

Pseudohyponatremia Revisited

A Modern-Day Pitfall

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● **Factitiously low sodium estimations are a hazard in most modern clinical laboratories. Most modern high-throughput analyzers use indirect ion-selective electrodes to estimate electrolyte concentrations in serum samples. This analysis is preceded by a dilution step of the sample. If the water concentration is altered by the presence of increased lipid or protein, the dilution step and the subsequent calculation of concentration by the analyzer results in a falsely low sodium value. This places patients at risk, particularly if the factitious result is acted upon by the physician. In this short review, we highlight this problem and review the methodology and situations where this artifact can occur and discuss strategies to circumvent this problem. When factitious results are suspected, whole blood sodium can be assessed using a direct ion-selective electrode, by measurement of osmolality, or by calculation of the serum water fraction and applying a correction to the reported value.**

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Electrolytes and glucose estimations are among the most commonly requested tests in clinical pathology laboratories. Vast numbers of these results are reported daily and, for the most part, are taken at face value by laboratory users. This technical review highlights the inherent dangers to patient safety if scant regard is paid to analytical errors that can arise under certain circumstances. It is the responsibility of laboratory personnel and clinicians alike to be informed of, and alert to, these analytical idiosyncrasies.

Hyponatremia is one of the most common disturbances of sodium metabolism in hospital patients, with a prevalence of 2% to 3%.¹ It occurs on a backdrop of hyperosmotic, isoosmotic, and hypoosmotic plasma; hence measurement of plasma osmolality is important in the assessment of hyponatremia. For example in the presence of hyperlipidemia or hyperproteinemia, measured serum sodium can also be depressed without concomitant depression of serum osmolality. This artifact

of measurement is termed pseudohyponatremia in the context of physiologically normal sodium levels and pseudonormonatremia when the result masks physiologically increased sodium.² It is self-evident that fluid management based on results that mask the true physiologic situation can lead to errors, with potentially serious clinical consequences and even death.³ There has been a tendency to downplay the dangers associated with unrecognized pseudohyponatremia,⁴ probably due to the mistaken belief that methodology that would avoid this phenomenon is in widespread use. In fact, two thirds of laboratories in the United States use methods that are prone to this anomaly.⁵ It should be noted that other indirectly measured analytes, such as potassium, calcium, and chloride, are subject to the same effects as sodium. Although the relative effect on all aqueous solutes is the same, the absolute change in sodium is far greater in view of its higher concentration in serum. The opposite phenomenon of pseudohypertremia can also occur as a result of severe hypoproteinemia.⁵ It is also widely and erroneously believed that only hypertriglyceridemia, and not hypercholesterolemia, is responsible for pseudohyponatremia. High cholesterol levels do not cause visible turbidity or lipemia in blood, compared with hypertriglyceridemia. High cholesterol is a known but uncommon cause of pseudohyponatremia in the context of obstructive jaundice, where the cases described in the literature have all involved lipoprotein X.^{6–9} Because the molecular weight of cholesterol is approximately 2.5-fold less than that of triglyceride, the propensity of cholesterol to cause pseudohyponatremia is therefore 2.5-fold less on a mole for mole basis.

Serum is composed of nonaqueous and water fractions, 7% and 93% of serum volume, respectively (Figure 1). Sodium is located in the serum water phase only. In clinical laboratories there are 2 methods for measuring electrolytes in plasma.⁵ Both methods use the principle of an ion-selective electrode (ISE), where a sodium-selective membrane is immersed into blood or serum and the sodium activity is measured as a function of the potential difference across the electrode. Ion-selective electrodes measure the activity of an ion, rather than its concentration. There is a specific thermodynamic definition of ionic activity, but for this purpose it can be considered to be equivalent to the concentration of the ion. Only atoms that are completely ionized are active, and this complete ionization occurs under conditions of infinite dilution, but the activity of sodium in serum approximates its

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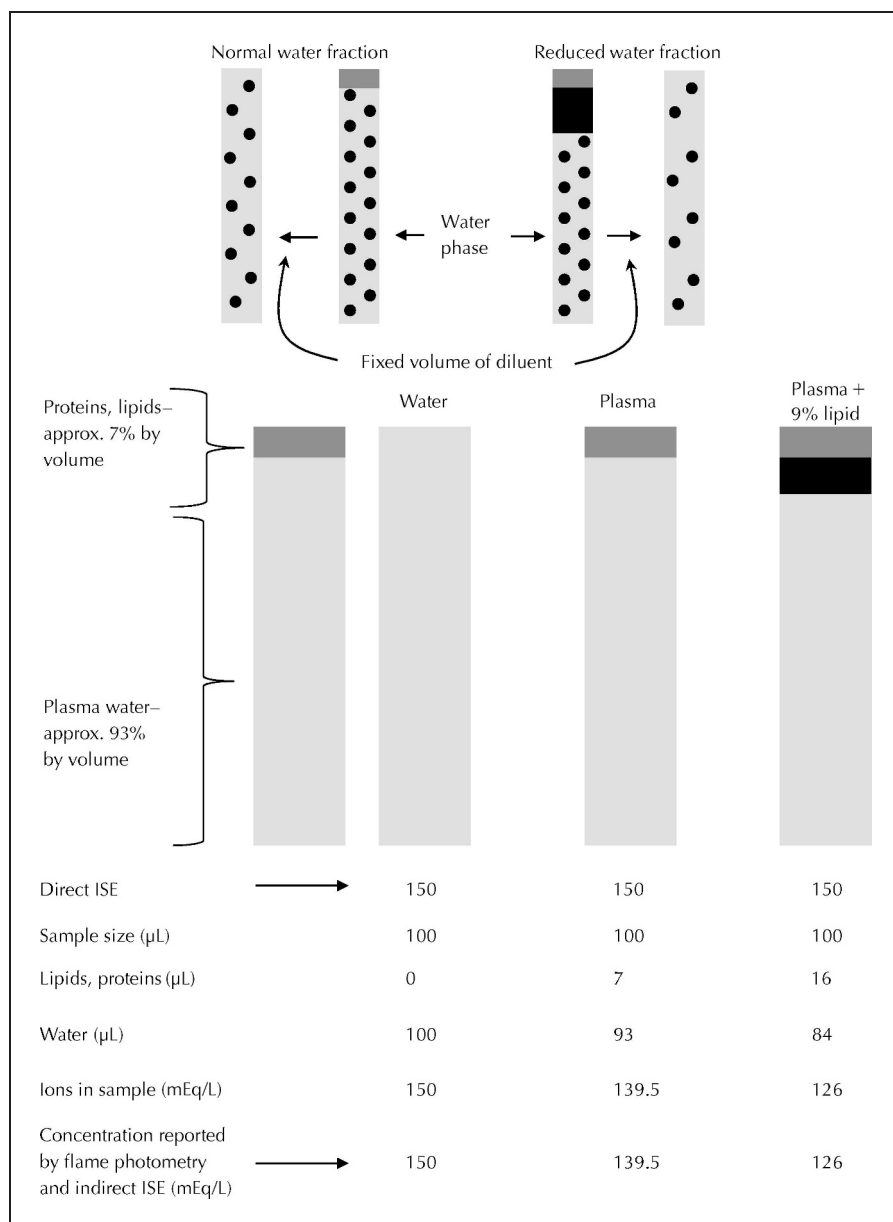


Figure 1. Effects of the predilution and calculation performed by the indirect estimation of sodium. Abbreviations: approx., approximately; ISE, ion-selective electrode.

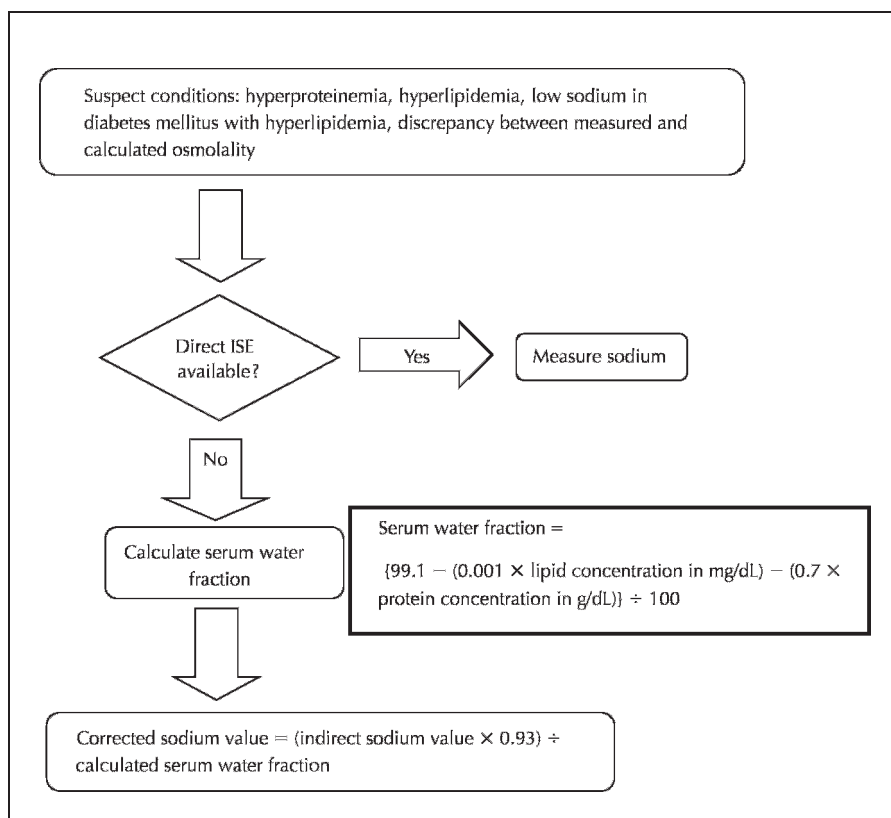
concentration in serum water.¹⁰ Direct potentiometry is used in blood gas analyzers and measures sodium activity in plasma water. Importantly, there is no dilution step. Sodium in serum water normally has a concentration of 150 mEq/L, and this value is independent of the volume occupied by the nonaqueous fraction in serum. The measured value for sodium in serum water is commonly converted to a concentration in total serum: 150 mEq/L sodium in serum water corresponds to a value of 139.5 mEq/L in total serum (Figure 1).

Most high-throughput laboratories use an indirect ISE, which entails a preanalytical serum dilution step, whereas blood gas machines make use of undiluted sample in the direct ISE. The basic principle of potentiometry is the same in both methods, but the indirect method uses an assumption that makes its use flawed under conditions of hyperlipidemia or hyperproteinemia.¹¹ If one considers

that the absolute amount of sodium in such cases (ie, in a smaller fraction of serum water) is decreased, then any dilution by a fixed amount will introduce a dilution error, which results in a decrease in measured sodium.

It is clear that normal sodium levels masquerading as depleted values can have serious consequences for patient safety. Indeed, as mentioned previously, in pseudonormonatremia, where genuinely elevated sodium values are measured as normal due to lipemia or hyperproteinemia, such samples present similar opportunity for errors in patient management. This can be avoided by measuring sodium by direct potentiometry, which would require clinical laboratories to convert to this system from the more common indirect ISE method. This may also require the adoption of new reference ranges, although this problem may be avoided by the use of corrected sodium values, as is the case with most blood gas analyzers. If a

Figure 2. A practical approach to suspected pseudohyponatremia. Abbreviation: ISE, ion-selective electrode.



result from a lipemic or hyperproteinemic sample is recognized as being misleading, another approach has been to first estimate the serum water fraction by the following equation¹²:

$$\begin{aligned} \text{Serum Water (\%)} \\ &= 99.1 - (0.001 \times \text{Lipid Concentration in mg/dL}) \\ &\quad - (0.7 \times \text{Protein Concentration in g/dL}) \end{aligned}$$

or in SI units

$$\begin{aligned} \text{Serum Water (\%)} \\ &= 99.1 - [1.1 \times 10^{-5} \times \text{Lipid (Triglyceride) Concentration in mmol/L}] \\ &\quad - (0.07 \times \text{Protein Concentration in g/L}). \end{aligned}$$

The indirectly measured sodium value is then multiplied by the normal serum water value of 93% and divided by the calculated value. This calculated value has then been adjusted to a normal serum water value. More complex methods involving the measurement of chloride in serum and its ultrafiltrate or the measurement of serum

osmolality before and after dilution have been proposed.¹³ It may, however, be of more practical value to follow the recommendations of Weisberg,¹⁴ providing that access to a direct-reading ISE instrument is possible. The recommendations are summarized later (Figure 2).

With the use of indirect sodium measurement for routine analyses, measurements using a direct-reading ISE should be undertaken under the following circumstances:

- If the specimen is overtly lipemic (lipemic samples can also be ultracentrifuged prior to analysis by indirect measurement of the aqueous infranatant) or hyperviscous. It should be noted that the correlation between visual turbidity and the concentration of triglycerides is poor.¹⁵
- If there is a significant discrepancy between measured osmolality (will be normal in pseudohyponatremia, assuming the other contributors are normal) and calculated osmolality.
- Any low sodium in a patient with diabetes mellitus and hyperglycemia (pseudohyponatremia secondary

Calculated Magnitude of Changes Caused by Increased Protein or Lipids When Analyzing Serum Sodium by Indirect Methods				
Protein Level, g/dL	Triglycerides, mg/dL	Measured Sodium, mEq/L	Calculated ("True") Sodium, mEq/L	Calculated Free Water Fraction, %
17	60	130	139	87.1
15	60	130	137	88.5
10	60	130	131	92
4	60	130	126	96.2
7	3000	130	133	91.2

to associated hyperlipidemia, in these patients, should be differentiated from true hyponatremia secondary to the positive osmotic effects of hyperglycemia). It should be noted that osmotically active substances, such as glucose, cause hyponatremia by increasing plasma water in vivo but per se do not cause a clinically significant hypoosmolar state associated with other causes of hyponatremia (this is also sometimes labeled as pseudohyponatremia). Interestingly, it has been observed that high glucose can also affect direct ISE resulting in artifactually increased sodium.¹⁶

If a direct-reading instrument is not available, the calculation of serum water, as explained previously, can be used as an approximation.

It should be noted that, although plasma water concentration can be estimated based on the measurements of total protein and lipids, the experimental validity of this estimate has been questioned.¹⁷ Plasma water can also be calculated using an alternative equation requiring prior measurement of sodium by both direct and indirect ISE¹⁷:

Plasma Water Concentration

$$= \frac{0.933 \times \text{Vol}_{\text{diluent}} \times [\text{Na}^+]_{\text{I-ISE}}}{[\text{Na}^+]_{\text{D-ISE}} \times (0.933 + \text{Vol}_{\text{diluent}}) - (0.933 \times [\text{Na}^+]_{\text{I-ISE}})}$$

In this study,¹⁷ plasma water concentration was determined by 3 methods: ISE, protein/lipid, and gravimetrically. There was greater correlation of the ISE-determined plasma water concentration with the gravimetric method.

In conclusion, hyponatremia is a common clinical finding, and it is clear that a systematic approach must be used. The magnitude of calculated changes caused by raised protein or triglycerides are illustrated in the Table. Due diligence should be given to results that are inconsistent with the clinical background or measured osmolality or to specimens that are macroscopically

abnormal. Failure to do so can have potentially grave consequences.

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