

Review Article

Pseudohyponatraemia – A literature review

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Abstract

Hyponatraemia often poses a diagnostic dilemma, brought about by inadequate work-up and inappropriate management. In order to make the correct diagnosis, an understanding of the pathophysiology and classification of hyponatraemia is essential. In this review, focus is made on the diagnosis of pseudohyponatraemia including the causes, when to suspect it and how to diagnose it. Different analytical methods are discussed, including flame emission spectrophotometry, and ion-specific electrode (ISE) potentiometry and the role they play in diagnosing pseudohyponatraemia. The measured and calculated osmolalities and their use to calculate the osmolal gap are explained. Finally, a discussion follows on the aetiologies of pseudohyponatraemia, strategies to circumvent this problem and the relevance of clinching the diagnosis in clinical practice.

Keywords

pseudohyponatraemia, hyperproteinaemia, hyperlipidaemia, ion-specific electrode potentiometry, osmolal gap

Measurement of serum sodium concentration is amongst the most commonly requested tests in clinical practice. A diagnosis of hyponatraemia is made in up to 2% to 3% of hospitalised patients.¹ However, it is frequently overlooked, misdiagnosed and mismanaged. Measurement of serum osmolality and assessment of fluid status are the crux to distinguishing between the different causes of hyponatraemia, while giving due consideration to the possibility of a spuriously low serum sodium level – *pseudohyponatraemia* (figure 1).

For around thirty years, flame emission spectrophotometry (FES) was the technique of choice for measuring the major cations, sodium and potassium. Although still in use as a reference method, in the 1980s FES was replaced across most laboratories by ion-specific electrode (ISE) potentiometry. The latter measures the potential difference across a reference electrode and a measuring electrode being exposed to the selected ion (in this case sodium). Two ISE techniques are available for measurement of plasma sodium concentration – direct and indirect ISE potentiometry. With direct ISE potentiometry, the sample is presented to the measuring electrode undiluted, whereas indirect ISE potentiometry requires that the sample is first diluted in a buffer.³ Of the two techniques, *indirect* ISE is the more widely used, as diluting the sample allows for the serum sodium ionic activity, measured in millivolts (mV), to be used as a close approximation of the serum sodium concentration. Only atoms that undergo ionisation are activated, and this ionisation takes place via a pre-analytical dilution of 1:10.⁴ This method is used in over two-thirds of laboratories across the United States and likewise affects the measurement of other similarly measured ions including potassium, chloride and calcium.⁵ However, since the concentration of sodium is far greater than that of the other ions, the analytical error is also greater. On the other hand, point-of-care machine analysers (such as blood-gas analysers) use *direct* ISE and measure the sodium activity without requiring a dilution step, hence allowing for direct measurement of the sodium

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concentration in plasma water.

In the healthy subject, water constitutes 93% of plasma volume, whilst the remaining 7% consists of undissolved particles, mostly lipids and proteins.⁶ All plasma electrolytes are confined to the aqueous phase and hence it is the concentration of sodium in the aqueous phase that is physiologically relevant. In patients with severe hyperlipidaemia or hyperproteinaemia, the increased amounts of protein or lipid in the non-aqueous phase will occupy more than 7% of the total plasma volume and will hence alter the 93:7 aqueous to non-aqueous ratio. This ratio of 93:7 is the basis for

measuring serum sodium concentration using *indirect* ion-specific electrode (ISE) potentiometry. If the non-aqueous phase increases at the expense of the aqueous phase, then the serum sodium can no longer be predicted from the total plasma volume (aqueous plus non-aqueous) using this ratio. In patients with pseudohyponatraemia the sodium concentration in aqueous phase of plasma is normal, however *indirect* ISE potentiometry measures the serum sodium in the *total* plasma volume, without taking into account instances when the aqueous phase occupies less volume than usual (figure 2).⁷

Figure 1

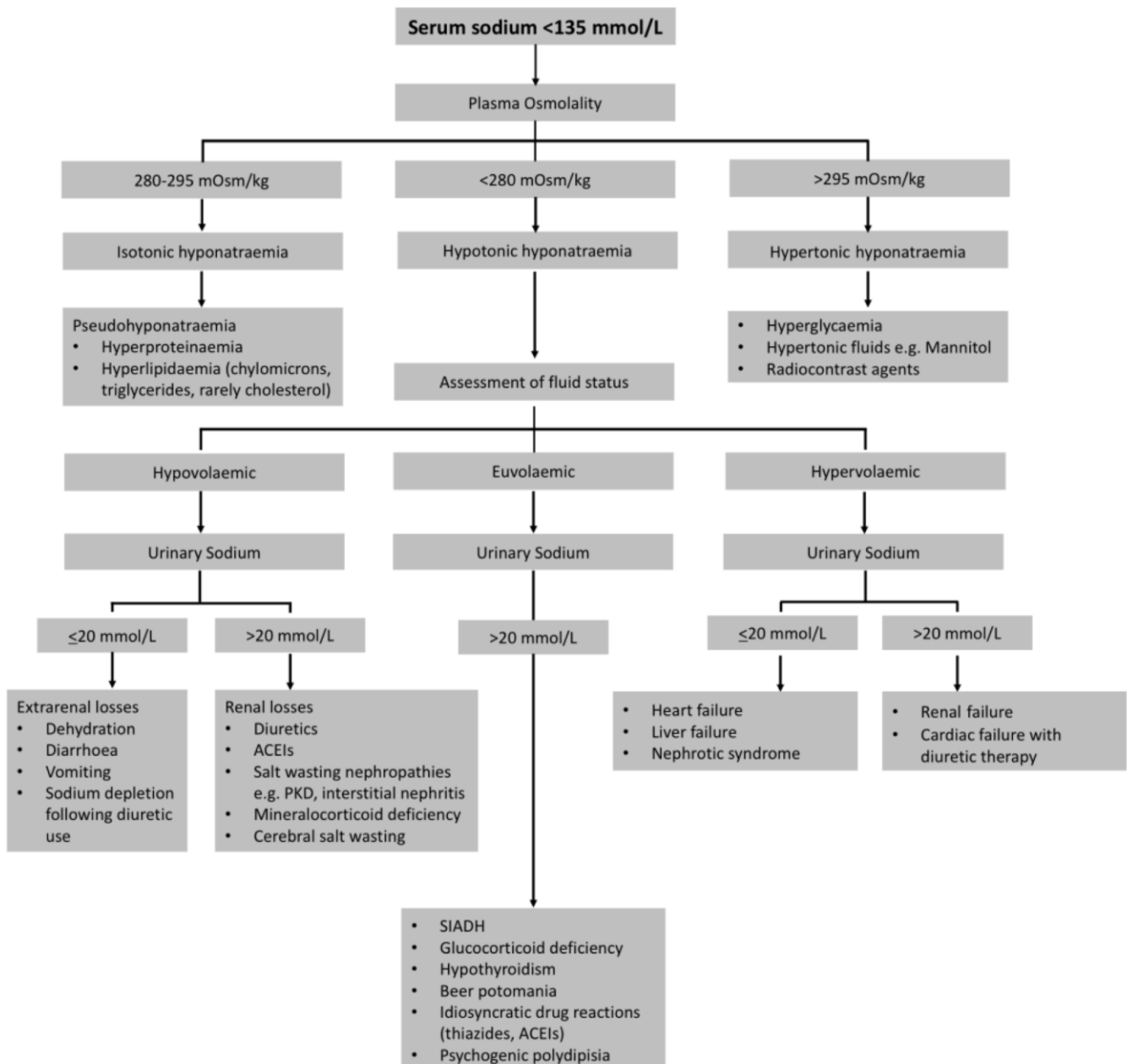
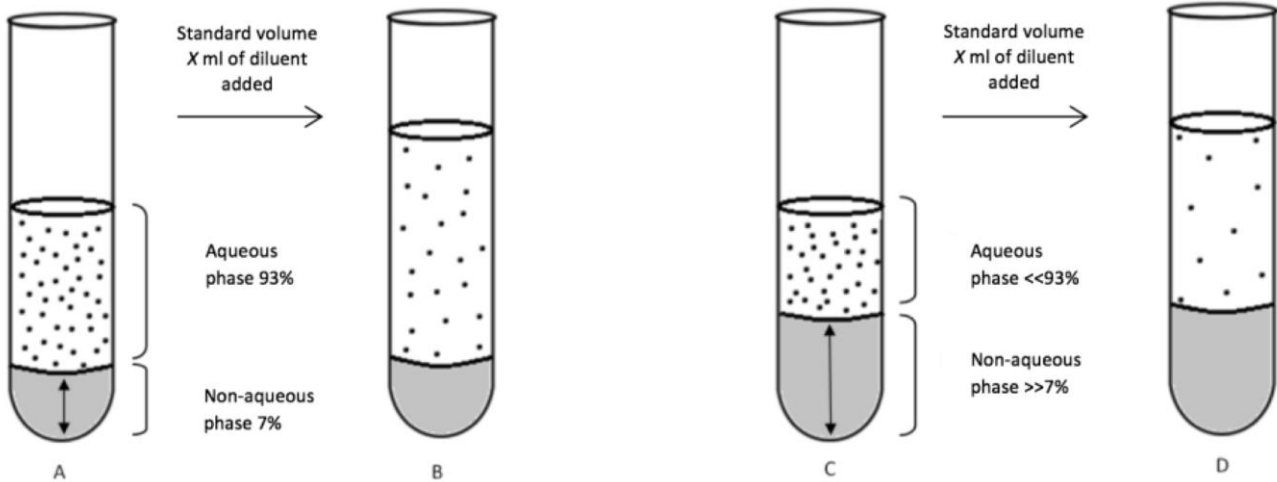


Figure 2

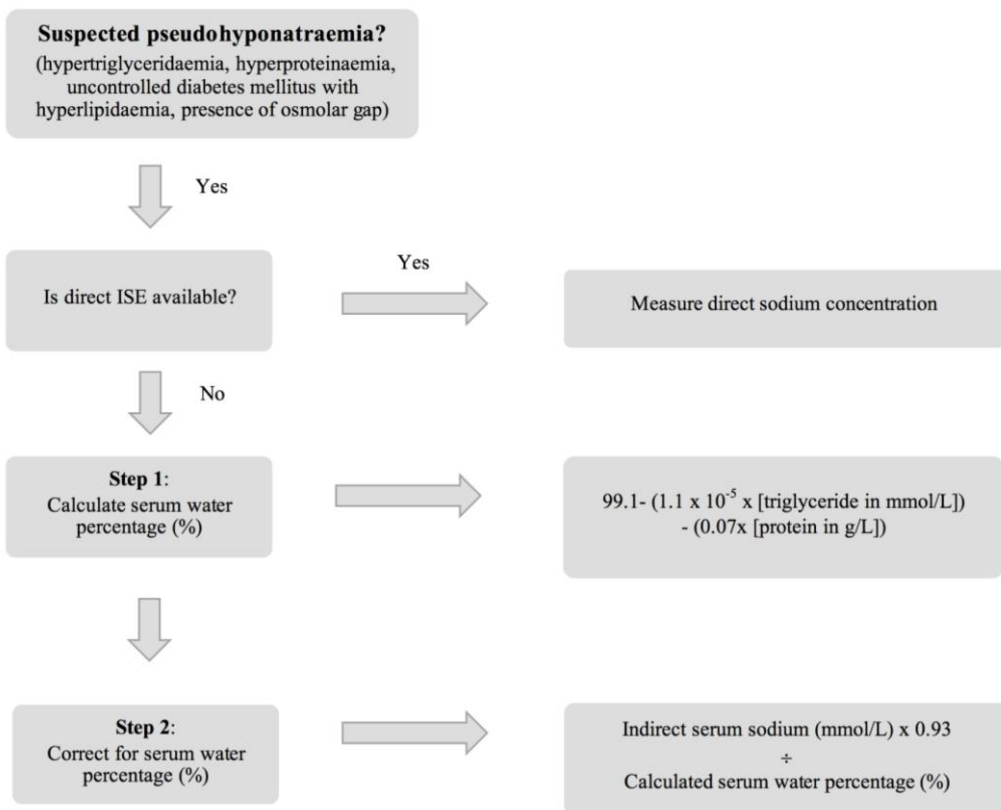


The easiest method to diagnose pseudohyponatraemia is by measuring serum sodium concentration using a direct ISE potentiometer (such as a blood gas analyser).⁸ If this is not available, plasma triglyceride and total protein concentration can be used to calculate the percentage water content of serum, with a value less than 93% being in keeping with a possible diagnosis of pseudohyponatraemia.⁹ The first step in calculating the serum sodium concentration requires the percentage of serum water, obtained using the following equation:¹⁰

$$\text{Serum water (\%)} = 99.1 - (1.1 \times 10^{-5} \times [\text{triglyceride in mmol/L}]) - (0.07 \times [\text{protein in g/L}])$$

The corrected sodium concentration is then calculated by multiplying the laboratory (indirect) serum sodium by 93% (i.e the normal serum water percentage) and dividing it by the calculated serum water % (calculated using the above equation). The second step allows for the adjustment of the calculated serum sodium to a normal serum water percentage (figure 3).

Figure 3



Pseudohyponatraemia should be suspected in the following circumstances:

- There is a significant discrepancy between the *measured* osmolality (which is normal in pseudohyponatraemia) and the *calculated* osmolality i.e. the presence of a raised osmolal gap, defined as the difference between the measured osmolality and the calculated osmolality (the calculated osmolality being lower than the measured osmolality in cases of pseudohyponatraemia). The measured serum osmolality remains unperturbed by changes in the ratio of the plasma constituents, as only the solutes which dissolve in the aqueous phase contribute to its measurement.¹¹
- The serum sodium does not correlate with the clinical signs.¹²
- Hyponatraemia in a patient suffering from uncontrolled diabetes mellitus. Of note, the pseudohyponatraemia in this case is secondary to an associated hyperlipidaemia and should be differentiated from hyponatraemia caused by hyperglycaemia. In the latter case, glucose acts as an active osmole causing water to move from the intravascular to the extravascular space and hence resulting in a true, dilutional hyponatraemia secondary to an osmotic diuresis. As a rule of thumb, an increase of plasma glucose of 5 mmol/L results in a decrease in plasma sodium of 1.6-2.4 mmol/L.¹³
- The specimen is grossly lipaemic. For every 12 mmol/L increase in serum triglyceride levels, serum sodium decreases by approximately 1.5 mmol/L.¹⁴
- In patients known to suffer from a paraproteinaemia or being treated with intravenous immunoglobulin (IVIg). In this case each gram of monoclonal protein decreases serum sodium by 0.7 mmol/L.¹⁵

Interestingly the phenomenon of pseudohypernatraemia can conversely arise in patients suffering from hypoproteinaemia.⁵ Also of note is that hypertriglyceridaemia is far more likely to cause pseudohyponatraemia than hypercholesterolaemia – this is because triglycerides have a 2.5-fold greater molecular weight ($C_{57}H_{104}O_6 = 885.4$ g/mol) compared to

cholesterol ($C_{27}H_{46}O = 386.7$ g/mol) which results in lack of visible turbidity when hypercholesterolaemia is the culprit.^{5,15,16} Nevertheless, although uncommon, hypercholesterolaemia has been described as a cause of pseudohyponatraemia in the context of obstructive jaundice and elevated levels of lipoprotein X.¹⁷⁻²² Extreme hypertriglyceridaemia, in excess of 10 mmol/L, results in an increase in the non-aqueous phase of plasma and contraction of the aqueous phase. Clinical manifestations may include lipaemia retinalis and eruptive xanthomata and unfortunately acute pancreatitis remains a very serious complication. It may result from a gene defect involving the activity of lipoprotein lipase (directly or indirectly) or may more commonly be precipitated by conditions such as poorly controlled diabetes, obesity, excessive alcohol consumption, hypothyroidism and lipodystrophy.²³

Conclusion

Pseudohyponatraemia is an artefactual reading occurring when the *measured* serum sodium is normal, but the *calculated* serum sodium is erroneously low, hence resulting in an increased osmolal gap.¹¹ The condition only arises in cases of severe hypertriglyceridemia and hyperproteinaemia (most commonly multiple myeloma²⁴), when serum sodium is measured using *indirect* ISE potentiometry or FES, both of which involve predilution of the blood samples. The exclusion of sodium from the non-aqueous phase is the basis for understanding why predilution photometry can result in pseudohyponatraemia if the plasma volume occupied by the aqueous phase changes. As the lipid concentration increases, the water content in plasma decreases, and hence, the larger the error of pseudohyponatraemia. Whilst it is rare for serum triglycerides or proteins to rise to such high levels as to result in pseudohyponatraemia, it is of paramount importance that this artefact is recognised and *not treated* as true hyponatraemia. When in doubt, serum sodium should be measured using direct ISE potentiometry, as failure to recognise pseudohyponatraemia may lead to inappropriate choice of treatment and death from hypernatraemia.²⁵⁻²⁶

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