Proceeding S.Z.P.G.M.I vol: 15(1) 2001, pp. 47-55.

Review Article

Hypoglycaemia - A Serious Medical Emergency - Review

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Most of the vital organs are dependent on intact vascular supply for their appropriate functions. This vascular supply not only provides oxygen for consumption but also glucose. Brain is the most sensitive organ and cannot tolerate hypoxia or hypoglycaemia for more than a few seconds to a few minutes respectively. Severe hypoglycaemia due to any cause is associated with a significant mortality and morbidity. As hypoglycaemia can potentially cause severe irreversible brain damage, therefore this emergency must be treated and reversed as a matter of utmost urgency.

Hypoglycaemia was defined by Third International Symposium on Hypoglycaemia as a blood glucose level of less than 50mg/dl or 2.8mmol/l[1]. On the other hand hypoglycaemia is defined as the documentation of low blood glucose concentration, associated with symptoms and relief of these symptoms by correction of the low blood glucose also known as Whipple's triad[2].

The definition of hypoglycaemia by the Diabetic Control and Complication Trial(DCCT) Research Group is perhaps the most useful guide as shown below[3].

It is defined as an event resulting in seizures, coma, confusion, irrational behaviour, or other symptoms consistent with hypoglycaemia e.g sweating, palpitations, hunger or blurred vision in conjuction with blood glucose <50mg/dl (2.8mmol/l) or confusion, irrational or uncontrollable behavior or convulsions or coma reversed by treatment that raises blodd glucose concentration or prodromal symptoms of hypoglycaemia e.g sweating, palpitations, hunger or blurred vision[1-4].

Body can tolerate a decrease in blood glucose up to certain extent. The usual figure quoted is blood glucose of 2.8mmol/l or 50mg/dl and at this level the patient experiences typical features of hypoglycaemia which will be discussed later in the article. However, if this is not treated then one develop a condition called neuroglycopoenia when brain functions start deteriorating and this happens at a blood glucose level of 2.2mmol/l or 39.6mg/dl. If this is not treated urgently, then irreversible brain damage occurs and the patient enters in a vegetative state which may linger on for many weeks to months just adding on to more problems.

Types of hypoglycaemia

There are a number of causes of hypoglycaemia but hypoglycaemic agents especially sulphonylurea, insulin and excess intake of alcohol constitute the major causes of attending emergency departments of busy hospitals. In hospitalized patients, hypoglycaemia is associated with diabetic treatment, liver diseases, severe sepsis, shock, chronic renal failure, pregnancy, neoplasia and even burns.[2]

Hypoglycaemia has been classified in different ways and one of the long established classification of hypoglycaemia as fasting and postprandial are no longer used as segregation by timing does not result in different events. Now a days the classification is based on clinical characteristics. Depending upon this these groups can be divided into the following:

1. Hypoglycaemia in healthy appearing patients
2. Hypoglycaemia in ill appearing patients
3. Hypoglycaemia in hospitalized patients

These causes are tabulated in the Table 1.

Table 1: Clinical classification of hypoglycaemic disorders.

1. **Healthy appearing patients.**
   No existing disease
   Drugs:
   - Ethanol
   - Salicylates
   - Quinine
   - Haloperidol
   - Macrolides

   Insulinoma
   Islet hyperplasia
   Factitious hypoglycaemia
   - Insulin
   - Sulfonylurea

Continued

Intense exercise
Ketotic hypoglycaemia

Coexisting disease
Drugs:
- Dispensing errors
- Disopyramide
- Beta blockers
- Ackee fruit poisoning

2. **Ill appearing patients.**
Cause or predisposing condition
Drugs:
- Pentamidine
- Trimethoprim
- Quinine for cerebral malaria
- Topical salicylates and renal failure
- Lithium[5]
- Alcohol

Illness or condition:
- Erythroblastosis fetalis
- Hyperinsulinaemia in infants due to maternal diabetes.
- Non pancreatic neoplasms[6]. Mesodermal(spindle cell fibrosarcoma, leiomyosarcoma, mesothelioma, rhabdomyosarcoma, liposarcoma, neurofibroma and reticulum cell sarcoma)
- Adenocarcinoma(hepatoma, gastric carcinoma, adrenocortico carcinoma and caecal carcinoma)
- Glycogen storage disease
- Reyes syndrome
- Hypopituitarism
- Growth hormone deficiency
- Addison's disease
- Sepsis
- Renal failure
- Starvation
- Anorexia nervosa
- Insulin antibody hypoglycaemia
- Chronic liver disease

3. **Hospitalized patient**
Cause or predisposeing condition
- Hospitalization for a predisposing illness
- Total parenteral nutrition and insulin therapy
- Shock

Artifactual Hypoglycaemia

A pseudo hypoglycaemia occurs in certain chronic leukaemias when the leukocyte count is markedly raised. The hypoglycaemia is due to utilization of glucose by the leukocytes. This is not associated with symptoms. Other causes include improper collection and storage, errors in analysis methodology, or confusion between blood and plasma glucose values. The plasma glucose is about 15% higher than corresponding whole blood glucose values.

Prevalence

The data on hypoglycaemia prevalence is sparse. At least one third of children with diabetes had experienced severe hypoglycaemia during the course of the disease[7]. In studies of patients in a hospital setting between 30-55% of patients with Type-1 diabetes had hypoglycaemia on blood monitoring especially during night[8,9]. Less information Is available about hypoglycaemic episodes in Type-2 diabetic patients. Two large studies done in Switzerland[10] and Sweden[11] reported incidences of 0.24 comas/1000 patients years and 0.19 comas/1000 patients year respectively.

Between 3-5% of deaths occur in patients with Type-1 diabetes[12,13]. In patients with Type-II diabetes, mortality with sulphonylurea induced hypoglycaemia is 10% with higher rate of occurrence in the elderly[14].

Another study[1], shows that there was an incidence of 1.2%. Mortality was 27% with no correlation with age or sex, and the risk factors included renal, malnutrition, liver disease, infections, shock, malignancy, burns and hyperkalaemia therapy.

Pathophysiology

The brain requires 120-140 gm of glucose per day for normal functions. Only special parts of brain can use ketone bodies in fasting state. Acute glucose deprivation triggers counter-regulatory mechanisms. The brain is unable to withstand hypoxia for more than 10 seconds to the least whereas brain can withstand low blood glucose level a little bit more. Total glycogen content of the brain is about 1.6 mg/gm of brain tissue in fasted animals, but available glycogen and glucose are used up in 2 minutes if the blood supply is totally occluded. Cortical regions are more sensitive to hypoglycaemia than vegetative centers in the brain stem. One of the important steps in hypoglycaemia is the cessation of secretion of endogenous insulin which occurs at a plasma glucose level of 80 mg/dl (4.3 mmol/l). Hypoglycaemia also triggers at least

four counter-regulatory hormones i.e glucagons, epinephrine, growth hormone and cortisol. Epinephrine and glucagon increase glucose by glycogenolysis and if secretion continues then it stimulates gluconeogenesis. Cortisol enhances supply substrate for gluconeogenesis while nor-epinephrine increases gluconeogenesis. Epinephrine also inhibits secretion of insulin which assists in restoring blood glucose concentration but is less important in the insulin-treated insulin-deficiency in the patient. Growth hormone decreases the utilization of glucose in various peripheral tissues and cortisol has also a similar action. If both epinephrine and glucagon fail to increase the response to hypoglycaemia then there is no compensatory increase in blood glucose. In long standing diabetics, the autonomic symptoms may not occur and resulting hypoglycaemia unawareness can be a clinical problem[15]. Same effect is produced by beta adrenergic blockers which block the sympathetic symptoms which cause awareness of hypoglycemic symptoms in case of hypoglycaemia[16-20].

Glucagon appears to be the most important. counter regulatory hormone, and recovery from hypoglycaemia is prompt if its secretion is intact. In its reduction catecholamines serve as counter regulatory mechanism. In non-diabetics, when blood glucose utilization increases sharply (as in exercise) or when glucose input is increased (as after meals), there is naturally little shift in glycaemia. Insulin secretion is regulated through feed back loop, with blood glucose. In patients with diabetes, these mechanisms are derranged and hypoglycaemia results because of an absolute or relative excess of insulin.

Somogyi effect is a post hypoglycaemic hyperglycaemia. Recent evidence is that epinephrine and growth hormone may be the major counter-regulatory hormones involved in this phenomenon.

Insulin is the commonest cause of severe hypoglycaemia in diabetic patients but less than one third of all episodes are treated by emergency medical services[21]. In the UK, 25-30% of the patients are affected annually with an incidence of 1.1-1.6 episodes per patient per year[22-24].

In insulin dependent diabetics, intensive insulin therapy to produce strict glycaemic control can result in a three fold increase in the incidence of severe hypoglycaemia as compared to conventional insulin regimens[25]. Hypoglycemia unawareness resulting in loss of warning symptoms becomes increasingly common the longer patients have diabetes and is associated with 4-5 fold increase in the risk of severe hypoglycaemia[26]. Combined deficiencies of glucagon and adrenaline, increase the risk of severe hypoglycaemia by 25 fold[27]. Other factors include following:

- History of previous severe hypoglycaemia
- Long duration of diabetes
- Recent fall in glycated haemoglobin
- High dose of insulin per kg body weight
- Sleep
- Age of the patient
- History of hypoglycaemia unawareness
- Counter regulatory hormonal deficiencies

During the first 5 years of Type-1 diabetes the normal glucagon response is lost[28]. Cortisol and adrenergic responses then compensate but with increasing duration of diabetes the normal cortisol response is lost first and then finally the adrenergic responses. Insulin autoimmune hypoglycaemia is extraordinarily rare, reported more commonly in Asians of all ages and races. There is a history of autoimmune disorder or use of drugs containing sulfhydryl. Insulin antibody titers are higher. Spontaneous remission is observed as there is no specific treatment. In intensively treated subjects, predictors of severe hypoglycaemia include history of severe hypoglycaemia, longer duration of Type1 diabetes and higher baseline HbA1c. The incidence of severe hypoglycaemia was higher in DCCT than the two smaller studies of intensive management of Type1 diabetes mellitus[29,30].

Sulfonylureas stimulate release of endogenous insulin and cause 1-2% of all cases of hypoglycemia requiring emergency treatment[31,32]. One has to restrict carbohydrate intake, reduce ethanol consumption, avoid use of other drugs which potentiate the effect and presence of hepatic and renal failure also result in decreased metabolism and excretion of these drugs resulting in their increased level and thus potentiating the effect.

Alcohol inhibits hepatic gluconeogenesis where as glycogenolysis is unaffected and hypoglycemia has been documented after heavy consumption in those patients whose glycogen stores are already depleted. It does not correlate with plasma alcohol levels. Impaired consciousness from hypoglycemia in patients who have a history of alcohol abuse may

wrongly be attributed to the effects of alcohol, therefore an urgent blood sugar level is mandatory. Alcohol taken particularly without food can cause severe hypoglycemia.

Symptoms

The clinical features are those of neuroglycopoenia and of autonomic (principally sympatho-adrenal) over activity. When hypoglycaemia develops rapidly then adrenergic symptoms predominate as follows:

Pallor	Hunger	Nervousness
Nausea	Angina	Tremulousness
Flushing	Anxiety	Sweating and palpitations

When hypoglycaemia is severe then neuroglycopoenic symptoms are more obvious. The lower the blood sugar, the severer are the neuroglycopoenic manifestations which include:-

-	Headache	Difficulty in awakening in the morning
-	Blurred vision	Senile dementia
-	Paraesthesia	Organic personality syndrome
-	Weakness	Transient hemiplegia
-	Tiredness	Transient aphasia
-	Confusion	Seizures
-	Drowsiness	Coma
-	Amnesia	Abnormal mentation
-	Incoordination	Behavioural changes

The following Table indicates plasma glucose levels in venous blood and the events taking place.

Plasma glucose mmol/l	mg/dl	Effect
4.6	83	inhibition of insuline secretion
3.8	70	glucagon, epinephrine, GH secretion
3.2	58	cortisol secretion
2.8	50	cognitive dysfunction
2.2	40	lethargy
1.7	30	coma
1.1	20	convulsions
0.6	11	permanent brain damage

Obviously, the onset of hypoglycaemic symptoms call for prompt treatment which is discussed in the later section of this article. Episodic hypoglycaemia might cause permanent brain damage[33-35].

Diagnosis

Hypoglycemia is a clinical diagnosis, confirmed of course by on the spot blood glucose determination. It should be suspected in patients who are diabetic and are on treatment i.e. either insulin or oral hypoglycaemic agents. A history of diabetes may be available from relatives or any information in the previous clinical record available at hand. In developed countries, an identification bracelet may be found on examination along with features of lipodystrophy at insulin injection sites. Sweating, tremors, tachycardia, wide pulse pressure and restlessness may occur. Hypothermia may also occur. Hypoglycaemia unawarness causes problems in management[36]. Test strips for capillary blood glucose are widely available but are misread and are inaccurate at low glucose concentration. It is important to note that treatment should not be with held for the sake of establishing a biochemical diagnosis.

Biochemical/laboratory Investigations

After exclusion of obvious causes of fasting hypoglycaemia i.e renal, hepatic failure, drugs, endocrinopathies etc the basic work up is to rule out hyperinsulinaemia.

1. **Fasting insulin/glucose levels:** Prolonged fast upto 72 hours with frequent blood glucose measurements. When hypoglycaemia occurs plasma insulin, C-peptide, cortisol and growth hormone levels should be obtained. Hypoglycaemia occurs in 60% in first 24 hours, 85% in 48 hours and 97-98% in 72 hours.

   A high level of insulin during the fast in relation to plasma glucose will confirm the diagnosis of hyperinsulinaemia. The glucose insulin ratio and other ratios i.e Turner etc. are not used any more to diagnose hyperinsulinaemia.

   After the fasting test, the criteria of insulinoma or hyperinsulinaemic hypoglycaemia depends on following:

   - Plasma insulin level > 6Uu/ml
   - C-peptide value >200pmol/ml
   - Pro-insulin level >5pmol/ml
   - Beta-hydroxybutyric acid level <2.7mmol/l
   - An increament of plasma glucose in

response to 1 mg of glucagons iv >25mg/dl
Absence from plasma of first and second generation sulfonylurea.

This is applicable whenever hypoglycaemia develops in fasting state or after meals i.e 2 to 4 hours post-prandial[37].

Insulin antibodies were once believed to be a firm evidence of factitious hypoglycaemia due to self administration of insulin (when beef or porcine insulin were used) but at present (in the era of human insulin) it is diagnostic of insulin autoimmune hypoglycaemia especially if titres are high[38].

After the diagnosis of hyperinsulinaemia one should proceed to localize the tumour. Various methods have been used including trans abdominal and endoscopic ultrasonography, triple phase computed tomography, angiography and octreoscaning etc. Trans hepatic portal vein sampling is abondened in most tertiary centers. The selective arterial calcium stimulation test not only regionalizes the lesion but also is a useful dynamic test to identify hyperfunctioning islet cell tissue[39].

Non-insulin pancreatogenous hypoglycaemia syndrome is a newly described entity of neuroglycopoenia occurring postprandially primarily in men who have negative results on 72 hours fast, negative results on radiological localization studies, positive outcome on calcium stimulation test,amelioration of symptoms by gradient guided partial pancreatectomy and presence of islet hyperplasia and nesidioblastosis in resected pancreata [40].

3. **Pro insulin levels:** Pro-insulin / insulin ratios are elevated in insulinomas i.e. >30%

2. **C-peptide suppression test:** The C-peptide suppression test may be used as a screening test. Interpretation of the test requires normative data appropriately adjusted for the patient's body mass index and age.

Measurement of C-peptide during the hypoglycemic episode helps to distinguish between the two conditions i.e. factitious administration of insulin and insulinoma. Patients with insulinoma have evidence of excessive insulin secretion as characterized by high value of insulin, proinsulin and C-peptide during hypoglycemia whereas patients who have self administration of insulin, due to suppressed functions of endogenous beta islet cells, C-peptide is reduced during hypoglycaemia where as insulin values are elevated. In patients taking factitiously oral sulfonylurea have laboratory results similar to those of the patient with insulinoma, such as elevated C-peptide value; their pro-insulin level, however is normal. In tumours, hypoglycaemia is associated due to secretion of Insulin Growth Factor (IGF-II). By binding to hepatic insulin receptors, IGF-II inhibits production of hepatic fructose and promotes hypoglycaemia. Utilization of glucose by tumorous cells is another hypothesis but not very strongly agreed upon.

MANAGEMENT

The management includes two steps, Firstly, the restoration and maintenance of euglycaemia and secondly treatment of complications.

Glucose

This is the most important step and mainstay of the treatment. Oral liquid carbohydrates may be given if the patient is semi conscious with intact swallowing reflex. In drowsy children buccal administration of glucose gels, jam or honey may be useful. In the unconscious patient 50 mls of 50% Dextrose solution given intravenously will raise the blood sugar from less than - 1.0 mmol/l to 12.5 mmol/l in 5 minutes[41]. The administration of such high concentration can be given by paramedical staff as well[42]. The complications of IV administration of glucose are thrombophlebitis and localised tissue necrosis if extravasation occurs.

Glucagon

This hormone is produced by alpha-cells of the pancreatic islets and increases blood glucose by stimulating hepatic glycogenolysis by stimulating activity of an enzyme called phosphorylase. It is also a beta cell secretagogue and stimulates insulin release from functioning islets. The dose is 1.0 mg s/c or i/m The route is either subcutaneous, intramuscular or intravenous[12], but intranasal preparation are coming up and require a special surfactant vehicle[43]. Recovery of consciousness is slightly slower than with intra venous dextrose[41] but glucagon can be given to uncooperative or

aggressive patients without the risks of venous thrombosis or tissue necrosis. Nausea, headache and vomiting are common side effects.

Minor side effects are present with intranasal route icluding tingling sensations in the nose for1-2 minutes.Intra nasal glucagons acts more rapidly than subcutaneous route[44,45].

It was shown that glucagon restored consciousness in 40 of 100 diabetic patients with in 15 minutes of administration, but a further 40 required intravenous dextrose[12]. This indicates that patients who have been hypoglycaemic for one or more hours have depleted their hepatic glycogen. In this situation intravenous dextrose is essential. Glucagon can be administered[13,46] at home by the relatives of the diabetic patient. It is essential to administer glucose after glucagons injection otherwise the patient may lapse in to hypoglycaemia

Glucagon should be avoided in sulfonylurea induced hypoglycaemia where glucagon will stimulate insulin release, so protracting hypoglycaemia.

In conditions associated with severe hepatic glycogen depletion i.e. prolonged starvation, inanition and hepatic failure, glucagon should be avoided.

Other Measures

When the patient has regained consciousness, he should be given oral carbohydrates and measures are taken to prevent recurrence by adjusting the dose of therapeutic regimens or treating the underlying cause. Continuous 5% or 10% dextrose may be required in patients who are unable to eat, in those who have not regained consciousness and when hypoglycaemia is expected to recur (large doses insulin or sulfonylurea). Blood glucose should be monitored frequently and maintained around 10-15 mmol/l which is best achieved by continuous infusion of dextrose, potassium chloride and insulin e.g 500 ml of 10% dextrose with 10mmol of potassium chloride and 16 units of soluble insulin infused at a rate of 100ml per hour.

Sulfonylurea induced hypoglycaemia might require intravenous dextrose for several days. Octreotide(which suppresses insulin release from pancreatic beta-cells) has been reported anecdotally to be a useful adjunct to intravenous dextrose in the treatment of sulfonylurea induced hypoglycaemia[47].

If there ia an evidence of insulinoma, one can opt for medical management first then surgical options latter. The commonly used drugs include diazoxide, phenytoin, propranolol, streptozocin and fluorouracil.

Treatment of Complications

Hypoglycaemia has mortality of 2-4% in most series[48] and has been implicated as a cause of unexpected sudden death in young adult patients with insulin treated diabetes[49]. It ia associated with significant morbidity[50].

The complications are summarized as following:

Neurological
- Convulsions
- Transient hemiplegia, TIA's
- Cerebral oedema
- Brain damage
- Cognitive impairment

Cardiac
- Myocardial ischaemia
- Transient arrhythmias

Infections
- Soft tissue (bruising)
- Fractures
- Joint dislocations

Ophthalmological
- Retinal detatchment
- Vitreous haemorrhages

Metabolic
- Hypokalaemia

Neurological Complications

Other than loss of consciousness and convulsions the important clinical consequences are the acute development of cerebral oedema and permanent disabling cognitive dysfunction.

A number of neuropsychological tests to analyze brain damage affecting cerebral hemispheres especially the frontal lobe can be performed. These tests include, digit span test, trail making test and maze test which have a higher sensitivity for detecting diffuse organic brain damage. The Necker cube test differentiates unilateral from bilateral frontal damage, and tapping test assesses motor functions and coordination between the two hemispheres[23].

Cerebral oedema is rare but a serious complication of severe hypoglycaemia and should be considered in patients who have failed to regain consciousness after restoration of blood glucose concentration to normal. Other causes of impaired consciousness such as alcohol intoxication, sedation, post ictal state, cerebral haemorrhage or thrombosis should be excluded. There for CT scan of the brain is mandatory primarily to exclude an alternative and remediable intra cerebral pathology.

Patient should be nursed in the intensive care unit and 20% IV mannitol in the dose of 20ml over 20 minutes should be administered and/or dexamethasone 4mg IV 6 hourly. High inspired oxygen concentrations i.e 100% using a face mask or controlled hyperventilation may also be beneficial. Convulsions should be treated with anti convulsant drugs. Cerebral oedema carries a poor prognosis with a 10% mortality and long term neurological damage occurs in 35% of the cases[12].

Generalised or focal convulsions are not uncommon during hypoglycaemia and get better with normalization of blood glucose. Transient hemiplegia may persist after hypoglycaemia has been treated[51,52] but no specific therapy is indicated. In protracted hypoglycaemic states neuronal necrosis can occur and may be mediated by excitotoxins[53].

Cardiac Complications

Myocardial ischaemia and dysrrhythmias such as atrial fibrillation and ventricular ectopics can be precipitated by hypoglycaemia[54-56] but revert to sinus rhythm after correction of hypoglycaemia. No specific therapy is required unless circulatory collaose occurs. Serum potassium normally falls[57] and will need active correction.

Infections

These occur in about 7% of the patients[24] and require appropriate treatment.

It is important to note that unnecessary, more complicated and expensive investigations can be avoided if blood samples are taken at the time of hypoglycaemia for insulin and C-peptide levels.

Hospitalized patients have a disrupted life style, they eat less palatable food, may have to be fasted for different tests or surgery and they are ill therefore don't eat well either which contribute to hospitalized induced hypoglycaemia especially in insulin dependent diabetics.

Nonetheless hypoglycaemia is dreaded by all diabetics[58] and death is a recognized complication of hypoglycaemia and multisystem damage may result one or repeated episodes of hypoglycaemia[59].

FUTURE AND PREVENTION

The cause of hypoglycaemia should be determined if possible, although it is difficult in diabetic patients treated with insulin. One should adjust therapy and give practical advice about the dosage schedule of insulin and oral hypoglycaemic agents, diet, exercise and alcohol consumption. Prophylactic measures to avoid hypoglycaemia in the diabetic patients are very important and involve careful education and frequent home blood glucose monitoring. Drugs which interfere with the counter-regulatory responses i.e beta blockers should be used cautiously or rather avoided in diabetics. Following this strictly can extremely help to avoid this serious medical emergency which can result in horrible consequences.

Recent advances in reference to hypoglycaemia are important to mention. These include:

- Glucose sensoring systems which sense hypoglycaemia and patient becomes aware of it to take necessary actions.
- Electronic systems
- Microdialysis tubes
- Glucowatch biographer
- Automated device for blood glucose monitoring

More over different trials of insulins have shown good results. Insulin lispro(Humalog) reduces the risk of hypoglycaemia and nocturnal hypoglycaemia quite significantly due to short action.

Other trial has been conducted with insulin glargine which is a long acting analogue of insulin and it has shown considerable decrease in overall episodes of ordinary and nocturnal hypoglycaemia.

Continuous subcutaneous insulin infusion (CSII) has shown that it reduces the frequent episodes of hypoglycaemia than multiple daily insulin injections (MDI).

An important aspect in context with hypoglycaemia is psychoeducational programme designed to improve accuracy of patient's detection

and interpretation of blood glucose results and to take appropriate actions accordingly.

Lastly it is stressed that to avoid such a serious and potentially lethal condition it is important to have more frequent screening, better treatment to encounter less frequent hypoglycaemic attacks and better education for earlier recognition and treatment.

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