Pseudohypoglycemia: A Pitfall in Everyday Practice

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ABSTRACT

Hypoglycemia is a common clinical finding, especially in the inpatient setting. However, laboratory testing may show falsely low blood glucose levels. It is crucial for clinicians to recognize the existence of pseudohypoglycemia and know when and how to test for it.

KEYWORDS: pseudohypoglycemia, false positives, diabetes, hypoglycemia, clinical testing

INTRODUCTION

Hypoglycemia is a common clinical entity, particularly in the inpatient setting. While hospitalized, patients' insulin regimens are often altered, and their oral intake may also be different than baseline, due either to their underlying acute medical condition or while awaiting invasive procedures. In one retrospective study from the Spanish National Health System, 2.8% of hospitalized patients with diabetes had recorded hypoglycemic events, and the presence of a hypoglycemic event was associated with an increased time to discharge and risk of in-hospital mortality.[1]

While clinicians may understandably take special precautions to avoid hypoglycemic events, there is an entity known as pseudohypoglycemia, where venous plasma glucose levels appear falsely low due to artifacts of laboratory testing methods. It has been reported in both patients with and without diabetes and is not associated with the same adverse effects as true hypoglycemia.[2,3] While its incidence is unknown, pseudohypoglycemia represents an important entity with which clinicians should be familiar, so as to avoid unnecessary testing and inappropriate treatments. Here, we present two cases of pseudohypoglycemia to illustrate this concept.

CASE PRESENTATION

Case One

A 49-year-old man with type 2 diabetes mellitus (T2DM) was admitted to the hospital because of recurrent chest pain. Other past medical history was significant for systemic sclerosis (SSc) with pulmonary hypertension (PH), schizophrenia, and recurrent vomiting of unclear etiology. Initial cardiovascular assessment was unremarkable, and his chest pain was attributed to severe PH secondary to his underlying SSc.

On examination, the patient was afebrile with a pulse of 78 beats per minute, a blood pressure of 110/75 mm Hg, and a respiratory rate of 18 breaths per minute. Physical examination revealed multiple manifestations of SSc, including skin thickening, decreased capillary refill, and peripheral cyanosis. Breathing was normal, and auscultation of the chest was unremarkable with good air entry bilaterally. Cardiovascular examination was significant for a hyperdynamic precordium, a normal S1, a loud S2 with grade 2/6 to 3/6 systolic regurgitant murmur at left lower sternal border, a right parasternal heave, and weak peripheral pulses. There was intermittent digital cyanosis. Echocardiography was suggestive of PH, with an estimated right ventricular systolic pressure of 75 mmHg. Esophagogastroduodenoscopy was consistent with a lack of peristalsis and gastroesophageal reflux disease.

During his hospitalization, the patient was found to have intermittently low capillary blood glucose (CBG) levels, as detected by the finger stick method, but there were no clinical symptoms of hypoglycemia. Specifically, there was no

Table 1. Capillary versus Venous Glucose Measurements, Case 1

Hospital Day	Time (h:mm)	Capillary Glucose (mg/dL)	Venous Glucose (mg/dL)
1	19:38	NA	146
1	20:00	42	NA
1	22:02	48	NA
1	23:47	164	NA
2	05:39	95	NA
	08:34	NA	116
2	12:49	25	NA
2	12:51	29	NA
2	13:18	111	NA
2	16:09	84	NA
	21:48	102	NA
3	09:17	NA	131
3	12:10	55	NA
3	16:00	31	146
3	20:15	20	NA
	23:37	158	NA

change in mental status, shivering, tachycardia, or sweating, even with CBG levels of as low as 20 mg/dL (**Table 1**). The patient was empirically treated for hypoglycemia with oral glucose, without any symptomatic changes. Initially, no simultaneous venous plasma glucose (VPG) levels were drawn. Later in his stay, simultaneous VPG and CBG levels were drawn, with the former found to be within normal range while the latter was persistently low (**Table 1**). Interestingly, when the patient was without peripheral cyanosis, CBG levels were normal.

Case Two

A 59-year-old man with a history of coronary artery disease with heart failure with reduced ejection fraction (ejection fraction 15%), T2DM, and peripheral arterial disease (PAD) was admitted to the hospital for a worsening diabetic foot ulcer requiring below-the-knee amputation. His course was further complicated with acute-on-chronic renal failure, requiring hemodialysis, and an acute non-ST-elevation myocardial infarction requiring inotropic support. Physical examination revealed 1+ radial pulses bilaterally with sluggish capillary refill and a non-palpable *dorsalis pedis* pulse on left foot with noticeable dry gangrene of his left toes. He had generalized 2+ pitting edema. The remainder of the physical examination was unremarkable.

The patient was found to have an elevated CBG level of 250 mg/dL, treated with insulin. Overnight, CBG readings of 50, 35, and 30 mg/dL were obtained via the finger stick method. He was administered multiple boluses of dextrose 50% solution (D50W) and subsequently started on an intravenous dextrose 10% infusion. At 08:00 AM, he had a finger stick method reading of 34 mg/dL and was again given a bolus of D50W. A repeat value in 30 minutes was 65 mg/dL. At this point, simultaneous CBG and VPG values were obtained on an hourly basis. Simultaneous VPG and CBG readings supported the diagnosis of pseudohypoglycemia (**Table 2**). For subsequent monitoring and diabetic management, glucose samples were obtained via the patient's central venous catheter, as he continued to demonstrate sluggish capillary refill and a marked discrepancy between CBG and VPG measurements.

Table 2. Capillary versus Venous Glucose Measurements, Case 2

Hospital Day	Time (h:mm)	Capillary Glucose (mg/dL)	Venous Glucose (mg/dL)
1	14:30	206	NA
1	15:30	150	NA
1	16:25	151	NA
1	17:25	144	NA
1	18:30	50	NA
	19:30	73	NA
1	20:15	156	NA
1	21:15	174	NA
1	22:20	35	NA
1	23:15	30	NA
	00:00	214	NA
2	01:45	195	NA
2	02:45	126	NA
2	04:00	112	NA
2	05:00	136	NA
	06:30	49	NA
2	07:00	120	NA
2	08:00	34	NA
2	08:30	65	NA
2	09:00	64	369
	10:30	91	225
2	11:30	56	225
2	12:30	163	240
2	13:50	51	259

DISCUSSION

The above cases demonstrate patients with significant discrepancies between CBG and VPG values. This, in combination with their lack of symptoms or subjective improvement with glucose administration, suggests that both patients had pseudohypoglycemia. However, given the significant risks associated with untreated true hypoglycemia, how can one reliably distinguish it from pseudohypoglycemia?

First, it is important to recall that hypoglycemia is a clinical diagnosis, rather than a descriptive feature of laboratory results. Hypoglycemia may be diagnosed when the three elements of Whipple's triad are met: a low VPG level, symptoms consistent with hypoglycemia, and reversibility of said symptoms upon administration of glucose. Because of the subjective nature of hypoglycemic symptoms, as well as their reversal, clinicians often place primary importance on low measured VPG values. The American Endocrine Society defines low VPG as less than 70 mg/dL, although some patients may experience symptoms above this value.[4] Pseudohypoglycemia, by contrast, is defined as apparent low blood glucose levels without the remainder of Whipple's triad.[5] This emphasizes, rather than minimizes, the significance of patient history and subjective assessments and recognizes that false-positive test results may occur.

Second, it is important for clinicians to keep in mind the existence of an entity known as "hypoglycemic unawareness," where true hypoglycemia is present but symptoms are not easily or correctly recognized by the patient. In a Malaysian cohort with 1,153 participants covering six months of retrospective and four weeks of prospective data, impaired awareness of hypoglycemia was present in 48.0% of patients with T1DM and 36.9% with T2DM.[6] Most

reported hypoglycemic events were self-managed by patients themselves, but 11.5% and 7.3% of patients with T1DM and T2DM, respectively, had hypoglycemic events severe enough to require another person to administer anti-hypoglycemic therapies. The study did not directly report the rate of severe events with apparent hypoglycemic unawareness. Regardless, this finding does complicate the clinical reliability of patient-reported hypoglycemia symptoms.

Distinguishing hypoglycemic unawareness from pseudohypoglycemia is inherently difficult, given that subjective symptoms (and their reversal with glucose administration) are a key feature in the clinical diagnosis of hypoglycemia. In the inpatient setting, we recommend apparently hypoglycemic patients be treated empirically; however, when sufficient clinical suspicion exists for pseudohypoglycemia, such as in patients without a known history of diabetes,[7] testing of venous and papillary blood glucose is the only way to definitively rule in or out pseudohypoglycemia.

The mechanism of this discrepancy between capillary and venous plasma measurements of glucose, as seen in our patients, may be better understood by looking at patients' underlying medical conditions seen in prior reports of pseudohypoglycemia. Associated conditions include hematological disorders, such as leukemias, hyperviscosity syndromes, and hemolytic anemias; here, the capillary-plasma measurement discrepancy is thought to be primarily due to *in vitro* glycolysis.[8-10] Pseudohypoglycemia has also been described in PAD, shock, and Raynaud's phenomenon, where the capillary-plasma difference is thought to be due to impaired microcirculation, leading to a slower transit time and increased local tissue uptake of glucose, resulting in an apparent lower CBG level relative to venous plasma samples.[11-16]

CONCLUSIONS

The finger stick method of glucose is logistically simple and fast, and thus is often the preferred method for frequent glucose monitoring. However, the cases presented here demonstrate the potential unreliability of CBG measurements under specific circumstances. Clinicians should be aware of the existence of pseudohypoglycemia and consider it in cases where the clinical signs and symptoms of hypoglycemia are absent. One helpful feature that may be used to confirm pseudohypoglycemia is a discrepancy between capillary and venous plasma measurements of blood glucose. Relatedly, if pseudohypoglycemia is suspected, simultaneous CBG and VPG samples should be drawn.

Pseudohypoglycemia has been most commonly described in patients with either hematologic conditions or conditions associated with impaired microvascular circulation. In our presented cases, we suspect both patients' pseudohypoglycemia was likely secondary to impaired microvascular circulation (from Raynaud's phenomenon secondary to SSc and chronic PAD with reduced cardiac output in the setting of an acute myocardial infarction, respectively). As a caveat, the existence of pseudohypoglycemia should not deter clinicians from empirically treating suspected hypoglycemia, especially in cases where eliciting symptoms may be difficult or impossible. However, if patients consistently demonstrate low CBG levels yet remain asymptomatic, providers should consider the possibility that pseudohypoglycemia may explain an otherwise confusing clinical picture.

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