

# Syncope and Hypoglycemia

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## ABSTRACT

**Objective:** This review focuses on syncope in diabetic patients who suffer from hypoglycemia. Clinically, transient loss of consciousness during hypoglycemia appears similar to vasovagal syncope. **Research Design and Methods:** Current understanding of this problem is based on physicians' personal experiences as well as on published case reports. It is difficult to explain a temporary loss of consciousness as a result of hypoglycemia. Demonstration that hypoglycemia can be transient, with the patient suffering from neuroglycopenia without autonomic symptoms due to delayed counter-regulation, might be a first step in confirming that a diabetic patient suffered from a transient loss of consciousness with spontaneous recovery. **Results:** Hypoglycemic syncope is uncommon, affecting 1.9% of diabetic patients using insulin therapy. It is characterized clinically by brief periods of unconsciousness with slow recovery and without loss of postural muscle tone. The difficulty in correlating loss of consciousness to hypoglycemia arises from mismatching symptoms, that is, there may be mental symptoms such as confusion, loss of memory or consciousness, in the absence of autonomic manifestations such as sweating or blurred vision. There are currently no established glucose values that define the level of hypoglycemia that causes loss of consciousness. **Conclusion:** Hypoglycemic syncope should be suspected in older diabetic patients with preserved postural tone, usually but not always using insulin therapy, who show a slow recovery from transient loss of consciousness with persisting neurological impairment and low blood glucose levels.

**Keywords:** Syncope, Diabetes, Hypoglycemia, Transient Loss of Consciousness

## 1. Introduction

Hypoglycemia is a well-known cause of coma which can be resolved by glucose infusion, and is thus the opposite of syncope, which is characterized by transient loss of consciousness (LOC) followed by spontaneous recovery. Authoritative textbooks and International Guidelines include hypoglycemia among the causes of syncope and classify it as a type of metabolic syncope [1,2]. Examples of true LOC which are not syncope include epilepsy, several metabolic disorders (including hypoxia and hypoglycemia), and intoxication. It is thus possible that hypoglycemia gave a transient, self-limited LOC that mimics syncope; however, hypoglycemia lacks acute, transient, and reversible hypotension and cerebral hypoperfusion, which is the patho physiological mechanism that underlies syncope.

Trials comparing aggressive versus conventional glycaemic therapy in diabetic patients frequently report patients experiencing hypoglycemic episodes, but no cases of transient LOC have been noted [3]. This discrepancy merits further investigation.

## 2. Methods

This review is based on my personal experience of leading and working in the field of syncope in the Autonomic Unit at the S. Maria Hospital supported by an up-to-date literature review performed by searching PubMed and the Cochrane Library.

## 3. Results

In clinical practice, patients who experience hypoglycemia associated with LOC are elderly, long-term diabetic patients, taking glucose-lowering drugs. When witnessed, such a crisis is described as a brief LOC that lasts minutes, either with preserved postural tone or associated with increased muscular tone and automatisms (*i.e.* dysskinetic contractions of the mouth, eye, and facial muscles) followed by a slow recovery of consciousness. The patient's subjective experience of hypoglycemic crisis is true LOC preceded by malaise and followed by a variable period of confusion. Patients experiencing this brief LOC with hypoglycemia have blood glucose levels that are generally below the normal. Administration of glu-

cose can stop the hypoglycemic crisis, but complete recovery of consciousness may be delayed [4]. Is this true syncope? Probably not. It is a LOC but can not be defined as syncope.

Hypoglycemia is characterized by symptoms related to blood glucose levels less than 70 mg/dl, the threshold value at which hormonal counterregulation begins. Physiologically, hormonal counterregulation establishes normal glycaemic values through the release of catecholamines via the sympathetic nervous system/adrenal glands and by activation of the hypophyseal/adrenal axis. Autonomic symptoms are due to neurohormonal compensatory activation. In the laboratory setting, blood glucose levels values less than 50 mg/dl indicate hypoglycemia.

Bedside hypoglycemia is classified as slight, moderate, or severe depending on symptom severity. Slight hypoglycemia produces symptoms related to activation of the autonomic nervous system (anxiety, tremor, swelling, tachycardia). In moderate hypoglycemia, symptoms arise from an inadequate supply of glucose to the brain, termed "neuroglycopenia"; symptoms vary widely depending on blood glucose levels and patient characteristics (non-diabetic or diabetic, young or elderly, having long-term diabetes, drug use, and basal neurological performance status). Symptoms characteristic of moderate hypoglycemia may include the following: blurred vision, drowsiness, short-term memory loss, attention deficit or difficulty concentrating, defective psychomotor skills, numbness, impaired ability to remain awake, neurological focalities, and seizures [5]. Severe hypoglycemia induces hypoglycemic coma.

Blood glucose values and symptoms are related as follows, depending on the patient's clinical characteristics, comorbidities, and basal glucose levels: values of 70 - 65 mg/dl activate neurohormonal counterregulation; values of about 54 mg/dl are associated with autonomic nervous system symptoms; and values below 50 mg/dl are associated with neuroglycopenia symptoms [6].

Hypoglycemic syncope is reported as isolated experiences [7]. Metabolic syncope is comprising about 5% of all syncope. Hypoglycemic syncope is the most common metabolic syncope, with a reported incidence of 0.6% in diabetic patients and 4% in diabetic patients who take insulin [7]. Instead, the true incidence of hypoglycemic syncope is unknown due to the lack of established diagnostic criteria.

Autonomic activation secondary to hypoglycemia is highly variable and is related to the presence or absence of diabetes as well as to the patient's age. Consequently, clinical presentation of hypoglycemia varies widely.

Use of continuous glucose monitoring systems has demonstrated that both healthy and diabetic patients can recover spontaneously from moderate hypoglycemia [8].

In the diabetic patient, moderate hypoglycemia is due to delayed counterregulation that is activated at lower blood glucose levels than in healthy controls. Slow recovery from moderate hypoglycemia is due to a delayed compensatory mechanism in diabetic patients taking glucose-lowering agents. Patients with insulin-dependent diabetes lack glucose counterregulation and suffer from moderate hypoglycemia more often than patients taking oral glucose-lowering agents [3]. The delayed hormonal counterregulation is the cause of progressive hypoglycemia which in turn causes the changes of consciousness ranging from slight confusion to LOC. This is the phenomenon termed "hypoglycemic syncope", related to moderate hypoglycemia. These patients suffer from neuroglycopenia. The incidence is about 0.1 - 0.3 episodes/patient/day [8].

Mental behavior during hypoglycemia has been studied experimentally in elderly diabetic patients. Many studies have confirmed that these patients experience memory loss, impaired consciousness, and visuospatial deficits during complex activities such as driving and walking [5].

Due to attenuated neurohormonal response, elderly diabetic patients who are over 65 years old present with different symptoms than do younger (24 - 49 year old) patients. Specifically, elderly patients present with subtle symptoms that may be difficult to detect clinically: minimal sweating, slight pallor, and confusion [9]. Due to an adaptive process of the central nervous system, repeated hypoglycemic episodes progressively worsen the patient's ability to recognize hypoglycemic symptoms. In the absence of sympathoadrenal symptoms, impaired mental status is the main clinical sign of hypoglycemia [10]. Subjects older than 65 years appear to be at particularly high risk of hypoglycemia and to suffer from cognitive function impairment [10].

Of note, in the elderly the perception of hypoglycemic symptoms was found to occur simultaneously with impairment of cognitive functions during gradual reduction in blood glucose levels [9]. This is in contrast to the well-known hierarchical succession of central nervous system responses to hypoglycemia in younger healthy adults, who normally perceive their hypoglycemic symptoms at higher glucose levels as a sympathoadrenal response (primarily epinephrine and norepinephrine) rather than as cognitive dysfunction [10].

The diagnosis of hypoglycemic syncope is challenging due to the lack of specific symptoms and universal clinical and laboratory criteria. Clinical suspicion arises when syncope occurs in a diabetic elderly male patient with a long history of use of oral glucose-lowering agents or, more frequently, insulin treatment. The syncope generally occurs during the day time during fasting. The patient experiences a LOC and generally cannot remember

subsequent events. The postural tone is characteristically preserved, but witnesses are aware that there is something wrong with the subject. The patient is pale, but sweating and elevated heart rate are not observed, and blood pressure is generally not different from the patient's usual blood pressure. Recovery is slow but may be quicker if sugar or food is administered, as often occurs during the crisis. Clinostatism does not reverse the crisis as it generally does vasovagal syncope. Consciousness returns slowly, and the patient gradually becomes able to speak (with slurred speech). Witnesses may note that the patient "was not him/herself" and that the patient returned to his/her normal mental status within a few hours. Thus, the patient experiences impaired mental status after the LOC episode.

Low blood glucose during the episode is highly diagnostic. When tested later (*i.e.* in the emergency department), the blood glucose level is generally borderline hypoglycemia (70 mg/dl); higher levels are rarely observed unless food or drugs have been administered.

We conducted an observational study, limiting patient enrollment to a single referral center in order to establish uniform diagnostic criteria and treatment options (which are generally lacking in published reports). Accordingly, we screened 18,556 consecutive patients who came to the emergency department from June 1, 2009 to December 31, 2009. The patients, who had a mean age of 74 years, were split into a diabetic group ( $n = 2,775$ ; 15% of all recruited patients; mean age, 74 years) and a non-diabetic group. Diabetic patients were identified who were taking oral glucose-lowering agents or insulin ( $n = 416$ ; 15% of all diabetic patients; mean age, 67 years). Among these patients, we selected those who had experienced a LOC without postural tone with a post-critical interval who fulfilled the criteria for hypoglycemic syncope. There were 8 such patients (1.9% of the 416 patients using oral glucose-lowering agents or insulin) with a mean age of 71 years (range: 66 - 84 years).

Diagnostic criteria included the following: LOC, preserved postural tone, slow recovery with persisting neurological impairment, and low blood glucose levels. Mean blood glucose levels at diagnosis were  $85 \pm 17.5$  mg/dl in the absence of medical treatment; however, it must be noted that blood glucose measurements lose diagnostic value if they are determined after any drug has been administered.

The difficulty in correlating LOC with hypoglycemia arises from mismatching symptoms, that is, neuroglycopenic symptoms in the absence of autonomic manifestations. There are no established glucose values that define hypoglycemia leading to LOC; paradoxically, for a diabetic patient suffering from impaired glucose regulation, the most common diagnostic test is not reliable for de-

termining hypoglycemic syncope.

#### 4. Conclusions

In conclusion, hypoglycemia is not a true cause of syncope, and impaired mental status due to hypoglycemia should not be defined as syncope. The relationship between hypoglycemia and epilepsy remains to be investigated in terms of epidemiology and clinical patterns, as some episodes could be classified as a secondary epileptic crisis induced by neuroglycopenia. It is possible that neuroglycopenia causes inappropriate neuronal discharge that is somewhat similar to that described for complex partial seizures. However, epidemiological data are still lacking, and although hypoglycemia is relatively frequent, hypoglycemic syncope is rare.

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