeutic insulin excess, in the setting of absent glucagon responses, lead to episodes of iatrogenic hypoglycemia. These episodes, in turn, cause reduced autonomic (including adrenomedullary) responses to falling glucose concentrations [26]. These impaired autonomic responses result in reduced symptoms of impending hypoglycemia (e.g., hypoglycemia unawareness) because epinephrine responses are reduced in the setting of absent glucagon responses. Thus, a vicious cycle of recurrent hypoglycemia is created and perpetuated [27]. The syndrome of hypoglycemia unawareness and the reduced epinephrine component of defective glucose counter regulation are reversible but require 2 weeks of scrupulous avoidance of hypoglycemia. This involves a shift of glycemic thresholds back to higher plasma glucose concentrations [28].

Hypoglycemia Risk Factor Reduction

A diagnosis of hypoglycemia unawareness can usually be made from the history. One should note that hypoglycemia unawareness implies that previous episodes of hypoglycemia have occurred, whether these are documented or not [29]. If low glucose levels are not apparent from the patient's self monitoring log, one should suspect hypoglycemia during the night. The presence of clinical hypoglycemia unawareness makes defective glucose counter regulation likely [30]. It is

possible to minimize the risk of hypoglycemia by applying the principles of modern therapy patient education and empowerment, frequent self monitoring of blood glucose, flexible insulin (and other drug) regimens, rational glycemic goals, and ongoing professional guidance and support [31]. If hypoglycemia is a recognized problem, first consider each of the conventional risk factors summarized earlier and recommend the appropriate adjustments of medications, diet, and life style [32]. Non selective beta blockers may attenuate the recognition of hypoglycemia and they impair glycogenolysis; a relatively selective antagonist is preferable when a beta blocker is indicated [33].

Reactive Hypoglycemia

Postprandial (reactive) hypoglycemia occurs only after meals and is self limited. Postprandial hypoglycemia occurs in children with certain rare enzymatic defects in carbohydrate metabolism such as hereditary fructose intolerance and galactosemia. Reactive hypoglycemia also occurs in some individuals who have undergone gastric surgery, which allows the rapid passage of food from the stomach to the small intestine. This type of *alimentary hypoglycemia* causes a rapid postprandial rise in plasma glucose levels and the release of gut incretins, which induce an exuberant insulin response and subsequent hypoglycemia. Administration of an glucosidase inhibitor, which delays carbohydrate digestion and thus glucose absorption from the intestine, can be considered for treatment of reactive hypoglycemia, although its efficacy remains to be established in controlled trials. If postprandial symptoms occur as an idiopathic disorder, caution should be exercised before labeling a person with a diagnosis of hypoglycemia. Indeed, a self diagnosis of hypoglycemia has often been reinforced by the finding of a "low" venous glucose concentration late after glucose ingestion. An oral glucose tolerance test should not be used in this setting. Plasma glucose falls as low as 2.4 mmol/L (43 mg/dL) after a 100 g glucose load in 5% of normal asymptomatic individuals, making it difficult to identify hypoglycemia based on the results of this test.

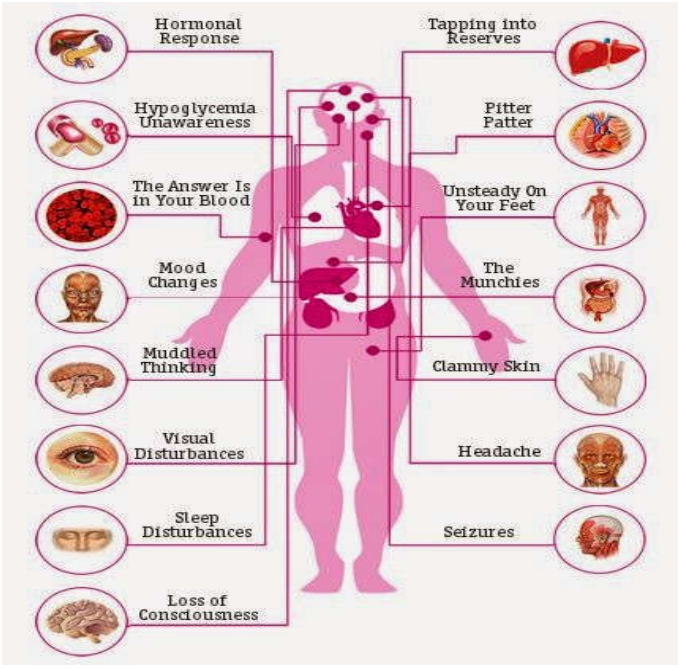

Fig 3 Hypoglycemia Effect on different parts

The diagnosis of postprandial hypoglycemia requires documentation of Whipple's triad after a typical mixed meal. The cause of repetitive postprandial symptoms in certain individuals is unknown, but they may be particularly sensitive to the normal autonomic responses that follow ingestion of a meal [34].

Fasting Hypoglycemia

There are many causes of fasting hypoglycemia. In addition to insulin and sulfonylureas used in the treatment of diabetes, ethanol use is a relatively common cause of hypoglycemia. Sepsis and renal failure are often complicated by hypoglycemia. Endocrine deficiencies, non cell tumors, and endogenous hyperinsulinemia (including that caused by an insulinoma) are rare causes of hypoglycemia. Enzymatic metabolic errors that cause hypoglycemia are also rare but are being recognized more frequently in infants and children [35].

Critical Illness

Rapid and extensive hepatic destruction (e.g., severe toxic hepatitis) causes fasting hypoglycemia because the liver is the major site of endogenous glucose production. The mechanism of hypoglycemia reported in patients with cardiac failure is unknown but likely involves hepatic congestion. Although the kidneys are a source of glucose production, it is perhaps too simplistic to attribute hypoglycemia in persons with renal failure to this mechanism alone. The clearance of insulin is reduced substantially in renal failure, and reduced mobilization of gluconeogenic precursors has been reported. Sepsis is sometimes complicated by hypoglycemia, which is multifactorial in origin. There is impaired endogenous glucose production, perhaps a result of hepatic hypoperfusion, and increased glucose utilization, which is induced by cytokines in macrophage rich tissues such as the liver, spleen, and ileum and in muscle. Nutrition is also often inadequate in the setting of sepsis. Hypoglycemia can be seen with prolonged starvation, perhaps because of a loss of whole body fat stores and the subsequent depletion of gluconeogenic precursors (e.g., amino acids), which necessitate increased glucose utilization [36].

Endocrine Deficiencies

Neither cortisol nor growth hormone is critical to the prevention of acute hypoglycemia, at least in adults. However, hypoglycemia can occur with prolonged fasting in patients with untreated primary adrenocortical failure (Addison's disease) or hypopituitarism. Anorexia and weight loss are typical features of chronic cortisol deficiency and likely result in glycogen depletion with increased reliance on gluconeogenesis. Cortisol deficiency is associated with low levels of gluconeogenic precursors, suggesting that substrate limited gluconeogenesis, in the setting of glycogen depletion, is the cause of the impaired ability to tolerate fasting in cortisol deficient individuals. Growth hormone deficiency can cause hypoglycemia in young children. In addition to extended fasting, high rates of glucose utilization (e.g., during exercise, pregnancy) or low rates of glucose production (e.g., following alcohol ingestion) can precipitate hypoglycemia in adults with hypopituitarism. Cortisol and growth hormone secretion should be evaluated in patients with fasting hypoglycemia when the history suggests pituitary or adrenal disease and when other causes of hypoglycemia are not apparent. Hypoglycemia is not a feature of the epinephrinedeficient state

that results from bilateral adrenalectomy when glucocorticoid replacement is adequate, nor does it occur during pharmacologic adrenergic blockage when other glucoregulatory systems are intact. There are case reports of fasting hypoglycemia attributed to isolated glucagon or epinephrine deficiency, although hyperinsulinemia was not excluded convincingly in neonatal cases and other counterregulatory defects may have contributed in the adults. Thus, the regular assessment of glucagon and epinephrine secretion is not warranted [37].

Non Cell Tumors

Fasting hypoglycemia, often termed non islet cell tumor hypoglycemia, occurs in some patients with large mesenchymal or other tumors (e.g., hepatoma, adrenocortical tumors, carcinoids. The glucose kinetic patterns resemble those of hyperinsulinism, but insulin secretion is suppressed appropriately during hypoglycemia. In most instances, hypoglycemia is due to overproduction of an incompletely processed form of insulin like growth factor (IGF) II. Although total IGF-II levels are not consistently elevated, circulating free IGF-II levels are high. Hypoglycemia results from IGF-II actions through the insulin or IGF-I receptors.

Endogenous Hyperinsulinism

Hypoglycemia due to excessive endogenous insulin secretion can be caused by: (1) a primary pancreatic islet cell disorder, typically a cell tumor (insulinoma), sometimes multiple insulinomas, or, especially in infants or young children, a functional cell disorder without an anatomic correlate;(2) a cell secretagogue, often a sulfonylurea, and, theoretically, a cell stimulating autoantibody;(3) an autoantibody to insulin; or (4) ectopic insulin secretion. None of these disorders is common. Endogenous hyperinsulinism is more likely to occur in an overtly healthy individual without other apparent causes of hypoglycemia such as a relevant drug history, critical illness, endocrine deficiencies, or a non cell tumor. Accidental, surreptitious, or even malicious administration of a sulfonylurea or insulin should also be considered in such individuals. The fundamental pathophysiologic feature of endogenous hyperinsulinism is the failure of insulin secretion to fall to very low rates during hypoglycemia. This is assessed by measuring insulin, proinsulin, and C peptide, which is derived from the processing of proinsulin. Critical diagnostic findings are a plasma insulin concentration 36 pmol/L (6 U/mL) and a plasma C peptide concentration 0.2 mmol/L (0.6 mg/mL) when the plasma glucose concentration is 2.5 mmol/L (45 mg/dL) in the fasting state with symptoms of hypoglycemia. Insulin and C-peptide levels do not need to be absolutely increased (e.g., relative to euglycemic normal values) but only inappropriately increased in the setting of fasting hypoglycemia. Plasma proinsulin concentrations are also inappropriately elevated, particularly in patients with an insulinoma. Sulfonylureas, because they stimulate insulin secretion, result in a pattern of glucose, insulin, and Cpeptide levels that is indistinguishable from that produced by a primary cell disorder. The measurement of sulfonylureas in plasma or urine distinguishes these conditions. Antibodies to insulin produce *autoimmune hypoglycemia* following the transition from the postprandial to the postabsorptive state, as insulin slowly dissociates from the antibodies. Total and free plasma insulin concentrations are inappropriately high. The distinguishing feature is the presence of circulating antibodies to insulin, but the need to measure these routinely is debated, since autoimmune hypoglycemia is rare. Autoantibodies to the insulin receptor are another rare cause of hypoglycemia and usually occur in the context of other autoimmune diseases. A few cases of ectopic insulin secretion (from a non cell tumor) have been reported [38].

Insulinoma and Other Primary Cell Disorders

Insulinomas are uncommon, but because approximately 90% are benign, they are a treatable cause of potentially fatal hypoglycemia. The yearly incidence is estimated to be 1 in 250,000. About 60% of cases occur in women. The median age at presentation is 50 years in sporadic cases, but it usually presents in the third decade when associated with multiple endocrine neoplasia type 1. Insulinomas arise within the substance of the pancreas in 99% of cases and are usually small (1 to 2 cm). About 5 to 10% of insulinomas are malignant, as evidenced by the presence of metastases. Insulinomas are almost always recognized because of hypoglycemia rather than mass effects. Unusually low plasma glucose concentrations may be required to produce symptoms and signs of hypoglycemia because recurrent hypoglycemia shifts the glycemic thresholds. Although symptomatic hypoglycemia can occur after an overnight fast, it often follows exercise. Rarely, symptomatic hypoglycemia occurs following meals, but most such patients have evidence of fasting hypoglycemia as well. Octreotide scans localize approximately half of insulinomas. Arteriography has been used extensively in the past, but false negative and false positive results occur, and it is generally preferable to use less invasive computed tomography (CT) or magnetic resonance imaging (MRI) scans, which detect 45 to 75% of tumors. Preoperative ultrasound is valuable for some patients. Intraoperative ultrasonography has high sensitivity and may localize tumors not identified by palpation. Surgical resection of a solitary insulinoma is generally curative. Diazoxide, which inhibits insulin secretion, and the somatostatin analogue, octreotide, can be used to treat hypoglycemia in patients with unresectable insulinomas.

Factitious Hypoglycemia

Factitious hypoglycemia, caused by malicious or self administration of insulin or ingestion of a sulfonylurea, shares many clinical and laboratory features with insulinoma. It is most common among health care workers, patients with diabetes or their relatives, and people with a history of other factitious illnesses. When this diagnosis is suspected, it is useful to seek previous medical records, which may reveal admissions for similar episodes. In individuals taking exogenous insulin, factitious hypoglycemia can be distinguished from insulinoma by the presence of high insulin levels without a concomitant increase in the C peptide level, which is suppressed by the exogenous insulin. As noted above, sulfonylureas stimulate endogenous insulin and can therefore be detected only by measuring drug levels in plasma or urine. Factitious or surreptitious hypoglycemia should be considered in every patient requiring a fasting test for hypoglycemia. In addition to laboratory tests, observing the patient's behavior may help make this diagnosis [39].

Diagnosis of the Hypoglycemic Mechanism

In an adult patient with documented hypoglycemia, a plausible hypoglycaemic mechanism and further diagnostic evaluation

can be guided by the history, physical examination, and available laboratory data. In the absence of documented spontaneous hypoglycemia, overnight fasting or food deprivation during observation in the outpatient setting, will sometimes elicit hypoglycemia and allow diagnostic evaluation. If there is a high degree of clinical suspicion, an extended fast lasting 48 to 72 h is often required to make the diagnosis. This procedure should be performed in the hospital with careful supervision and should be terminated if the plasma glucose drops to 2.5 mmol/L (45 mg/dL) and the patient has symptoms. It is essential to draw blood samples for appropriate tests before administering glucose or allowing the patient to eat [40].

Urgent Treatment

Oral treatment with glucose tablets or glucose containing fluids, candy, or food is appropriate if the patient is able and willing to take these. A reasonable initial dose is 20 g of glucose. If neuroglycopenia precludes oral feedings, parenteral therapy is necessary. Intravenous glucose (25 g) should be given using a 50% solution followed by a constant infusion of 5 or 10% dextrose. If intravenous therapy is not practical, subcutaneous or intramuscular glucagon can be used, particularly in patients with type 1 diabetes mellitus.

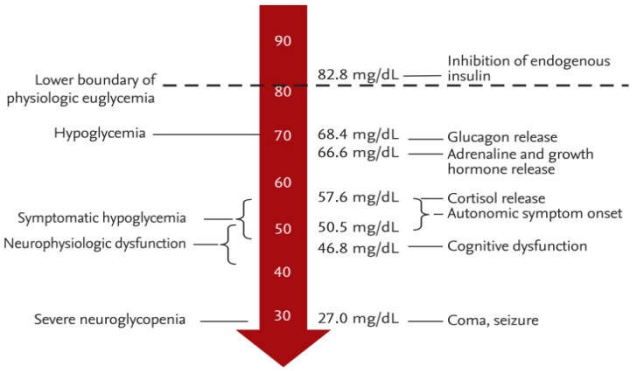

Fig 4 Emergency Medicine

Because it acts primarily by stimulating glycogenolysis, glucagon is ineffective in glycogen depleted individuals (e.g., those with alcohol induced hypoglycemia). It also stimulates insulin secretion and is therefore less useful in type 2 diabetes mellitus. These treatments raise plasma glucose concentrations only transiently, and patients should be encouraged to eat as soon as practical to replete glycogen stores [41, 42].

Prevention of Recurrent Hypoglycemia

Prevention of recurrent hypoglycemia requires an understanding of the hypoglycaemic mechanism. Offending drugs can be discontinued or their doses reduced. It should be remembered that hypoglycemia caused by sulfonylureas may recur after a period of several hours or days. Underlying critical illnesses can often be treated [43]. Cortisol and growth hormone can be replaced if deficient. Surgical, radiotherapeutic, or chemotherapeutic reduction of a non cell tumor can alleviate hypoglycemia, even if the tumor cannot be cured; glucocorticoid or growth hormone administration may also reduce hypoglycemic episodes in such patients [44]. Surgical resection of an insulinoma is often curative; medical therapy with diazoxide or octreotide can be used if resection is not possible and in patients with a nontumor primary cell disorder [45]. The treatment of autoimmune hypoglycemia (e.g., with a glucocorticoid)is more problematic, but this disorder is often self limited [46]. Failing these treatments, frequent feedings and avoidance of fasting may be required [47]. Uncooked cornstarch at bedtime or an overnight infusion of intragastric glucose may be necessary in some patients [48-50].

CONCLUSION

Diabetes Mellitus is a costly disease for developing economies of the global. It is necessary to have an improved understanding of its hypoglycemia and management (treatment). Supports from government authorities, scientists, clinical practitioners and nongovernmental organizations can be reduce the incidence of Diabetes mellitus and its complications significantly

Financial Support and sponsorship
Nil
Conflicts of interest
None declared

References

1. Frier BM. How hypoglycaemia can affect the life of a person with diabetes. *Diabetes Metab Res Rev*. 2008; 24:87-92.
2. Seaquist ER, Anderson J, Childs B, *et al*. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013; 36:1384-1395.
3. Frier BM. Defining hypoglycaemia: what level has clinical relevance. *Diabetologia*. 2009; 52:31-34.
4. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013; 36:1033–46.
5. Ligthelm RJ, Kaiser M, Vora J, Yale JF. Insulin use in elderly adults: Risk of hypoglycemia and strategies for care. *J Am Geriatr Soc* 2012; 60:1564-70.
6. Dadan J, Wojskowicz P, Wojskowicz A. Neuroendocrine tumors of the pancreas. *Wiad Lek*. 2008; 61(1-3):43-47.
7. van Heerden JA, Edis AJ, Service FJ. The surgical aspects of insulinomas. *Ann Surg*. 1979;189(6):677-682
8. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009; 94(3):709-728.
9. Waiel A. Bashari, Naomi E. Riddel, Samson O. Oyibo. A Man With Whipple's Triad Secondary to a Malignant Insulinoma. *J Med Cas*. 2015;6(7): 07-308
10. Everlon Cid Rigobelo. Hypoglycemia - Causes and Occurrences. In tech publishers, Rijeka, Croatia. 2011; 1-14.
11. Philip E. Cryer. Diverse Causes of Hypoglycemia Associated Autonomic Failure in Diabetes. *J of Med*. 2004; 2(7): 2272-2279.
12. M. Stumvoll, C. Meyer, A. Mitrakou, V. Nadkarni, J. E. Gerich. Renal glucose production and utilization: new aspects in humans.spinger.1997; 40: 749-757.
13. Graveling AJ, Frier BM. Hypoglycaemia: an overview. *Prim Care Diabetes*. 2009; 3:131-139.
14. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin treated Type 2 diabetes: frequency, symptoms and impaired awareness. *Diabet Med*. 2003; 20:1016-1021.

15. Zammitt NN, Streftaris G, Gibson GJ, *et al*. Modeling the consistency of hypoglycemic symptoms: high variability in diabetes. *Diabetes Technol Ther*. 2011; 13:571-578.
16. El Khoury M, Yousuf F, Martin V, Cohen RM. Pseudohypoglycemia: a cause for unreliable finger stick glucose measurements. *Endocr Pract*. 2008; 14:337-339.
17. Guillod L, Comte Perret S, Monbaron D, *et al*. Nocturnal hypoglycaemias in type 1 diabetic patients: what can we learn with continuous glucose monitoring? *Diabetes Metab*. 2007; 33:360-365.
18. Weber KK, Lohmann T, Busch K, *et al*. High frequency of unrecognized hypoglycaemias in patients with type 2 diabetes is discovered by continuous glucose monitoring. *Exp Clin Endocrinol Diabetes*. 2007; 115:491-494.
19. Donnelly LA, Morris AD, Frier BM, *et al*. Frequency and predictors of hypoglycaemia in type 1 and insulin treated type 2 diabetes: a population based study. Diabet Med. 2005;22:749-755
20. Frier BM. Hypoglycaemia in diabetes mellitus: Epidemiology and clinical implications. *Nat Rev Endocrinol* 2014; 10:711-22.
21. . Moen MF, Zhan M, Hsu VD, *et al*. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009; 4: 1121-1127.
22. Philip E. Cryer. Mechanisms of Hypoglycemia Associated Autonomic Failure in Diabetes. *J Diabe.*2013; 6(7): 369:362-372.
23. G B Bolli E, Tsalikian, W Haymond , P E Cryer,J E Gerich. Defective glucose counterregulation after subcutaneous insulin in noninsulin dependent diabetes mellitus. Paradoxical suppression of glucose utilization and lack of compensatory increase in glucose production, roles of insulin resistance, abnormal neuroendocrine responses, and islet paracrine interactions.1984; 73(6): 1532-1541.
24. Bakatselos SO. Hypoglycemia unawareness. *Diabetes Res Clin Pract*. 2011;1: 93:92-96.
25. Unger J, Parkin C. Recognition, prevention, and proactive management of hypoglycemia in patients with type 1 diabetes mellitus. *Postgrad Med.* 2011; 123:71-80.
26. Schopman JE, Geddes J, Frier BM. Frequency of symptomatic and asymptomatic hypoglycaemia in type 1 diabetes: effect of impaired awareness of hypoglycaemia. *Diabet Med.* 2011; 28:352-355.
27. Banarer S, Cryer PE. Sleep related hypoglycemia associated autonomic failure in type 1 diabetes: reduced awakening from sleep during hypoglycemia. *Diabetes*. 2003; 52:1195-1203.
28. . Jones TW, Porter P, Sherwin RS, *et al*. Decreased epinephrine responses to hypoglycemia during sleep. N *Engl J Med*. 1998; 338: 1657-1662.
29. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329:977-86.
30. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352:837-53.
31. Lipska KJ, Ross JS, Wang Y, *et al*. National trends in US hospital admissions for hyperglycemia and hypoglycemia among medicare beneficiaries, 1999 to 2011. *JAMA Intern Med* 2014; 174:1116-24.
32. Engler B, Koehler C, Hoffmann C, *et al*. Relationship between HbA1c on target, risk of silent hypoglycemia and glycemic variability in patients with type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2011; 119:59-61.
33. Lipska KJ, Montori VM. Glucose control in older adults with diabetes mellitus; More harm than good. *JAMA Intern Med* 2013; 173:1306-7.
34. Kevin Stuart, Annmarie Field, Jessie Raju, Sudarshan Ramachandran. Reactive Hypoglycaemia: Varying Presentation Patterns on Extended Glucose Tolerance Tests and Possible Therapeutic Approaches. Case Reports in Medicine. 2013; 1:1-5.
35. S.Del Prato, A.Riccio, S.Vigil de Kreutzenberg, M.Dorella. Mechanisms of fasting hypoglycemia and concomitant insulin resistance in insulinoma patients .*J Diab.*1993; 42(1):24-29.
36. Ignacio Aramendi, Gastón Burghi, William Manzanares. Dysglycemia in the critically ill patient: current evidence and future perspectives. *Rev Bras Ter Intensiva*.2017; 29(3):364-372.
37. Elora Mukherjee, ichard Carroll. Endocrine and Metabolic Emergencies: Hypoglycaemia. *Adv End Dis.*2011; 2(2): 81–93.
38. Chang Yun Woo, Ji Yun Jeong, Jung Eun Jang, Jaechan Leem, Chang Hee Jung, Eun Hee Koh, Woo Je Lee. Clinical Features and Causes of Endogenous Hyperinsulinemic Hypoglycemia in Korea. *J Diab Met.*2015; 1:1-16.
39. Stuart Berkowitz, James E. Parrish,James B. Field. Factitious hypoglycemia. *Amer J Med*.1971; 51(5): 669–674.
40. Fred D. Hofeldt, Peter H. Forsham .Diagnosis and classification of reactive hypoglycemia based on hormonal changes in response to oral and intravenous glucose administration. *Am J Cli Nut*.1972;35(11): 1193–1201
41. A Brackenridge, H Wallbank, R A Lawrenson, D Russell Jones. Emergency management of diabetes and hypoglycaemia. *J Eme Med*.2006; 23:183-185.
42. A Brackenridge, H Wallbank, R A Lawrenson. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin dependant diabetes mellitus. *N Engl J Med* 1993; 329:977–86.
43. Tan P, Chen HC, Taylor B, Hegney D. Experience of hypoglycaemia and strategies used for its management by community dwelling adults with diabetes mellitus: a systematic review. *Int J Evid Based Healthc*. 2012; 10:169-180.
44. Vindedzis S, Marsh B, Sherriff J, *et al*. Dietary treatment of hypoglycaemia: should the Australian recommendation be increased? *Intern Med J.* 2012; 42:830-833.
45. Cox DJ, Gonder Frederick L, Polonsky W, *et al*. Blood glucose awareness training (BGAT-2): long term benefits. *Diabetes Care*. 2001; 24:637-642.

46. Hermanns N, Kulzer B, Kubiak T, *et al*. The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients with type 1 diabetes. *Diabetes Metab Res Rev*. 2007; 23:528-538.
47. Chelliah A, Burge MR. Hypoglycaemia in elderly patients with diabetes mellitus: Causes and strategies for prevention. *Drugs Aging* 2004; 21:511-30.
48. Chiasson, JL.; Josse. RG. & Gomis, R. Acarbose for prevention of type 2 diabetes mellitus: the stop NIDDM randomized trial. *The Lancet*. 2002; 359:2072-2077.
49. Kimura, T. Development of mulberry leaf product with a glucosidase inhibitor for the prevention of type2 diabetes mellitus. Nippon Shokuhin Kagaku KogakuKaishi. 2010; 57(2):57-62.
50. Katherine L. Griffing. Hypoglycemia Prevention in Hospital Patients: A Quality Improvement Project to Prevent Severe and Recurrent Hypoglycemia. Bri Exc. 2016; 34(4):193-199.

How to cite this article:

Siva Rami Reddy E (2018) 'Hypoglycemia: A Complete Review', *International Journal of Current Advanced Research,* 07(2), pp. 10281-10288. DOI: http://dx.doi.org/10.24327/ijcar.2018.10288.1733

****