

Management of Hypoglycemia in Nondiabetic Palliative Care Patients: A Prognosis-Based Approach

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ABSTRACT: Hypoglycemia due to underlying terminal illness in nondiabetic end-of-life patients receiving palliative care has not been fully studied. For example, we do not have adequate information on the frequency of spontaneous hypoglycemia in patients as occurs during the different stages of palliative care. Depending on the case-mix nature of the palliative care ward, at least 2% of palliative care patients may develop hypoglycemia near the end of life when the remaining life expectancy counts down in days. As many as 25%–60% of these patients will neither have autonomic response nor have neuroglycopenic symptoms during a hypoglycemic episode. Although it is not difficult to diagnose and confirm a true hypoglycemia when it is suspected clinically, an episode of hypoglycemic attack may go unnoticed in some patients in a hospice setting. Current trends in palliative care focus on providing treatments based on a prognosis-based framework, involving shared decision-making between the patient and caregivers, after considering the prognosis, professional recommendations, patient's autonomy, family expectations, and the current methods for treating the patient's physical symptoms and existential suffering. This paper provides professional care teams with both moral and literature support for providing care to nondiabetic patients presenting with hypoglycemia.

KEYWORDS: hypoglycemia, nondiabetic, palliative care, shared decision, lucid moments, treatment withholding, prognosis based

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Introduction

Hypoglycemia can occur in nondiabetic patients receiving hospice or palliative care and is often one of the many symptoms that occur because of an underlying terminal illness. The emphasis on the patient being nondiabetic is because iatrogenic antihyperglycemic-induced hypoglycemia is typically not among the differential diagnoses for the hypoglycemic attack. Almost all causes of hypoglycemia in nondiabetic patients with a terminal illness are irreversible; hence, the management of such patients is very different from those patients not in the terminal phase of a disease. This paper discusses the epidemiology, evidence-based recommendations, etiology, and mechanisms of hypoglycemia, as well as the diagnosis criteria, workup, and management of this condition, in hospice care or inpatient palliative care wards.

Epidemiology of Hypoglycemic Attacks in Palliative Care Wards

Although the prevalence of hypoglycemia, which either prompts patient admission or occurs during hospitalization, varies depending upon the case-mix nature of the different hospice or palliative care units, it is rarely discussed in the

literature. In a recent retrospective case note review of a cohort of consecutive 65 patients from an Australian specialist palliative care unit, there was only one incident of hypoglycemia occurring during hospitalization.¹ One of the reasons for the low incidence rate might have resulted from the relaxed antihyperglycemic control in this group of frail diabetic patients, and the fact that nondiabetic hypoglycemic attacks are truly uncommon. Table 1 summarizes the incidence of hypoglycemia and the asymptomatic rate in nondiabetic patients as per the care settings.

Glucose Homeostasis

Glucose homeostasis is essential for survival of several vital organs/tissues such as the brain, cells of the renal medulla (which can produce epinephrine to counteract hypoglycemia), and red blood cells that are obligate glucose users. In cachectic patients, despite decreased glycogen stores in the liver, endogenous glucose production is increased due to increased hepatic glucose recycling via lactate, a phenomenon termed the Cori cycle.² In nondiabetic patients, hypoglycemia activates the autonomic nervous system (ANS) through parasympathetic nerves, sympathetic nerves, and adrenal medullary



Table 1. Incidence of hypoglycemia and the asymptomatic rate in nondiabetic patients as per the different care settings.

FIRST AUTHOR ^{REF} /YEAR	NO. OF PATIENTS	ELDERLY >65 YEARS	SETTING	INCIDENCE OF NONDIABETIC HYPOGLYCEMIA (%)	ASYMPTOMATIC (%)
Palliative care setting					
Currow, D.C. ¹ /2011	65	NA	Specialist palliative care unit	1.5%	NA
Nonpalliative care setting					
Tsujimoto, T. ¹³ /2015	59,602 visits (including diabetics)	63.3 ± 20.0 (mean ± SD)	Emergency department	0.27% (severe type)	NA
Nirantharakumar, K. ¹⁴ /2012	37,898 inpatient admissions	43.5%	Computer-based patient information system	0.28%	NA
Mannucci, E. ¹⁰ /2006	678	100%	Gerontology & geriatrics ward	8.6%	25%
Kaganski, N. ¹⁵ /2003	5,404 (including diabetics)	100%	Geriatric & medical ward	3.0%	NA
Shilo, S. ¹⁶ /1998	60 (all hypoglycemic)	100%	Geriatric & medical ward	NA	61.6%

epinephrine, which in turn mediates the majority of the glucagon response to moderate and severe hypoglycemia.³ Defects in the central nervous system (CNS), the peripheral nervous system, and the ANS islet itself, which can arise from either functional defects caused by glucose dysregulation or structural defects caused by the autoimmune damage of the islet, will result in hypoglycemic unawareness.³ Hypoglycemia unawareness has been defined as an increase in the threshold (more severe hypoglycemia required) for activation of counterregulatory glucagon secretion, leading to the CNS adaptation that results in reduced awareness of hypoglycemia in an individual.⁴ Hypoglycemia unawareness can explain why certain patients with moderately severe laboratory hypoglycemia are still asymptomatic.

Etiology and Mechanisms of Hypoglycemia in Nondiabetic Patients

Hypoglycemia triggers the counterregulatory response to restore plasma glucose levels to appropriate concentrations. To meet this challenge, the counterregulation process involves the sympathetic nervous system, glucagon, and glucocorticoids.⁵ Even in otherwise healthy elderly individuals, the glucose counterregulatory response will have only subtle impairment during moderate hypoglycemia, but this impairment will no longer be detectable during more severe hypoglycemia.⁶ Nevertheless, in patients with major organ dysfunction caused by a terminal-stage illness, the physiological counterregulatory mechanism becomes defective. The ensued defective gluconeogenesis during a negative energy balance and food-deprived state will result in hypoglycemia.

Insulinoma as the cause of hypoglycemia is not expected to occur in hospice or palliative care wards, in which terminally ill patients were transferred from other primary care units. Therefore, this article will not discuss further the particular condition of insulinoma-induced hypoglycemia.

In nondiabetic palliative care patients, hypoglycemia occurs most commonly in response to multiorgan dysfunctions or failures. As mentioned earlier, the prevalence of hypoglycemia in nondiabetic patients related to critical illness is not well documented. Organ failure will result in a reduction of endogenous glucose production, and most critical illnesses increase metabolic stress, thereby increasing glucose utilization by tissues. Inadequate oral intake, along with the insufficient production of glucose during a severe illness, may increase the risk of hypoglycemia. Hepatic or renal failure may result in hypoglycemia if the patient develops anorexia, vomiting, and inadequate oral intake and has impaired hepatic or renal gluconeogenesis. Hepatic failure impairs both hepatic gluconeogenesis and the glycogenolysis counterregulatory response, cutting off the regular supply of glucose required to maintain adequate plasma levels. Not only in frank liver failure setting, but hypoglycemia is also associated with increased mortality in patients with acute decompensated liver cirrhosis. In this setting, it is not yet clear whether hypoglycemia is



jointly responsible for the increased short-term mortality or is only a consequence of the severity of the disease or the complications.⁷

To make the scenario worse, multiorgan failures can trigger endocrine organ dysfunctions, such as adrenal or pituitary gland dysfunction, fueling the risk of developing hypoglycemia.

Symptomatology of Hypoglycemia in Nondiabetics

Classical hypoglycemia is diagnosed by Whipple's triad, ie, the three distinct findings based on clinical and biochemistry examinations^{8,9}: detection of a low plasma glucose level <55 mg/dL (<3 mmol/L) using a precise method (not including the home glucose-monitoring method), detection of symptoms of neuroglycopenia, and relief of the symptoms with the administration of sugar. Symptoms and the signs associated with an episode of hypoglycemia can be separated into two categories: autonomic response and neuroglycopenia. The autonomic response includes sweating, weakness, palpitations, tremor, tachycardia, hunger, nervousness, and paresthesias. These symptoms and signs are nonspecific and can be overlooked, particularly in hospice patients. Neuroglycopenia is a specific term reserved for defining the complications of hypoglycemia, such as confusion, irritability, visual disturbance, loss of consciousness, seizure, and transient focal neurological deficits. It should be noted that symptoms of hypoglycemia are often very individual and change over time.

The lower limit of the normal fasting plasma glucose concentration in nondiabetic persons is typically 70 mg/dL (3.9 mmol/L). By the time the plasma glucose level reaches 60 mg/dL (3.3 mmol/L), the magnitude of the increased discharge of ANS neurotransmitters, catecholamine and acetylcholine, is such that autonomic symptoms including sweating, palpitations, tremor, tachycardia, hunger, and nervousness occur. The hypoglycemic threshold can vary among subjects; when plasma glucose goes down to 50 mg/dL (2.8 mmol/L), neuroglycopenia may occur.

A significant portion of patients (from 25% to ~60%) who develop hypoglycemia display no obvious neuroglycopenic or autonomic symptoms and signs (hypoglycemia unawareness; Table 1). Therefore, palliative care teams should always maintain a high level of suspicion to ensure the early detection of any hypoglycemic event, particularly in patients who wish to accomplish unfinished personal goals.

How far Should We Go for the Hypoglycemia Workup?

A detailed review of the pretransfer medical record is essential after a detailed physical examination focusing on any newly developed infection, medication history, worsening of organ failure, recent onset of an acute change in mental status or neurological deficit, and recent diet and intake history. Hypoglycemia detected using a handheld glucose monitor should be confirmed using a precise laboratory method that is

performed in a medical laboratory using hexokinase, glucose oxidase, or glucose dehydrogenase enzymes. The etiology of most nondiabetic spontaneous hypoglycemia in palliative care settings can be attributed to an underlying medical condition such as any critical illness including severe sepsis, end-stage renal disease, malnourishment with or without cachexia, cortisol deficiency, hepatic failure, peritoneal carcinomatosis, and multiorgan failures.

Management Through a Prognosis-Based Framework

Patients' prognosis largely depends on the underlying illness, although the uncertainty inherent in prognostication should be considered. Nondiabetic hypoglycemia in palliative care settings mainly results from multiorgan failures (or mostly severe liver, renal, or cardiac failure), sepsis, or inanition, which is an exhausted state resulting from prolonged poor food and water intake, a defect in assimilation, or cancer cachexia. Cortisol deficiency will cause hypoglycemia. The life expectancy of a patient with organ failure causing spontaneous hypoglycemia is very limited.

An observational retrospective study of the prognostic value of hypoglycemia in nondiabetic elderly patients aged over 65 years hospitalized to a geriatrics ward suggests that hypoglycemia is a prognostic marker of inhospital mortality, even after adjustment for comorbidity, indices of malnutrition and pharmacological treatments.¹⁰ The inhospital mortality is reported as high as 41.4% with an adjusted odds ratio at 2.17 (95% confidence interval 1.25–3.85).¹⁰ Therefore, we will focus on a practical prognosis-based framework, including the following trajectories: Trajectory 1 (prognosis of <1 month), Trajectory 2 (prognosis very limited, usually <1 week), and Trajectory 3 (dying). Our decision-making recommendations for some hypothetical scenarios with different trajectories are presented in Table 2.

Besides the prognosis, other important points that warrant consideration are patient autonomy, if a lucid moment with the patient is desired by the patient or family, and current methods for controlling symptoms. If the clinical course of a patient is expected to be in line with Trajectory 3, such as in scenario 1 or scenario 3 when death is imminent, we suggest not treating hypoglycemia, as survival and life quality improvements are expected to be limited. On the other hand, if the course goes along Trajectory 1, and a lucid moment can be obtained without intolerable suffering (scenario 2), we suggest treating hypoglycemia according to the patient/family's wishes. The decision-making in the above examples is relatively straightforward because all the key factors are apparent. However, physicians are often presented with conflicting factors, resulting in the dilemma of whether to treat for hypoglycemia or not, such as in scenario 4.

Shared decision-making is a practical model for problem-solving in palliative care settings and is considered an essential component of good quality care in critical illness.¹¹ When provided with adequate information translated from the currently



Table 2. Decision-making for the management of hypoglycemia in patients with a terminal-stage illness under hospice and palliative care.

	HYPOTHETICAL SCENARIO 1	HYPOTHETICAL SCENARIO 2	HYPOTHETICAL SCENARIO 3	HYPOTHETICAL SCENARIO 4
Death imminent	Yes	No	Yes	No
Lucid moments desired by the patient/family	No	Yes	Yes	Yes
Other symptoms' control	Poor	Good	Poor	Good
Patient autonomy	Does not favor treatment	Favor correction	Not recorded	Does not favor treatment
Family's attitude	Does not favor treatment	Favor correction	Favor correction	Favor correction
Medical decision	Treatment withhold	Treat hypoglycemia	Do not recommend treatment	Shared decision-making with family

available evidence about the pros and cons of each available option, patient/families can make better-informed decisions, according to the physician's opinion, and their preferences, values, goals, and wishes. An example showing the key steps involved in a shared decision-making discussion between the physician and families for a therapeutic trial for treating hypoglycemia is presented in Table 3.

Practice of Time-Limited Therapeutic Trials

Time-limited therapeutic trials in palliative care settings are a way of aiding decision-making by administering treatment over a predefined period. If the treatment does not take effect during the observation time, physicians and families can withdraw it with reason, without feelings of guilty from *abandoning* a patient. Treating hypoglycemia temporarily may be of value in a terminally ill patient with prognostic uncertainty (life expectancy may be more than weeks), or in a patient with personal affairs to be attended to before dying. Time-limited trials are a viable option when an agreement of whether or not to treat a patient cannot be reached among the patient, family, and physician. However, to avoid medical

futility, the goals and duration of a therapeutic trial, and the indicators for trial termination, should be clearly established.

Treatment for Hypoglycemia in the Palliative Care Setting

The purpose or goal of treatment for nondiabetic patients with an end-stage disease during a hypoglycemic attack is to help regain consciousness, albeit the regained consciousness may not be durable because of the underlying untreatable conditions. Once treatment for hypoglycemia is decided, we suggest attaining a peripheral venous access immediately when the patient is unconscious or unable to ingest carbohydrate. The drug of choice is glucagon, which may be administered either subcutaneously or intramuscularly at a dose of 0.5–1.0 mg.¹² We can expect the recovery of consciousness within approximately 15 minutes. An earlier UK study using 1 mg intravenous glucagon treatment reported the recovery of a normal level of consciousness at around seven minutes.¹² In the real-world setting, a hospice ward or palliative care ward does not constantly keep glucagon at hands; therefore, intravenous administration of 25 g of 50% glucose (dextrose)

Table 3. Application of the time-limited therapeutic trial model to a family discussion regarding shared decision care for a terminally ill patient with nondiabetic spontaneous hypoglycemia.^{17–19}

Communication goal	What the care team would say.
Give the diagnosis and initiate discussion	Your loved one has hypoglycemia, which means her/his blood glucose level is so low that brain functions cannot be maintained, and we need to discuss the best way to care for her/him.
Give treatment options	We have a choice between raising the glucose level back to normal, which may require continuous IV drip because the patient cannot eat or drink OR focusing primarily on her/his comfort.
Introduce complications from treatment	We can raise the glucose level up, but because your loved one also has other discomforts that are difficult to treat, she/he might suffer even more when consciousness returns.
Elicit the patient's value and family's attitude	Your loved one is going to die in <1 week. If you know that she/he has any unfinished business, and/or you want to achieve lucid moments with her/him, a time-limited (short-term) treatment for her/his hypoglycemia can be provided. Acknowledge that family wishes may not be the same as the patient's wishes.
Reassure to help the patient be comfortable	You are the proxy for the patient. If your wishes are to avoid glucose replacement, we can focus our efforts on helping her/him be comfortable and allow nature to take its course.
Reconcile goals	From your perspective, what is the best outcome that we could have for the patient in this situation? What do you think about that outcome?
Identify a timing at which the initial treatment decision can be re-evaluated	If your loved one is still unable to gain consciousness after treatment, or if she/he is very uncomfortable and suffering a lot, we should sit down and talk about all our options at that point.



followed by a subsequent glucose in the form of 10% dextrose is often needed.

Communication skills are highly required in such end-of-life decision-making. Reassurance of the patient's comfort after completing the trial should be emphasized to families. Some examples of appropriate wording for discussing time-limited trials are listed in Table 3.

For some of the patients whose hypoglycemia has been discovered at admission, the decision to treat or withhold treatment for hypoglycemia should be included in end-of-life care plans.

Conclusion

Although it is not difficult to diagnose and confirm a true hypoglycemia when it is suspected clinically, an episode of hypoglycemic attack may go unnoticed in some patients in a hospice setting. Current trends in the palliative care focus on providing treatments based on a prognosis-based framework, involving shared decision-making between the patient and caregivers, after considering the prognosis, professional recommendations, patient's autonomy, family expectations, and the current methods for treating the patient's physical symptoms and existential suffering. This paper will provide professional care teams with moral and literature support for providing care to nondiabetic patients presenting with hypoglycemia.

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Author Contributions

Conceived the study and designed the review: VCK. Analyzed the data: VCK and P-HL. Wrote the first draft of the manuscript: VCK. Contributed to the writing of the manuscript: VCK. Agreed with the manuscript results and conclusions: VCK and P-HL. Jointly developed the structure and arguments for the paper: VCK and P-HL. Made critical revisions

and approved the final version: VCK. All the authors reviewed and approved the final manuscript.

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