Review Articles

Hypoglycemia in the diabetic patient[#]

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Abstract

Today, hypoglycemia is an inevitable consequence of diabetes intensive treatment, especially with insulin therapy.

The authors review the clinical aspects of hypoglycaemia in diabetes. After a brief introduction about glucose metabolism, glucoregulation and counter regulatory failure, they describe the symptoms, causes and consequences, the hypoglycaemia unawareness, its prevention and treatment.

Key words: hypoglycaemia, hypoglycaemia unawareness.

Introduction

There are numerous possible causes of hypoglycemia - more than a hundred. Some of the causes are so rare that they are never observed, even by those with longer experience.

Hypoglycemia induced by diabetes treatment is common, and is observed on a daily basis. It is also, incidentally, the main impediment to intensive treatment. Conversely, the absence of hypoglycemic episodes in a diabetic treated with insulin causes professionals to doubt whether its treatment is reliable.

Before discussing the topic in depth, a brief review is given of glucose metabolism, glucose counter-regulation, and its failure in cases of diabetes.

Glucose metabolism

With short-term fasting, the production of glucose is used mainly by the brain, with only a small portion being captured by other tissues, such as the muscles, which can use other alternative sources of energy. The main source of glucose is liver *glycogen* (60-80%); the remainder is produced from neoglycogenesis, the main substrates of which are glycerol, obtained from triglyceride hydrolysis, and amino acids, obtained from proteins.

However, in longer fasting periods, major hormonal changes occur, such as a marked reduction in insulin and an increase in *glucagon*. These changes promote glycogenolysis and neoglycogenesis, with the liver metabolism being focused on ketogenesis and favoring the transfer of fatty acids to the mitochondria. Lipolysis is facilitated in the adipose tissue, through the reduction in insulin levels and the increase in growth hormone. Meanwhile, the reduction in circulating T3 leads, on one hand, to a decrease in the baseline metabolism (<25%) in order to save energy and, on the other hand, to a limitation of protein degradation (for each gram of synthesized glucose, 1.75g of protein is necessary).

With a longer fasting period, metabolic adjustments occur, particularly in the Central Nervous System (CNS) which begins to use ketone bodies as its main source of energy. As the concentration of ketone body increases, their use also increases, to the point where, in longer fasting periods, the brain reduces the glucose consumption, from about 100 to 35 g/day. The glycogen deposits are depleted, and neoglycogenesis becomes the sole source of glucose. The relative importance of its precursors is altered, significantly lowering the contribution of the amino acids in order to preserve the proteins essential for life. The kidney has become an important neoglycogenesis organ, using glutamine as its main substrate.

In diabetic patients who are taking insulin, the most important difference in relation to a healthy individual is the relatively high insulinaemia levels, independent of the decreasing glycaemia levels, with hypoglycemia being an inevitable consequence, and all this is aggravated in long-term disease, due to the failure of hormonal counter-regulation and delay in restoring glycaemia levels.

Glycaemia Regulation

Insulin is the main factor in glycaemic regulation,

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suppressing the endogenous production of glucose through the reduction in neoglycogenesis and promoting the formation of glycogen and glycolysis, in addition to its effects on the metabolism of fats (stimulating the synthesis of fatty acids in the liver and inhibiting their use, suppressing ketogenesis) and proteins (stimulating protein synthesis and inhibiting proteolysis).

Glucagon, adrenalin, growth hormone and cortisol are the most important factors for glycaemic counter--regulation.

In tested hypoglycemia, glucagon increased by about 2 to 3 times, with a very rapid onset (minutes) and a transient effect, quickly stimulating glycogenolysis in a transitory manner, and neoglycogenesis, but having no effect on the protein or fat metabolisms. In acute hypoglycemia, adrenalin can be rapidly increased by about twenty times, with a prolonged effect, stimulating the hepatic production of glucose and inhibiting its use, while stimulating lipolysis and ketogenesis. Growth hormone and cortisol take a longer time to increase (hours). Both stimulate glucose production, decreasing its use and stimulating lipolysis; while the former promotes protein synthesis, the latter promotes its degradation.

During hypoglycemia, neurotransmitters such as noradrenalin (sympathetic post-ganglionic neurons) are released, with similar effects to those of adrenalin, and acetylcholine (parasympathetic neurons), and an inhibiting effect on the hepatic production of glucose.

Failure of hormonal counter-regulation

It is commonly observed that diabetic patients lose the ability for the autonomic symptomatic response that is characteristic of hypoglycemia.

Causes of hormonal counter-regulation failure of glycaemia include age, level of metabolic control, occurrence of repeatedly frequent hypoglycemia, use of medications, and autonomic neuropathy. The importance of the duration of diabetes was clearly demonstrated by Bolli et al., in a study on type 1 diabetic patients, divided into three groups, according to the length of time the patient had had the diabetes (less than one month, between one and five years, and more than ten years): No change occurred to the counter-regulation response in the first group, a change in glucagon response occurred in the second group, and in the third group, which was associated with autonomic neuropathy, there was a marked

TABLE I
Autonomic symptoms

Natural, sudden appetite
Slight sweating
Sudden asthenia
Inner trembling
Intense, voracious hunger
Pale skin
Profuse sweating
Tachycardia
Palpitations
Nausea
Vomiting

reduction in the glucagon and adrenalin responses.[1]

Whereas in patients with long-term diabetes, the occurrence of hypoglycemia is aggravated due the delay in hormonal counter-regulation, in diabetes resulting from pancreatectomy, this defense is particularly compromised by the total absence of *glucagon* in the pancreas, and mortality by hypoglycemic coma is higher than in insulin-dependent diabetes.

Little is known regarding counter-regulation in type 2 diabetes.

Symptoms of hypoglycemia

The symptoms of hypoglycemia vary from one individual to another, and can vary within the same individual, due to the environment, sleep, etc.

The symptoms can be classified into three groups:
1. Autonomic symptoms These are produced by the activation of sympathetic and parasympathetic divisions of the Autonomic Nervous System, due to a direct effect of neuronal stimulation of the target organs, and are increased by hormonal secretion, particularly of adrenalin (*Table I*).
2. Neuroglycopenic symptoms These are caused by a lack of cerebral glucose, probably influenced by other factors that have not yet been clarified (*Table II*).
3. Non-specific symptoms These are repeatedly reported by diabetic patients, but with no logical explanation. They include paresthesia of the nuke, blurred vision, waking up in the middle of the night, as though it were morning, and crying for no reason, etc.

TABLE II

Neuroglycopenic symptoms

Slight confusion

Headache

Bradypsychism

Difficulty concentrating

Repeated yawning

Apathetic, inane expression

Intense asthenia

Drowsiness

Dysarthria

Aphasia

Emotional incontinence

Being disoriented

Parestesias (lips…)

Diplopia

"Ddrunken" behavior

Psychotic crises

Primitive actions (sucking…)

Catatonia

Epileptiform crises

Coma

Death

Many external influences may affect the symptomatic response to hypoglycemia, such as physical activity, sleep, environmental temperature, alcohol consumption, taking beta-blockers, sedatives, and body posture.

For example, a diabetic patient who takes physical exercise and pays no attention to tachycardia, or a glassworker who relates sweating to the temperature in his working environment.

During sleep, diabetic patients are particularly vulnerable to hypoglycemia because sleep alters the threshold for autonomic activation, and it is not uncommon to see cases of diabetic patients who, when woken up, begin to feel a range of adrenergic symptoms, or become voraciously hungry for no apparent reason. The fact of lying down itself can also contribute to the lack of symptoms.[2]

During sleep, some diabetic patients suffer from extremely severe hypoglycemia, manifested by epileptiform crises similar to a *grand mal* seizure, which is frequently attributed to idiopathic epilepsy, and incorrectly medicated as such. In fact, the same can occur with a diabetic patient who is awake, if the autonomic symptoms are blocked by neuropathy or by beta-blockers, or more commonly, due to "response burn-out" caused by repeated long-term hypoglycemia.

Alcohol fundamentally alters the interpretation of the symptoms, and not their actual identification;[3] conversely, beta-blockers may reduce or even eliminate the palpitations.

Main causes of hypoglycemia in the diabetic patient

The most common causes of hypoglycemia in the diabetic patient are delayed consumption of food, which commonly occurs when patients are attending medical consultations, or traveling, or through incorrect splitting of meals, errors in the insulin dosage or taking inappropriate doses of sulphonylurea, unforeseen physical exercise without supplementary ingestion of carbon hydrates, or a reduction in anti-diabetic therapy, particularly if administered immediately after rapid insulin injection.[4]

Physical exercise may be a cause of late onset hypoglycemia, often manifesting a long time after the exercise (6-15 hours) and causing severe night-time hypoglycaemia.[5]

Renal failure causes hypoglycemia due to several factors, including lower insulin clearance and the simultaneous presence of anorexia, weight loss, gastroparesis and frequent treatment with beta-blockers for high blood pressure.

Alcohol abuse is an important cause of hypoglycemia in diabetic patients, not only because it interferes in counter-regulation by inhibiting hepatic neoglycogenesis, but because it can go unrecognized by the diabetic patient. In addition, the signs of alcohol intoxication may be similar to the signs of hypoglycemia (*Table III*).

Unnoticed hypoglycemia

Described soon after the application of insulin by Josin and colleagues,[6] an inability of consciously recognize the onset of hypoglycemia is widely observed in long-term diabetics, as they progressively lose autonomic manifestations during a crisis, with an increasing prevalence of neuroglycopenic symptoms that tend to remain. Unnoticed hypoglycemia is beco-

Incorrect splitting of meals

Incorrect insulin dosage

Physical exercise (immediate and late hypoglycemia)

Acute remission at the start of treatment

Improvement in metabolic control

Weight loss

Post partum diabetes

Renal failure

Hepatic failure

Alcohol abuse

Change of injection site

Effects of temperature (sauna…)

Injection depth (IM)

Gastroparesis

Poor absorption

Counter-regulation failure

ming increasingly common, even among short-term diabetics, due to the so-called "intensive" treatments, which are currently focused on better prevention of the later complications of diabetes.

In the DCCT trial, for example, 36% of hypoglycemia was not recognized by the diabetic patients.[7]

While in these patients, restoring this ability may be easily achieved, almost always when the limits of the metabolic balance loosen, in patients with long--term disease, the recovery of this ability is usually impossible, and the only alternative is to attempt to prevent the occurrence of hypoglycemia as far as possible (insulin regimes as "physiological" as possible, frequent determination of capillary glycaemia, especially at bedtime…).

The exact cause of this fact is yet not known, though it is probably related to a cerebral "adaptation" to hypoglycemia in acute cases.[8] Neuropathic or iatrogenic blockage of the autonomic syndrome is the obvious cause in certain cases. The extremely gradual decrease in glycaemia occurs with sulphonylureas and was first observed with the introduction of the first delayed action insulin, protamine zinc insulin, this "slow hypoglycemia" is one of the first causes of this phenomenon. Nevertheless, in our experience, by

far the main cause of unnoticed hypoglycemia in an insulin-dependent diabetic patient is neuroglycopenia without vegetative early symptoms and with frequent long-term hypoglycemia, incorrectly treated by removing sugar from diet (which should be reserved for serious symptoms…) and by any other food with slower digestion.

Immediately after the clinical application of "human" insulin begun, it was suggested that it is responsible for this loss of acute perception of hypoglycemia. However, Jorgensen and colleagues, in a study involving 39 clinical trials and 12 epidemiological studies, concluded that this was false, because only one of them proved it.[9]

Neurological consequences of hypoglycemia

Severe neuroglycopenia can cause profound changes to the CNS through several mechanisms, including a lack of glucose in the neurons; secondary, localized changes to the blood stream; neuronal ischemia; and edema of the brain, due to the treatment.

Transient hemiplegia is sometimes observed in adults, but is extremely rare in children. While in some cases, it is attributed to localized atherosclerotic lesions, with the disappearance of episodes after its removal, its presence is not easy to explain when it appears in children or, alternatively, on both sides in the same diabetic patient in different hypoglycemic crisis (vascular spasm?).

Convulsive crises, particularly at the night, are common in diabetic patients treated with insulin, and can manifest transitory or permanent electro-encephalographic changes, similar to those of idiopathic epilepsy. In the diabetic patient treated with anticonvulsants and recurrent crises, hypoglycemia is immediately suspected as the primary cause. In fact, the association between hypoglycemia and epilepsy is a "vicious cycle" – it is not only deep hypoglycemia that can trigger epileptogenic foci; in manifest or latent epilepsy, in particular, even mild hypoglycemia may be convulsant.

Cases of muscle weakness were reported after serious and repeated hypoglycemia, which is attributed to lesion of the *peripheral nervous system*. However, this system is not absolutely dependent on glucose (except for the cranial nerves), and may use other sources, such as fatty acids and amino acids, a condition that is probably due to anterior horn necrosis in the bone marrow.[10]

Hypoglycemia and vascular disease

Hypoglycemia may have drastic consequences for the diabetic patient with advanced macrovascular disease.

The occurrence of cardiac arrhythmia during hypoglycemia, such as auricular, ventricular or nodal extrasystoles, is common, and acute auricular fibrillation was repeatedly observed in insulin shocks, which were used in the past to treat schizophrenia, and in experimental hypoglycemia, disappearing when glycaemia was adjusted. They are due, on one hand, to the release of catecholamines and consequent increase in ectopic activity; hypokalaemia; and the positive inotropic effects of insulin, and, on the other hand, to the effect of localized glycopenia, both in the myocardium and the conduction tissue itself.

The increase in cardiac rate and debit leads to higher oxygen consumption – in the patient with advanced atherosclerosis, with stenosed arteries, effective compensation cannot occur and myocardial ischemia is the final outcome. However, angina pectoris is not frequently reported, probably due to the co-existence of advanced neuropathy, given that several cases of silent ischemia (ST depression) have been reported in monitored patients. Acute myocardial infarction may occur in extreme cases, although few cases have been described.

Hypoglycemia can also aggravate microangiopathy due to localized effects on the tissues. The aggravation of retinopathy within the initial months after changing from conventional treatment to intensive treatment is also well-known,[7] as well as the triggering of vitreous hemorrhage caused by a sudden reduction in ocular pressure, due to the hypoglycemia.

Hypoglycemia in type 2 diabetic patients

Its incidence is much lower than in insulin-dependent diabetes (IDD), and is largely increased in combined treatment (oral anti-diabetic + insulin).

Among the sulphonylureas, chlorpropamide and glibenclamide are the drugs mostly responsible for hypoglycemia events, although any one of them may have a potential risk, particularly gliquidone, which, despite its short half-life (less than 2 hours), has already been reported in cases of hypoglycemic coma.

Chlorpropamide is largely responsible for cases of prolonged and recurrent hypoglycemia, due to its long half-life (20-40 hours), while glibenclamide, with a shorter half-life (10-16 hours), has a marked hypoglycemic effect, not only because of the major suppres-

sion of the glucose hepatic debit, but also because of its deposition in the pancreatic islets. Overdose is a more significant factor than prolonged half-life; even with the "old" short-term administration of Tolbutamide, hypoglycemia, once diagnosed and treated, can occur, now and then, over the subsequent two days. It is as though the sulphonylurea were functioning as a "short-term insulinoma"...

There is no doubt that many cases of sulphonylurea-induced hypoglycemia are not duly accredited as such, particularly among, the elderly, but are attributed, instead, to dementia, psychosis, TIA or even stroke.

When treatment with insulin is begun in type 2 diabetic patients, the risk of hypoglycemia and its consequences are high, especially because the patients are older (age, as a factor by itself, decreases hypoglycemia counter-regulation).[11]

Preventing hypoglycemia

Educating the diabetic patient is fundamental for preventing hypoglycemia.

The diabetic patient who is properly educated will be able to recognize hypoglycemia from its initial signs, and treat it immediately with sugar, and only then with slow-absorbing carbohydrates. The patient should carry out a self-assessment after each event, to determine its cause. Eating the correct amounts at the correct times is essential, as is taking supplementary carbohydrates for the planned exercise. The patient should always carry sugar in some form (sucrose, glucose…) and a diabetic identification card explaining the hypoglycemia treatment. Patients must have injectable glucagon at home, to be administered, where necessary, by the closest family member, who should be previously instructed. Glycaemia levels should be measured regularly, particularly at bedtime.

Treating hypoglycemia

1. Hypoglycemia identified by the diabetic patient

First measure (urgent): Ingestion of sucrose (20-25 g) or glucose.

Complete disappearance of symptoms

Second measure (compulsory): Ingestion of slow absorption CH.

2. Hypoglycemia with moderate changes in consciousness

Offer sucrose "mashed" (due to the risk of aspiration!). Use gentle persuasion, bearing in mind the

patient's psychological state at this moment (negativism, disorientation, aggressiveness, affirmation of the ego).

3. Hypoglycemia with serious changes in consciousness

At home, by the family members (reluctance of some): glucagon = 1 mg (SC, IM.)

Intranasal glucagon (spray) will, it is hoped, make administration easier, in the near future.

At the hospital, hypertonic solution of glucose at 50mg% (50 ml = 25 g)

4. Hypoglycemia in children

Similar to adults (20-25g of sucrose).

Glucagon: 0.5 mg in children under 6-8 years; 1 mg in older children.

Intravenous glucose:

hypertonic glucose bolus: 0.2 – 0.5 g/kg

Perfusion of 4-6 mg/kg/minute*

5. Hypoglycemia in non-dependent insulin diabetic patients taking sulphonylurea (and/or insulin)

Considerations:

• Identify the sulphonylurea (most prolonged treatment!)

• Identify other potentiating drugs (salicylates, sulphamide, warfarin, probenecid, non-steroidal anti-inflammatory...).

• Ask the patient if they are taking beta-blockers.

• Do not administer glucagon (due to its insulin stimulating effect)

• Restart administration of sulphonylurea at a lower dose only after 1 to 2 days of permanent glycosuria.

6. Hypoglycemia in diabetic patients taking acarbose in association with sulphonylureas

Do not treat with sucrose (disaccharide).

Treat with glucose.

Never use acarbose in conjunction with insulin therapy.

Lack of appropriate treatment for diabetic patients

There are many reasons for non complying with the adequate treatment of hypoglycemia: psychological blockage when taking sugar, lack of adequate instruction, fear of subsequent hyperglycemia (following massive glycosuria), not having sucrose, treatment with other CHs (biscuits, cakes...), which will delay the recovery of normoglycaemia due to delayed digestion, failure to notice the hypoglycemic crisis, etc. ■

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* It is advisable not to administer high amounts of glucose, as this has been attributed as the cause of the death in a small number of children following the induction of hypoglycemia for endocrinological diagnosis[12]