REVIEW

NEUROGLUCOPENIA IN DIABETES

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An abnormally low glucose concentration can be caused by a number of factors, such as drugs, tumors, altered gastrointestinal anatomy and failure of both endocrine and non-endocrine tissues. Hypoglycemia occurs commonly in diabetics on treatment. One third of these patients suffer from one episode of severe hypoglycemia and lose consciousness at some time during their life time.

Brain is the only organ besides heart, that suffers functional and structural impairment under conditions of hypoglycemia. The normal brain has a glucose reserve of 1-2 gm (10 mmol/100gm of brain tissue) mostly in the form of glycogen. Since glucose is utilized by brain at a rate of 60-80 mg/minute, the reserve will sustain the cerebral function for about 30 minutes only, once glucose is not available (2).

DEFINITION

One major problem is how to define hypoglycemia, i.e. what concentration of glucose is abnormally low? An important consideration is whether whole blood or plasma glucose concentrations are being measured. The glucose concentration in plasma or serum is 15% (not 15mg/dl, sometimes written as 15mg%) higher than in whole blood. The conditions under which the blood sample is drawn are also important. For instance, a plasma glucose concentration of 54mg/dl is abnormal after an overnight fast, but not 4 hours after a carbohydrate-rich meal or an oral challenge with dextrose (Table 1).

Table 1. Criteria for Definition of Hypoglycemia

Glucose conc. (mg/dl)	Condition of Patient	
	Fasting	Fed State
Plasma	<60	<50
Whole blood	<50	<40

Anti Diabetic Drugs

Hypoglycemia is a common side-effect of treatment with insulin, sulphonylureas or meglintides. It does not occur with metformin, α-glucosidase inhibitors, thiazolidinediones or dietary management alone. Each year, 25-30% of all insulin-treated patients suffer one or more episodes of severe hypoglycemia, i.e. that requiring the assistance of others. The risks of mild and severe hypoglycemia increase steadily as glycemic control is improved. Sulphonylureas-induced hypoglycemia occurs less frequently than with insulin. Many episodes of hypoglycemia in the elderly may be misdiagnosed as vascular or cardiac events.

Other Factors predisposing diabetic patients to hypoglycemia include :

1. Inadequate food intake
2. Exercise
3. Weight loss
4. Renal failure, which reduces the clearance of insulin and sulphonylureas
5. Drugs that increase the bioavailability of sulphonylureas
6. Alcohol
7. Adreno-cortical, thyroid or pituitary failure
8. Impaired awareness
9. Long duration of diabetes
10. Sleep

Insulin sensitivity and the risk of hypoglycemia increase dramatically after delivery of the placenta in a diabetic pregnancy and the energy drain of lactation also favors hypoglycemia. Alcohol inhibits gluconeogenesis and glucose production by the liver, and therefore, predisposes to hypoglycemia, which may be delayed, prolonged and severe. The Diabetes Control and Complication Trial (DCCT) research group had observed that 55% of all the

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hypoglycemic episodes occur in sleep and in 33% of the episodes there were no warning signs. 30% of the episodes were associated with seizures and coma (4).

Non-selective β-adrenoceptor blocking drugs, but not β_1-selective agents, inhibit sympathetic-mediated glycogenolysis and gluconeogenesis in the liver and therefore delay recovery from hypoglycemia.

The continuing fall in blood glucose levels normally triggers a fixed hierarchy of events. They are as follows:

1. Inhibition of insulin secretion (at ~ 4.6 mmol/l);
2. Release of glucagon and adrenaline (~ 3.8 mmol/l);
3. Hypoglycemic symptoms (~ 3.0 mmol/l).
4. Cognitive function is progressively impaired below 2.8 mmol/l, and
5. Coma usually supervenes with glucose values < 1.0 mmol/l. (3)

PATHOPHYSIOLOGY

The exact pathophysiology of the cerebral disorder secondary to hypoglycemia has not been fully elucidated. It is known that hypoglycemia reduces oxygen uptake and decreases cerebral blood flow. There is evidence that the excitatory amino acid glutamate, is ultimately involved in functioning of neurons, when blood glucose falls. The brain can utilize glucose substrates like ketoacids to a variable extent for its metabolic needs. Hypoglycemia also acts on adrenal glands and autonomic nervous system to induce corrective gluconeogenesis. However, in the face of severe and sustained hypoglycemia, these substrates are not adequate to preserve the integrity of cerebral neurons (2). The initial changes are seen in mitochondria, first in dendrites and then in the soma. Ultimately there is rupture of cell membrane and cell death (5).

SYMPTOMS

People have different thresholds for neuroglycopenia and effective hypoglycemic level is different in various people or may even differ in the same individual at different times. This threshold is affected by the rate of fall, the size of fall and the habitual glycemic levels (1).

Hypoglycemic symptoms can be classified as (Table 2) :

a) *Autonomic* i.e. due to sympathetic or parasympathetic discharge (e.g. sweating, palpitations, tremor, hunger).

b) *Neuroglucopenia*

Mild to moderate (<2.8 mmol/dl)
- Intellectual impairment
- Impaired cognitive functions
- Depressed psychomotor skills
- Incoordination
- Drowsiness

Severe hypoglycemia
- Confusion
- Irritation
- Aggressive behavior
- Automatism

Profound hypoglycemia (<1 mmol/dl)
- Convulsions and Coma

Table 2. Signs and Symptoms of Hypoglycemia

Adrenergic	**Neuroglucopenic**
Weakness	Headache
Sweating	Hypothermia
Tachycardia	Visual disturbance
Palpitations	Mental dullness
Tremor	Confusion
Nervousness	Amnesia
Irritability	Seizures
Tingling of mouth & fingers	Coma
Hunger	
Nausea	
Vomiting	

Normal : Adrenergic symptoms » 60 mg/dl
Neuroglucopenic symptoms ≤50 mg/dl

Diabetics : Hypoglycemic unawareness
Experience only the neuroglucopenic symptoms

c) *Non-specific* (malaise, nausea, headache).

Other *physiological effects* of hypoglycemia include :

i. Diversion of blood flow from skin and kidneys to brain, liver and muscle;
ii. Widened pulse pressure
iii. Transient mobilization of leukocytes
iv. Increased platelet activation and blood viscosity, which may compromise the microcirculation.

COUNTER REGULATORY MECHANISMS

Blood glucose levels recover after hypoglycemia due to direct sympathetic stimulation of hepatic glucose output, and the actions of counter-regulatory hormones, of which glucagon and adrenaline are the most potent.

Glucagon (whose secretion is stimulated directly by glucopenia) and adrenaline, released from the adrenal medulla, both stimulate hepatic gluconeogenesis and glycogenolysis, and adrenaline also increases proteolysis and the supply of gluconeogenic amino acids. Growth hormone, cortisol and vasopressin have weaker, but synergistic roles.

Many patients with long-standing type 1 diabetes mellitus do not mount adequate glucagon and adrenaline responses to hypoglycemia, and this greatly delays recovery. Failure of glucagon secretion may be due to insensitivity of the a cell to hypoglycemia. The adrenaline defect is probably due to specific failure of the central nervous system to recognize hypoglycemia, as adrenaline responses to other stimuli (e.g. exercise) are preserved. This central autonomic failure may also account for alterations in glycemic thresholds for symptoms and neuro-endocrine responses, and perhaps for hypoglycemic unawareness. This may be due to cumulative brain damage, due to recurrent hypoglycemia (5).

EFFECT OF HYPOGLYCEMIA

Severe and prolonged hypoglycemia may result in permanent impairment of intellectual functions, Korsakoff amnesia and protracted coma. However, lower degree of chronic hypoglycemia can have varied manifestatins (Table 3).

Table 3. Sequelae of Hypoglycemia

1. Fits (which can cause fractures and dislocations),
2. Acute hemiplegia
3. Intellectual impairment
4. Personality and behavioral changes.
5. Drowsiness
6. Lethargy
7. Reduced psychomotor skills
8. Deterioration of social behavior
9. Confusion
10. Tremors
11. Chorea
12. Cerebellar ataxia
13. Amyotrophy

Subacute Hypoglycemia : may manifest as drowsiness, lethargy, reduced psychomotor skills, deterioration of social behavior and confusion.

Chronic Hypoglycemia : leads to gradual deterioration of intellectual functions, tremors, chorea, ataxia (cerebellar) and amyotrophy (7).

When blood glucose level descend to 50 mg/dl, the initial autonomic symptoms appear and then gradually give way to confusion, drowsiness and, excitement. Occasionally, it leads to overactivity or bizarre behavior (2). In the next stage, forced sucking, grasping, restlessness, muscle spasms and decerebrate rigidity occurs. In children, the manifestations are mainly behavioral and learning disabilities, whereas in adults, they may present as vertebro-basilar insufficiency and transient ischemic attacks (8).

Severe hypoglycemia can result in focal neurological deficit causing hemiplegia and focal or generalized convulsions. Blood glucose level of 10 mg/dl are associated with deep coma, dilated pupils, pale skin, shallow respiration and hypotonia of all the limbs and is known as *"Medullary phase"* of hypoglycemia. The manifestations of hypoglycemia are reversible before the medullary phase has set in. Once medullary phase sets in and persists for some time, recovery is often incomplete (2).

Up to 7% of all patients developing hypoglycemia, develop convulsions (9). These have been attributed to altered integrity of neuronal membrane, elevated ammonia and depressed GABA and lactate levels (10). Permanent neurological deficit is rare, but is seen in diabetic patients who are alcoholics also (11).

Focal neurological deficit was shown by Melouf and Brust in only 3 out of 125 patients. All of them had hemiplegia and recovered with glucose given intravenously (12). In another study by McCrimman et al, out of 55 patients studied, none had focal neurological deficit (8).

Very few patients surviving chronic and protracted hypoglycemia may develop cortical or hippocampal atrophy and may remain in a vegetative state (5). Adult diabetics exposed to severe and recurrent hypoglycemia over several years develop slight but significant reduction in I.Q., with subtle changes in cognitive functions (13). Hypoglycemia accounts for 2-4% of all deaths of type 1 diabetes. Severe sulphonylurea-induced hypoglycemia carries a mortality of up to 10%.

HYPOGLYCEMIA UNAWARENESS

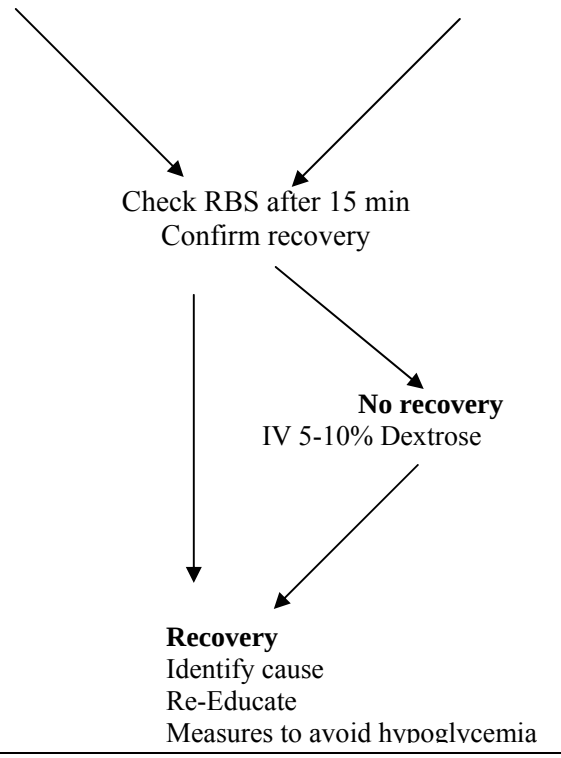
The absence of warning signs in patients with hypoglycemia is known as "hypoglycemia unawareness". 25% of the diabetic patients are unaware of hypoglycemic episodes and this impairment increases with duration of diabetes. 50% of diabetics with a disease of more than 20 years duration have some degree of impaired awareness and are more prone to develop severe hypoglycemia (3).

The DCCT research group recommends that diabetic patients on anti-diabetic drugs; especially on treatment with insulin, should be frequently monitored to avoid behavior such as taking excessive insulin/OHAs, delaying or missing meals, excessive exercise without dosage adjustments and excessive consumption of alcohol (4).

TREATMENT

Hypoglycemia should be treated immediately by oral glucose (15-20 g) or if the patient is unable to swallow safely, with intravenous glucose (30-50 ml of 50% solution) or intramuscular or subcutaneous glucagon (1 mg). Patients usually recover within minutes. Failure to do so may be due to cerebral edema or a postictal state. Hypoglycemia induced by sulphonylureas may be very prolonged; it must not be treated with glucagon (which stimulates insulin secretion) and may require intravenous glucose infusion for hours or even days (1) (Fig 1).

Fig 1. Treatment of Hypoglycemia in Diabetes



PROPHYLAXIS

Prevention of hypoglycemia must be of high priority. Adequate education of the patients and their relatives is necessary to emphasize that hypoglycemia can be avoided and treated effectively at an early stage.

1. Patient should carry an identity card or wear a bracelet stating that they are diabetics.
2. Relatives, friends and colleagues at work or at school should be made familiar with the signs of hypoglycemia and its emergency management.

3. Importance of regular meals and snacks should be emphasized and treatment adjusted appropriately.

4. Very strict glycemic control should be avoided where the risk of significant hypoglycemia outweighs the potential benefits.

Proper education of the patients regarding all these possibilities will go a long way in preventing future attacks of hypoglycemia.

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