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Brief Observation

Hyponatremia with an Osmolar Gap, Pseudohyponatremia or Hyper-Osmolar Hyponatremia? ☆,☆☆

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ABSTRACT

Pseudohyponatremia is frequently misunderstood and often mistaken for other types of hyponatremia. In this study, we present a case of pseudohyponatremia resulting from hypertriglyceridemia. We provide an in-depth analysis of the pathophysiological mechanisms involved, comparing them with those of other hyponatremic disorders, and outline the diagnostic approach used to identify this atypical form of hyponatremia. Recognizing and accurately diagnosing non–hypo-osmolar hyponatremia is paramount, as these conditions are treated differently than other forms of hyponatremia.

Introduction

Hyponatremia, defined as a serum sodium (Na^+) concentration of <136 mEq/L, is a common disturbance in hospitalized patients with an incidence of 14%-30%, and prevalence of 6%-42%.[1-3] Assessment of hyponatremia requires a multistep approach that begins with measurement of plasma osmolality. This step is critical in identifying hypo-osmolar hyponatremia, the most common type of hyponatremia. Using the serum osmolality formula: Osmolality = 2 (Na^+) + blood urea nitrogen/2.8 + glucose/18, we can see sodium makes up most of the serum osmolality thus when sodium is low, we would expect serum osmolality to be low as well. When hyponatremia is present and the serum osmolality is not low, then the typical correlation between sodium levels and osmolarity is disrupted, suggesting either hyper/iso-osmolar hyponatremia or pseudohyponatremia. Hyper/iso-osmolar hyponatremia occurs when there is an osmotically active compound pulling water into the vascular space.[4] This process will dilute the sodium causing hyponatremia yet, maintain a normal or elevated serum osmolality due to the presence of this osmotic compound. On the other hand, pseudohyponatremia is a lab error due to elevated lipids and protein in the blood.[5] We present a case of pseudohyponatremia and discuss the diagnostic process and in-depth review of hypertriglyceridemia induced pseudohyponatremia.

To this day, is still shrouded in misconceptions, creating a tendency to downplay the effects of this condition, leading to errors and potentially hazardous consequences.

Case Presentation

A 30-year-old male with past medical history of type 2 diabetes mellitus, on metformin, presented to the emergency department for abdominal pain. There were no other relevant past medical, family, or surgical history and no known allergies. The patient denied alcohol, tobacco, or illicit drug use. On physical exam, the patient was visibly in pain, tachycardic, lungs clear to auscultation, his abdomen was soft, tender to palpation in right upper quadrant with no guarding or rebound, and no evidence of edema or subcutaneous nodules. Upon drawing the blood, the nurse noted a milky substance in all vials drawn (Figure 1). Laboratory data (Table 1) was relevant for a lipase of 343 U/L, severe hyponatremia of 114 mEq/L, serum glucose 233 mg/dL, serum osmolality of 315 mOsm/Kg, point-of-care (POC) testing showed a sodium of 138 mmol/L and triglycerides were over 5000 mg/dL. CT abdomen/pelvis with contrast was consistent with necrotizing pancreatitis due to hypertriglyceridemia. Nephrology was consulted for hyponatremia.

The patient was diagnosed with pseudohyponatremia based on clinical picture and laboratory results. After supportive care the pancre-

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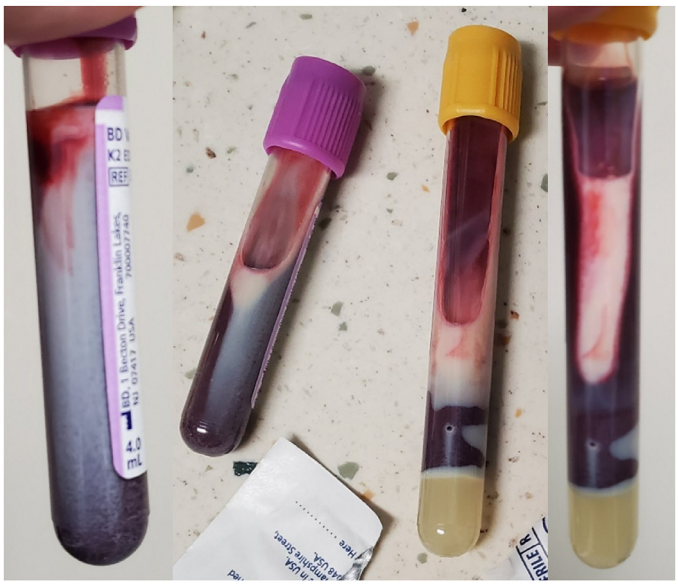

Figure 1. Photos of patient's blood taken upon admission to the hospital showing the extent of the milky white portion of the blood due to his triglyceridemia.

Table 1
Patient's Initial Laboratory Data

Bloodwork	
Sodium: 114 mEq/L	Creatinine <0.2 mg/dL
Chloride 81 mEq/L	Protein 5.3 g/dL
Potassium 3.6 mEq/L	AST 75 U/L
Bicarbonate 18 mEq/L	ALT <3 U/L
BUN 8 mg/dL	Lipase 343 U/L
Glucose 184 mg/dL	Platelets 205 K/uL
Serum osmolality 315 mOsm/kg	Triglycerides >5000 mg/dL
WBC 14.2 K/uL	Hemoglobin 13.5 g/dL
POC labs	
Sodium 138 mEq/L	Potassium 3.2 mEq/L
Chloride 112 mEq/L	Bicarbonate 18 mEq/L
BUN 6 mg/dL	Creatinine 0.2 mg/dL
Glucose 233 mg/dL	
Urine labs	
Osmolality 830 mOsm/kg	Sodium 85 mEq/L
Potassium 85 mEq/L	Chloride 94 mEq/L

Abbreviations: POC, point-of-care; BUN, blood urea nitrogen; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase

atitis and hypertriglyceridemia improved, and the serum sodium also returned to normal (Figure 2). The patient was discharged home after a 3-day hospital course.

Discussion

The evaluation of hyponatremia begins with evaluating the serum osmolality to determine whether the hyponatremia is hyposmolar or hyper/iso-osmolar. Calculated serum osmolality should be compared to measured serum osmolality and if the difference is greater than 10 mOsm/kg (serum sodium (mmol/L) × 2 + serum blood urea nitrogen (mg/dL)/2.8 + serum glucose (mg/dL)/18), hypo-osmolar hyponatremia is not present. This calculation comparing the measured and calculated serum osmolalities is referred to as the osmolar gap. In the presence of an osmolar gap, further workup should be pursued to differentiate between hyper/iso-osmolar hyponatremia and pseudohyponatremia.[6] When an osmolar gap is present, the next step is to differentiate between hyper/iso-osmolar hyponatremia and pseudohyponatremia. Hyper/iso-osmolar hyponatremia occurs when there is an osmotically active compound pulling water into the vascular space. This

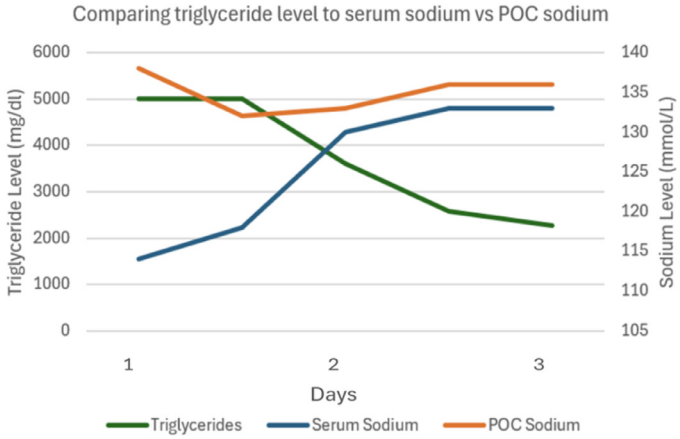

Figure 2. Comparing the POC sodium (orange line) and serum sodium (blue line) as compared to triglycerides level (green line) in our patient we can see that as triglycerides decrease over time, the serum sodium increases proportionally. This all occurs with the POC sodium remaining stable. Patients triglyceride level was > 5000 mg/dL and would be expected to be higher than what is depicted on this graph.
Abbreviations: POC, point-of-care

Table 2
Causes of Pseudohyponatremia

Elevated Cholesterol Components	Elevated Protein
Hypertriglyceridemia	Chronic infectious disease states (ex. hepatitis C, HIV)
Hyperlipidemia	Monoclonal gammopathies
Lipoprotein X accumulation	Lymphoproliferative disorders
Familial hypercholesterolemia	Myelodysplastic syndrome
	Immunoglobulin deposition disease
	Intravenous immunoglobulin (IVIG)

Abbreviations: HIV, Human immunodeficiency virus

dilutes the sodium, causing hyponatremia yet this osmotically active compound present in the blood maintains the serum osmolality. Pseudohyponatremia is a lab error due to the presence of hyperlipidemia or hyperproteinemia (Table 2). The main way to differentiate these would be to obtain a POC sodium, whereas in hyper/iso-osmolar hyponatremia the POC sodium is low, and in pseudohyponatremia the POC sodium is normal. Once a nonhypoosmolar hyponatremia is diagnosed, the urine osmolality has a lower diagnostic utility. In this case, his elevated urine osmolality was likely from the increase in antidiuretic hormone secretion due to the pancreatitis pain, stress and nausea but was not helpful in diagnosing anything because patient was never truly hyponatremic.

In order to understand pseudohyponatremia, one must understand how sodium is measured. Sodium is currently measured using ion-selective electrodes (ISE), which has many benefits, including high accuracy, high precision, rapid, low cost with small sample sizes, and measurements over a wide range of results.[7] The two types of ISE measurements are direct-ISE and indirect-ISE. Direct-ISE is utilized in POC, blood gas analyzers, and whole blood measurements. In comparison, indirect-ISE is commonly used in automated analyzers, where the samples are diluted prior to measurement. This dilution step allows for lower sample volume, which increases the measurable concentration range.[7] Discrepancies can be seen between these two methods when abnormalities of protein or lipids are present. The term, the "electrolyte exclusion effect" describes this effect.[8] When measuring a substance using indirect-ISE, after dilution and measurement, a back-calculation needs to be done to determine the concentration before the initial dilution. This back-calculation assumes the blood is 93% water, which is consistent with the percentage in a normal individual.[9] In the setting of elevated proteins or lipids, the water concentration decreases and may be as low as 80%.

Therefore, this standardized value of 93% oftentimes leads to falsely low sodium results. Sodium concentration in serum water (sw), not serum, that determines its osmotic actions, and the relationship between them can be seen as [Na]sw = serum [Na] / serum water content.[10,11]

Conversely, direct-ISE measurements do not require a dilution step, eliminating the need for a back-calculation and thus providing a more accurate sodium result. This discrepancy of sodium values due to elevated lipids or proteins is pseudohyponatremia, a condition first discussed in the 1950's.[12] Therefore, in evaluating hyponatremia and ruling out pseudohyponatremia, a direct measurement of sodium is preferred.[13] Etiologies that can produce pseudohyponatremia include hypercholesterolemia/hypertriglyceridemia and hyperproteinemia states (table 2).[14] The prevalence of pseudohyponatremia is around 17-20%.[15,16] Many textbooks claim that pseudohyponatremia is rare due to modern instrumentation, but this is inaccurate, as more than two thirds of the laboratories in the United States are still using indirect-ISE measurement to measure electrolytes.[17] The failure to rule out pseudohyponatremia remains a common pitfall in the evaluation of hyponatremia.[18]

If direct-ISE is unavailable, lipids can be removed via ultracentrifuge techniques or other laboratory-based removal systems.[19-21] If neither is accessible, equations have been developed to estimate the true sodium value by determining the water content of the blood through the following formula[9,22]:

$$\text{Serum water}\,(\%) = 99.1 - \left(0.001 \times \text{lipid concentration}\,\left[\text{mg/dL}\right]\right) - (0.7 \times \text{protein concentration}\,\left(\left[\text{g/dL}\right]\right).$$

The indirect sodium measurement should be multiplied by the normal serum water of 93%, then divided by the calculated value to approximate the "corrected" sodium.

Other formulas exist to help predict the plasma water concentration but are more complicated.[23,24] Caution must be used when applying these formulas because they are only estimations and can sometimes be inaccurate. For example, one case reported a predicted sodium level of 121 mEq/L, while the direct-ISE measurement was 131 mEq/L.[25] Despite the availability of lipid-removing procedures, a direct-ISE remains the gold standard. In the setting of lipemic or hyperviscous blood samples, it is recommended to check a direct-ISE sodium measurement.[26,27]

A major point of confusion and common error for many physicians is incorrectly diagnosing hyperglycemia as pseudohyponatremia. Specifically, hyperglycemia can produce hyperosmolar hyponatremia due to the osmotic effects of glucose, which pulls water into the vascular space, resulting in the dilution of sodium without creating hypo-osmolality. This is not pseudohyponatremia because water is being shifted, whereas in pseudohyponatremia, no water is displaced. In pseudohyponatremia, abnormal lipid or protein levels alter the percentage of water in the blood, resulting in an inaccurate back calculation of sodium when measured indirectly.

The two most common causes of lipemic blood samples are intravenous lipid infusions (fat emulsions for parental nutrition and propofol) and diabetes.[22,28] Notably, up to 70% of patients with diabetes may present with hypertriglyceridemia, which may complicate the serum sodium assessment in these individuals.[22] Additionally, in a prospective study of 127 alcoholic patients, 17% had hyponatremia and of these hyponatremic patients, pseudohyponatremia from hypertriglyceridemia was found to be the second most common etiology of hyponatremia.[29] In pancreatitis patients, those who presented with hyponatremia were significantly more likely to have hypertriglyceridemia.[30]

There is an inverse correlation between the degree of hypertriglyceridemia (and hyperproteinemia) and indirect-ISE measured serum sodium.[31-33] For every 500-885 mg/dL increase of triglycerides or 10 mmol/L increase in total lipids (total cholesterol + triglycerides), there is approximately a 1 mmol/L decrease of sodium.[19,34] An in-vitro study mixing different lipid concentrations with blood samples demonstrated that sodium starts to decrease around a lipid concentration of 650mg/dL[35] whereas another study demonstrates that sodium starts to become abnormal when triglyceride level is around 1500 mg/dL.[36] A laboratory in Belgium uses a triglyceride threshold of 1500 mg/dL to pursue a more reliable sodium determination.[37] If hyperlipidemia and hyperproteinemia are present together, the result will be additive, lowering the indirect-ISE measurement further.[38]

In all populations, direct sodium measurements and indirect measurements are not interchangeable as they show significant disagreement between measurements when significant dyslipidemias or dysproteinemia are present.[39-45] Thus, because of these potential differences of sodium measurements, when treating hypo-osmolar hyponatremia, the same measurement methodology should be utilized.[46] But in the case of pseudohyponatremia, we recommend a direct-sodium measurement be utilized until the underlying cause (hypertriglyceridemia or hyperproteinemia) be corrected. The International Federation of Clinical Chemistry and Laboratory Medicine, The European Society of Endocrinology, The European Society of Intensive Care Medicine and European Renal Association-European Dialysis and Transplant Association all recommend direct-ISE measurement for sodium when working up dysnatremias or in the setting of abnormal plasma water concentration to prevent these adverse events.[47,48]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Leonardo Pozo Garcia: Data curation, Writing – original draft. **Livia Frost:** Data curation, Writing – review & editing. **Bryan M. Tucker:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

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