



Tinjauan Pustaka

## Hypoglycemia: Updates on Diagnosis and Treatment

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### ABSTRACT

#### Abstract

*Hypoglycemia is a condition where blood glucose concentration decreases below 70 mg/dL with or without signs or symptoms. Hypoglycemia symptoms may vary from mild to life-threatening conditions, or be classified based on the severity as mild-moderate and severe hypoglycemia. Mortality in patients with severe hypoglycemia was 3 times greater than in patients who experienced mild-moderate hypoglycemia. Management of hypoglycemia is classified based on its severity. Appropriate therapy is needed for hypoglycemia patients because untreated hypoglycemia will reduce the patient's quality of life. Understanding symptoms, prevention, and the management of hypoglycemia is needed, especially in patients who have experienced severe hypoglycemia so that it does not lead to recurrence or fatal condition.*

**Keyword:** Hypoglycemia, Diagnosis, Treatment

#### Abstrak

Hipoglikemia adalah kondisi di mana konsentrasi glukosa darah menurun di bawah 70 mg/dL, dengan atau tanpa tanda dan gejala. Gejala hipoglikemia dapat bervariasi mulai dari ringan hingga kondisi yang mengancam jiwa, atau diklasifikasikan berdasarkan tingkat keparahannya menjadi hipoglikemia ringan-sedang dan berat. Mortalitas pada pasien dengan hipoglikemia berat tiga kali lebih besar dibandingkan dengan pasien yang mengalami hipoglikemia ringan-sedang. Penatalaksanaan hipoglikemia diklasifikasikan berdasarkan tingkat keparahannya. Terapi yang tepat sangat diperlukan bagi pasien hipoglikemia karena hipoglikemia yang tidak ditangani dapat menurunkan kualitas hidup pasien. Pemahaman mengenai gejala, pencegahan, dan penatalaksanaan hipoglikemia sangat penting, terutama bagi pasien yang pernah mengalami hipoglikemia berat agar tidak terjadi kekambuhan atau kondisi fatal.

**Kata kunci:** Hipoglikemia, Diagnosis, Pengobatan

#### What is already known?

Hypoglycemia is a condition where blood glucose levels drop below 70 mg/dL, commonly occurring in diabetes patients using insulin or sulfonylureas, with an increased risk of severe hypoglycemia in unawareness cases.

#### What does this study add?

This study updates the guidelines for diagnosing and managing hypoglycemia, emphasizing the importance of self-monitoring blood glucose and tailored treatment strategies based on severity.

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### Introduction

According to the Indonesian Endocrinology Association, hypoglycemia is a condition where blood glucose concentration decreases below 70 mg/dL with or without signs or symptoms. Hypoglycemia symptoms may vary from mild to

life-threatening condition. Hypoglycemia can occur in patients with and without diabetes. The exact incidence of hypoglycemia is difficult to determine, but mild hypoglycemia is common. Asymptomatic

events are more difficult to detect and therefore are not reported.<sup>1-6</sup>

Hypoglycemia is commonly observed in diabetes patients receiving anti-diabetic drug therapy, particularly insulin and sulfonylureas, a condition referred to as iatrogenic hypoglycemia. While drug therapy remains the most frequent cause, other contributing factors such as malnutrition, hyperkalemia, diabetic ketoacidosis, uncomplicated hyperglycemia, alcohol intoxication, or the inability to eat have also been reported in the literature.<sup>7</sup>

Hypoglycemia can be discovered accidentally during routine blood glucose monitor without clinical presentations of hypoglycemia. This is usually experienced by patients with a slow decrease in glucose levels or disruption of the glucose counter-regulatory response. A condition where hypoglycemia has occurred but warning symptoms in the form of autonomic symptoms do not appear is called unawareness hypoglycemia or impaired awareness of hypoglycemia. Rudijanto, et al in 2018 conducted a study and found that the majority of diabetes patients (82.4% type 1 and 67.2% type 2) experienced unawareness hypoglycemia. The incidence of unawareness hypoglycemia in diabetic patients increases 3-6 times.<sup>2-4,8-11</sup>

The goal of therapy is to detect and manage low blood glucose levels to eliminate the risk of organ injury and relieve symptoms. *Self monitoring of blood glucose* (SMBG) is done to detect blood glucose levels by itself. ADA recommends self-monitoring blood glucose at least 6-8 times a day. Appropriate therapy is needed for hypoglycemia patients because untreated hypoglycemia will reduce the patient's quality of life. Therapy in hypoglycemia patients is differentiated according to the clinical condition and the degree of hypoglycemia.<sup>9-13</sup>

Unawareness of hypoglycemia can increase the occurrence of severe, life-threatening hypoglycemia, so education about the symptoms and effects of hypoglycemia is needed. This supports the author's intention in understanding the clinical approach and management of hypoglycemia.

## Method

This was a narrative review aimed at summarizing the understanding of hypoglycemia, including updates on the clinical approach to its

diagnosis and management. We included articles published in English and Indonesian, selecting original research articles, case reports or series, and guidelines issued by expert associations. The inclusion criteria for the articles were as follows: primary research articles published within the last ten years and textbooks published within the last ten years. Additionally, expert consensus and guidelines were included regardless of publication year if deemed significant. The result of this review was presented descriptively.

## Result and Discussion

### Etiology and Risk Factors

The cause of hypoglycemia is multifactorial, the main causes are iatrogenic due to anti-diabetic drugs, infectious diseases accompanied by sepsis, hormone deficiencies, and autoimmune diseases. A study by Su, et al stated that the risk of hypoglycemia occurs in patients with inadequate food intake, alcohol consumption, drug interactions, and chronic liver or kidney disease. Hypoglycemia can also occur due to certain rare causes such as pancreatic cell tumors or non-islet tumors, organ failure, autoimmune conditions, inborn errors of metabolism, alcohol consumption, starvation, and excessive exercise. According to Yale, risk factors for hypoglycemia are excessive insulin doses, exercise, sleep, age, and history of severe hypoglycemia.<sup>4,9,15,19,20</sup>

Other causes of hypoglycemia in patients with diabetes include errors in administering the dose, time, and type of insulin, insufficient amount of carbohydrates consumed (fasting), eating late or fasting at night, decreased glucose production in the liver (excessive alcohol consumption), increased energy consumption or decreased liver glycogen stores during excessive exercise or excessive weight loss efforts, slow gastric emptying (gastroparesis), and decreased insulin clearance (progressive renal failure).<sup>8</sup>

### Glucose Homeostasis

If blood glucose levels decrease beyond physiological levels, the body will activate the counter-regulatory response (CRR) mechanism to return blood glucose levels to normal. The CRR response begins with a decrease in insulin secretion and is followed by an increase in glucagon and epinephrine secretion. The role of hormones that regulate blood glucose is explained in Table 1.<sup>4</sup>

Table 1. Hormones that play a role in CRR mechanisms.<sup>4</sup>

Hormones	Produced by	Mechanisms
Insulin	Pancreatic beta cells	Suppresses liver glycogenolysis Suppresses hepatic gluconeogenesis Suppresses endogenous glucose production
Glucagon	Pancreatic alpha cells	Stimulates liver glycogenolysis Stimulates hepatic gluconeogenesis
Epinephrine	Adrenal medulla ( <i>chromaffin cells</i> )	Suppresses liver glycogenolysis Suppresses hepatic gluconeogenesis Stimulates renal gluconeogenesis Suppresses pancreatic insulin secretion Restrict tissue glucose use
Cortisol and Growth Hormone	Adrenal cortex and anterior pituitary ( <i>somatotropic cells</i> )	Increases endogenous glucose production Decreases glucose clearance

Hormones like *glucagon-like peptide-1* (GLP-1) and *ghrelin* also *cholecystokinin peptide Y* will be secreted in response to glucose load ingested. GLP-1 is secreted by L cells in the distal gastrointestinal tract in response to carbohydrates, stimulates pancreatic beta cells to secrete insulin, and suppresses alpha cells, inhibiting gastric emptying and causing feelings of fullness and weight loss.<sup>11</sup>

Decreased blood glucose levels cause activation of the autonomic center in the hypothalamus, namely the ventromedial area of the thalamus, and then stimulate the sympathoadrenal system which causes symptoms of sweating, increased heart rate contractility, and tremors.<sup>4,11</sup>

### Body Response to Hypoglycemia

Autonomic activation in hypoglycemia may result in various symptoms progressing from sweating and palpitations to cognitive dysfunction and seizures. Hypoglycemia can lead to coma and even death, depending on its severity or duration. Sudden cardiac death may happen, although rarely, due to ischemic changes. Impaired cognitive function can have long-term effects and potentially damage intellectual function. Hypoglycemia often causes brain dysfunction that will improve after the blood glucose level is back to normal.<sup>8,14</sup>

Severe hypoglycemia may worsen the severity of neurocognitive dysfunction in diabetes patients and is also associated with an increased risk of dementia and cerebellar ataxia. Severe

hypoglycemia can also damage the cortex and hippocampal areas, and permanently impair cognitive function in young people and older adults. Hypoglycemia in diabetic individuals has a 1.5- to 2.5-fold increased risk of dementia, which may be associated with the development of cerebral microvascular disease.<sup>8,9</sup>

Hypoglycemia activates the sympathoadrenal system and epinephrine release due to changes in hemodynamics through increased heart rate, systolic blood pressure in the peripheral, and myocardial contractility and cardiac output, whereas there will be a reduction in systemic blood pressure and peripheral artery resistance.

### Clinical Manifestations of Hypoglycemia

The body's first response at the start of hypoglycemia is an increase in the hormone adrenaline or epinephrine, causing neurogenic symptoms, such as trembling, clammy and pale skin, anxiety, blurred vision, or twinges due to adrenergic effects as well as excessive sweating and hunger due to cholinergic activity. In advanced stages, hypoglycemia will occur as neuroglycopenic symptoms, such as difficulty thinking, confusion, headaches, seizures, and even coma.<sup>4,16,24</sup>

Autonomic symptoms will appear if the blood glucose level is below 60 mg/dL, while neuroglycopenic symptoms tend to appear if the blood glucose level is below 50 mg/dL. Autonomic symptoms are divided into adrenergic symptoms (palpitations, tachycardia, anxiety, and tremors) and cholinergic symptoms (sweating, hunger, and nausea). Neuroglycopenic symptoms include weakness, behavioral changes, visual changes, confusion, dysarthria, dizziness, amnesia, lethargy, seizures, loss of consciousness, and coma. Brain death has been known to occur in cases of untreated hypoglycemia.<sup>25</sup>

### 3.5 Diagnostic Criteria of Hypoglycemia

Hypoglycemia can be concluded from the history, physical examination, and laboratory data. Whipple triad helps to diagnose hypoglycemia, which consists of signs and symptoms of hypoglycemia, and low blood glucose level and improves the clinical condition after blood glucose is back within the normal range after administration of glucose.<sup>11,14</sup>

Hypoglycemia symptoms act as an alert but differ from person to person. Elderly individuals, particularly those who are frail or have cognitive impairments, need careful monitoring, as their symptoms can be mild or mistaken for other conditions. Autonomic symptoms stem from the activation of the sympatho-adrenal system, while neuroglycopenic symptoms occur due to insufficient glucose supply to the brain. Since

glucose is essential for brain metabolism and cognitive processes, severe hypoglycemia ultimately results in cognitive dysfunction.

ADA classified hypoglycemia into 3 levels. Level 1 is defined as a blood glucose level between 54-70 mg/dL. Level 2 is a blood glucose level below 54 mg/dL, this is the threshold for neuroglycopenic symptoms beginning to occur and requires immediate action to treat hypoglycemia. If a patient is at level 2 hypoglycemia but has no adrenergic or neuroglycopenic symptoms, they are likely experiencing hypoglycemia unawareness. Level 3 is defined as a severe condition characterized by changes in mental status and/or physical function that require assistance from others for recovery.<sup>17,26</sup>

PERKENI classified hypoglycemia into mild hypoglycemia and severe hypoglycemia. Seaquist, et al classifies hypoglycemia as severe hypoglycemia, symptomatic hypoglycemia, asymptomatic hypoglycemia, possibly symptomatic hypoglycemia, and pseudohypoglycemia.<sup>1,27</sup>

The Joint British Society defines hypoglycemia as a blood glucose level below 4.0 mmol/L. If symptoms occur despite glucose levels remaining above this threshold, a small carbohydrate snack is recommended for relief. Hypoglycemia is classified into three levels of severity: mild (alert, oriented, and able to swallow), moderate (conscious but displaying confusion, disorientation, or aggression), and severe (unconscious, experiencing seizures, or highly aggressive, requiring no oral intake).<sup>28</sup>

### Management of Hypoglycemia

Hypoglycemia is a medical emergency. The goal of treatment for hypoglycemia is to detect and manage blood glucose levels back within normal range, eliminate the risk of injury, and relieve symptoms quickly. Avoidance of overtreatment is important as it can result in rebound hyperglycemia and weight gain.<sup>4,15</sup>

### Management of Mild-Moderate Hypoglycemia

All guidelines recommend initial treatment of hypoglycemia with fast-acting glucose and continued with long-lasting glucose. ADA advises that patients should continue to be counseled to treat hypoglycemia with fast-acting carbohydrates if blood glucose levels are 70 mg/dL (3.9 mmol/L) or less. In T2D, protein can improve insulin response without increasing plasma glucose concentrations. So, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia. Once glucose returns to normal, individuals should be advised to eat a meal or snack to prevent recurrent hypoglycemia. ADA recommends the "15-15 Rule" by giving 15 grams

of carbohydrates and checking blood glucose again after 15 minutes. If blood glucose is still below 70 mg/dL, repeat treatment until blood glucose is at least 70 mg/dL. After blood glucose returns to normal, eat snacks to ensure blood glucose does not drop again. This method aims to prevent blood glucose from increasing.<sup>17,29</sup>

If the patient is conscious, give 15-20 grams of glucose (2-3 tablespoons of sugar) dissolved in water. Foods containing fat can slow down the response to rising blood glucose. Check blood glucose every 15 minutes, if hypoglycemia is still present, treatment can be repeated. PERKENI stated if hypoglycemia persists after 45 minutes or 3 feeding cycles, start to administer glucose fluids, a 10% dextrose infusion of 150-200 mL within 15 minutes.<sup>30</sup>

Vindedzis, et al support the initial treatment of 20 grams of carbohydrate at 10-minute intervals before repeating the treatment. *Diabetes Canadian Expert Committee* recommends that mild to moderate hypoglycemia should be treated with oral carbohydrate consumption of 15 grams in the form of glucose or sucrose solution. Patients should recheck blood glucose in 15 minutes and retreat with 15 grams of carbohydrates if blood glucose remains below 70 mg/dL. Meanwhile, severe hypoglycemia in conscious patients is treated by consuming 20 grams of oral carbohydrates and rechecking blood glucose every 15 minutes.<sup>15,29</sup>

According to the Joint British Society, the management of mild hypoglycemia: if the patient is conscious and able to swallow, administer 15-20g of fast-acting carbohydrates (e.g., glucose tablets or fruit juice). Recheck blood glucose after 10-15 minutes and repeat if still below 4.0 mmol/L. Once stabilized, provide long-acting carbohydrates (e.g., biscuits or milk) to maintain glucose levels. For moderate hypoglycemia: If the patient is confused or disoriented but can still swallow, give fast-acting carbohydrates. If unable to take orally, use glucose gel or 40% glucose applied between the gums and teeth. Reassess after 10-15 minutes, and if hypoglycemia persists, repeat treatment and consider IV dextrose or IM glucagon.<sup>28</sup>

### Management of Severe Hypoglycemia

PERKENI recommends to stop antidiabetic drugs immediately in patients with severe hypoglycemia. If symptoms of neuroglycopenia are present, start parenteral therapy of 20% dextrose 75-100 ml, and check blood glucose every 15-30 minutes. If the target of blood glucose below 70 mg/dL has not been achieved, the procedure can be repeated. If blood glucose has reached the target, maintenance is given with 10% dextrose at a rate of 100 ml/hour until the patient can eat. Intramuscular administration of glucagon 1 mg can be given as an alternative but caution must be

exercised in patients with malnutrition, alcohol abuse, and liver disease. Evaluate hypoglycemia triggers.<sup>30</sup>

In severe hypoglycemia but the patient is still conscious, so give 20 grams of oral glucose then check blood glucose 15 minutes later. If blood glucose remains <70 mg/dL then repeat giving 20 grams of glucose, likewise for the next 15 minutes. Meanwhile, in severe hypoglycemia and the patient is unconscious, give 10-25 grams of glucose (25-50 ml of D40% solution intravenously or give an injection of 1 mg of glucagon intramuscularly. If the hypoglycemia is resolved and the patient is conscious, then continue to eat to prevent repeated hypoglycemia.<sup>31</sup>

Kapoor, et al explained if severe hypoglycemia cannot be resolved, glucagon 1 mg can be given intravenously to adults or children weighing >25 kg. Glucagon may be considered a first-line treatment for severe hypoglycemia in diabetic patients receiving insulin. Glucagon has a short half-life (8-18 minutes) thereby preventing delays in treatment and the need for hospitalization during severe hypoglycemia. Parenteral glucagon is given to T1D patients, while IV glucose is generally used in T2D patients.<sup>8,32</sup>

According to the Joint British Society, the management of severe hypoglycemia: If the patient is unconscious, experiencing seizures, or extremely aggressive, seek urgent medical support. Stop IV insulin, and if possible, administer 10% IV dextrose (100–200mL over 15 minutes). If IV access is unavailable, give 1 mg IM glucagon. Recheck blood glucose after 10 minutes, and repeat treatment if still below 4.0 mmol/L. If the patient remains nil by mouth (NBM), continue a 10% glucose infusion until oral intake is safe.<sup>28</sup>

### Management of Severe Hypoglycemia in Critical Illness

There are several conditions in which severe hypoglycemia cannot be resolved by administering intravenous glucose, so other therapies are needed which are expected to improve the hypoglycemia condition, which is hypoglycemia due to adrenal insufficiency caused by critical conditions such as sepsis, adrenal crisis, or insulinoma. These patients can be given hydrocortisone 200 mg/day in divided doses or by intravenous drip at 10 mg/hour for patients with septic shock.<sup>32</sup> Corticosteroids are expected to increase blood glucose by reducing insulin sensitivity in target tissues, gluconeogenesis, and reducing glucose uptake in tissues.<sup>33-35</sup>

### Prevention of Hypoglycemia

There are 3 strategies for managing hypoglycemia, namely preventing hypoglycemia,

using therapy with a low risk of hypoglycemia, and treating hypoglycemia. All diabetic patients who received insulin therapy must be explained about the risks, prevention, detection, and management of hypoglycemia. Avoid medication that may increase the risk of recurrent hypoglycemia, monitor blood glucose frequently, and recognize *unawareness hypoglycemia*.<sup>8,15</sup>

Lifestyle modification is an important factor in preventing hypoglycemia, which includes a balanced diet, eating in small amounts regularly, SBGM, and avoidance of excessive eating. If hypoglycemia persists and persists despite patient compliance, then modification of therapy is necessary. This may include revising glucose targets and administering drugs or combinations of drugs that have a low risk of hypoglycemia.<sup>10</sup>

Independent blood glucose monitoring is a periodic blood glucose examination carried out using a glucometer by DM patients and/or their families. SMBG can provide information regarding daily blood glucose variability such as blood glucose before eating, one or two hours after eating, or in other special conditions. Monitoring blood glucose itself is the best way to prevent hypoglycemia. This monitoring should be done before and after eating, before and after exercise, or before bed. This examination should also be carried out when there is a change in the patient's routine, such as a change in insulin administration schedule, increased physical activity, or time travel.<sup>10,36</sup>

The results of self-blood glucose monitoring can be influenced by glucometer factors (strip damage, weak battery, expired strips), user skill factors (insufficient number of blood samples due to incorrect puncture methods or the blood sample that comes out in the form of plasma), intrinsic factors of DM sufferers (high or low hematocrit), and therapeutic factors (oxygen therapy, medication, or hemodialysis).<sup>36</sup>

### Conclusion

Hypoglycemia is a state where blood glucose decreases below 70 mg/dL with or without signs or symptoms. Hypoglycemia can occur due to various reasons, the most common reason being routine consumption of anti-diabetic drugs, especially insulin, and sulfonylureas. Unawareness of hypoglycemia needs caution because it can result in life-threatening conditions. Management of hypoglycemia is classified based on the severity, which are mild-moderate and severe hypoglycemia. Self-monitored blood glucose is the best way to prevent hypoglycemia. An understanding of how to detect symptoms of hypoglycemia, how to prevent it, and how the manage hypoglycemia is needed, especially in

patients who experience severe hypoglycemia so that it does not lead to a fatal condition.

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