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Hyponatremia in peritoneal dialysis patients

(Hyponatrémie chez les patients en dialyse péritonéale)

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Summary

Hyponatremia is the most common disorder of body fluid and electrolyte balance encountered in clinical practice, and also in peritoneal dialysis (PD) population. Depending on the severity and the speed of drop in sodium concentration, the symptoms can vary from asymptomatic hyponatremia to mild and non-specific symptoms or severe and life-threatening situations. Hyponatremia is associated with high morbidity and mortality. Its pathophysiology is complex, specifically in patients undergoing PD. The etiological workup can be cumbersome but is of paramount importance for early and appropriate treatment. In this article, we review the clinical manifestations as well as the pathophysiology and the specific etiologies of hyponatremia in peritoneal dialysis patients, and we propose a diagnostic algorithm.

Résumé

L'hyponatrémie est le trouble de l'équilibre hydro-électrolytique le plus fréquemment rencontré en pratique clinique, ainsi que chez les patients bénéficiant de la dialyse péritonéale (DP). Selon la gravité et la rapidité d'installation, les symptômes peuvent varier entre hyponatrémie asymptomatique à des symptômes légers et non spécifiques ou à des situations graves et potentiellement mortelles. L'hyponatrémie est associée à une morbidité et une mortalité élevées. Sa physiopathologie est complexe, notamment chez les patients en DP. La mise au point étiologique peut être fastidieuse mais reste primordiale afin d'assurer une prise en charge précoce et appropriée. Dans cet article, nous revoyons la littérature concernant les manifestations cliniques, la physiopathologie ainsi que les étiologies spécifiques d'hyponatrémies en dialyse péritonéale, et nous proposons un algorithme diagnostique.

Key words : Hyponatremia, peritoneal dialysis, overload, extracellular volume

Mots clés : Hyponatremia, peritoneal dialysis, overload, extracellular volume

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INTRODUCTION

Definition of hyponatremia and measurement.

Sodium is a finely regulated electrolyte for which homeostasis is crucial in order to maintain an effective extracellular osmolality (number of milliosmoles of solutes per kilogram of solvent, measured in mOsm/Kg) and therefore intracellular volume (1). Single or combined disturbances in the external balances of water, sodium, and potassium result in dysnatremias (2). Hyponatremia is defined as a serum sodium concentration below the usual target value of 135 mmol/l (the range being 130 to 137 mmol/l) (2), and is either acute (<48h) or chronic (≥48h) (3). Hyponatremia can be associated with osmotic cell swelling, osmotic cell shrinking, or no change in the intracellular volume. Hypotonic hyponatremia induces osmotic swelling of cells (true hyponatremia) and is typically associated with a low serum osmolality (<275 mOsm/kg). However, hypotonic hyponatremia may be associated with normal or high serum osmolality in uremic patients with low sodium values but excessive loads of seric urea solute (4). Hypertonic (or translocational) hyponatremia results from an excess of solutes with extracellular distribution, other than sodium salts (e.g. glucose or mannitol), causing osmotic exit of fluid from the intracellular compartment, hyponatremia, and elevated serum tonicity and osmolality (>290 mOsm/kg) (4). Isotonic hyponatremia with normal cell volume (artifactual hyponatremia) is encountered when low sodium values are reported by methods requiring pre-measurement dilution of the serum sample, and plasma solid content is abnormally high due to hyperlipidemia or hyperproteinemia; and sodium measured by the direct ion-specific electrode is within the normal range (1,4).

Incidence/Prevalence of hyponatremia in peritoneal dialysis patients (anuric or not)

Hyponatremia is the most common disorder of body fluid and electrolyte balance encountered in clinical practice (5). In the PD population, hyponatremia is also frequent. Its prevalence would range from about 5% up to 75%, depending on its definition. However, most data suggest an approximate prevalence around 10% to 25% in PD (6). No data are available regarding the cause-specific prevalence of hyponatremia in PD patients.

In PD patients, the etiological workup of hyponatremia can be cumbersome. In this article, we review the clinical manifestations as well as the pathophysiology and the etiologies of hyponatremia in PD patients, and we propose a diagnostic algorithm.

DISCUSSION

Outcome and risk factors in peritoneal dialysis

Hyponatremia has been reported as a risk factor for all-cause mortality in PD patients (7), although the pathophysiological mechanisms by which hyponatremia increases the risk for mortality in patients with CKD are not well-understood.
Hyponatremia is recognized as an independent marker of survival, in particular in specific subgroups of patients, namely, hypoalbuminemic patients, deeply anemic patients with higher baseline levels of GFR and C-reactive protein, and faster peritoneal solute transport rates. Other factors potentially reinforcing the prognostic significance of hyponatremia include lower lean

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body mass levels, nonprescription of renin-angiotensin-aldosterone system antagonists, and use of icodextrin-based PD solution (8). Hyponatremia is associated with a low residual renal function and excessive weight (probably fluid) gains.

In the PD population, hyponatremia increases the risk for several adverse outcomes, such as hospitalization for infections (9), protein-energy malnutrition (10), and poor peritonitis outcomes (11), in addition to a higher incidence of new cardiovascular events (7,12).
Risk factors for the development of hyponatremia include lower glomerular filtration rate, female gender, lean body weight, race other than African American, diabetes mellitus, and hypoalbuminemia (7). Use of icodextrin is another inverse correlate of serum sodium, and the only consistent predictor of a decline of natremia, once PD was started.

Clinical manifestations

The severity of symptoms in patients with acute hyponatremia generally reflects the severity of cerebral overhydration, which is related to the degree of hyponatremia (13).
Symptoms of acute hyponatremia can vary from mild and non-specific (fatigue, nausea, confusion, headache) to severe and life-threatening (vomiting, cardiorespiratory distress due to non-cardiogenic pulmonary edema and/or hypercapnic respiratory failure, abnormal and deep somnolence, seizures, coma, cerebral herniation). The depth, rapidity of development, and duration of hyponatremia determine its severity (4). Severe symptoms of hyponatremia are caused by increased intracranial pressure due to brain edema. As water shifts from the extracellular to the intracellular compartment due to the difference in effective tonicity between brain and plasma, brain cells (mainly astrocytes) begin to swell. This usually occurs when hyponatremia rapidly progresses, the brain having too little time to adapt to its hypotonic environment. Over time, brain cells reduce the number of osmotically active particles within themselves (mostly potassium and organic solutes) in an attempt to restore the brain volume. This process takes around 24 to 48 hours, hence the reason for using the 48h threshold to distinguish acute (<48 h) from chronic (≥48 h) hyponatremia.

Chronic hyponatremia can present with more subtle symptoms. Such abnormalities include gait disturbances, falls, concentration and cognitive deficits (14). In patients with advanced CKD, the neurological manifestations of uremia can be confounded with the manifestations of dysnatremias. In fact, there are few studies focusing on clinical manifestations of hyponatremia in CKD patients. One study reported an altered mental state in patients on PD with hyponatremia (15).
Patients suffering from chronic hyponatremia are at higher risk of osteoporosis, sustaining more bone fractures than normonatremic people due to an osteoclastic activation causing higher calcemia and suppressed parathyroid hormone levels (16–18). These findings were confirmed by a study on US incident/prevalent PD patients, which showed that higher parathyroid hormone levels were associated with a lower likelihood of having a low sodium (7). Furthermore, there are emerging data on a probable direct link between hyponatremia and impaired immunity (19).

Pathophysiology and etiologies of hyponatremia in PD patients

The pathophysiology of hyponatremia in CKD patients and more specifically in PD patients usually results in a single or combined disturbances. Here we review the pathophysiological mechanisms and the etiologies of hyponatremia in PD patients and propose a diagnostic algorithm for PD-related hyponatremias.

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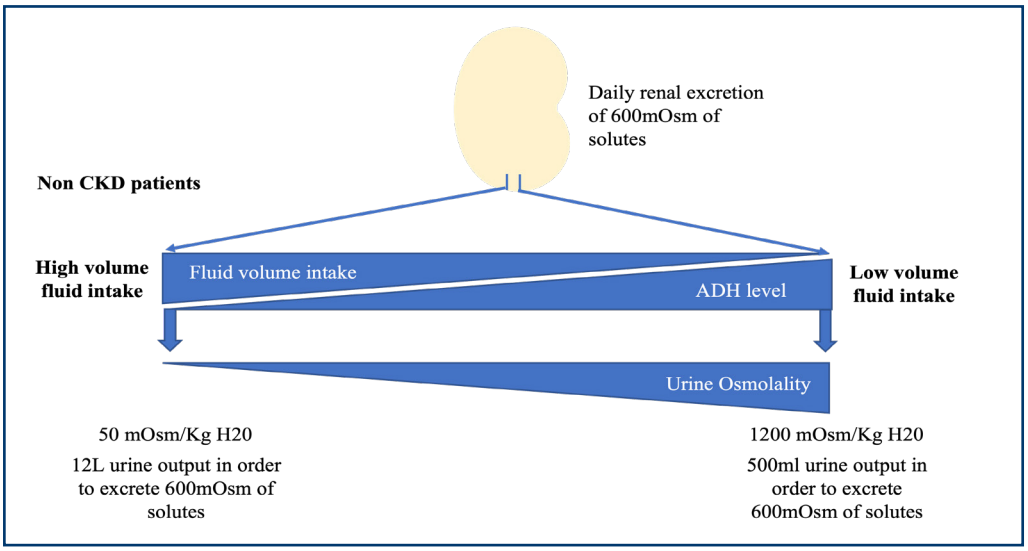

Figure 1. Overview of the regulation mechanism of osmolality in the setting of solute excretion and according to volume fluid intakes in non-CKD patients

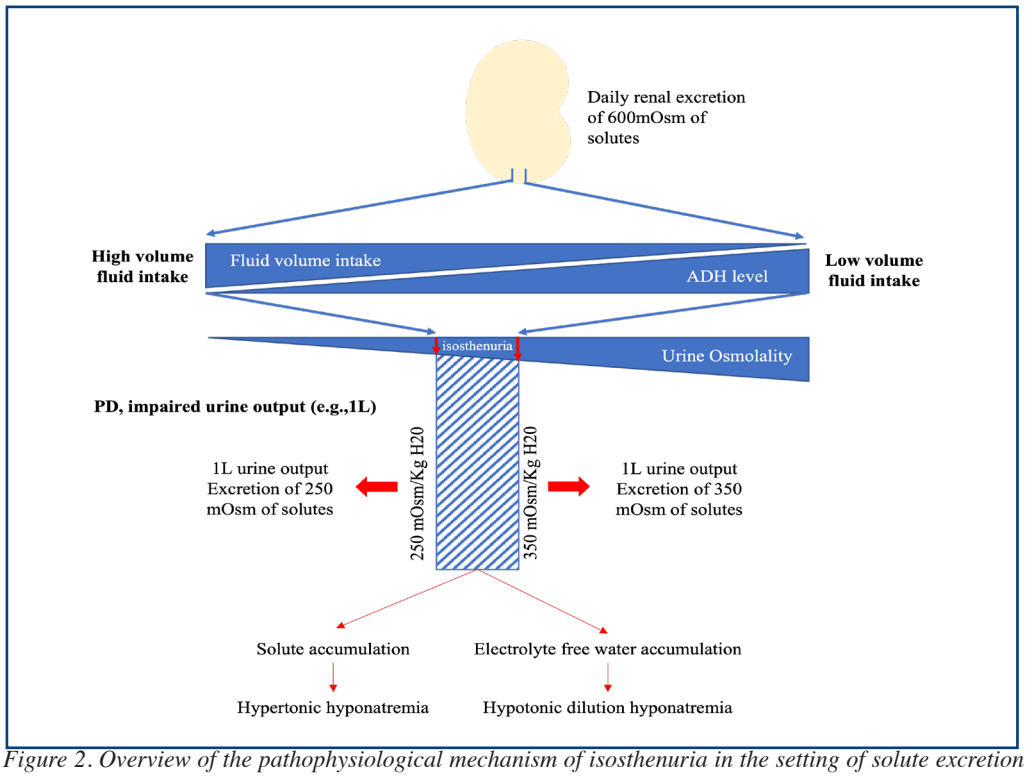

Figure 2. Overview of the pathophysiological mechanism of isosthenuria in the setting of solute excretion (exemple of 600mOsm of solute) and according to volume fluid intakes in CKD patients with or without preserved urine output.

Electrolyte-free water balance, urine concentration

Normal regulation of electrolyte-free water balance is represented in Figure 1.

Patients with CKD maintain their capacity to regulate free water balance until advanced phases of the renal disorder (8). They may also initially maintain their capability to excrete normal ingested solutes (e.g., sodium, potassium salts and azotemic compounds) in the urine in order to maintain

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sodium and potassium balance and serum concentrations of creatinine and urea. This may require an increased urine volume (Figure 1). However, as kidney function declines, patients with more advanced stages CKD are losing the ability to dilute or concentrate urine. The latter is called isosthenuria and leads to an insufficient response of the distal nephron to ADH and therefore to an impaired capacity to manage changes in plasma osmolality (Figure 2.). In other words, free water clearance becomes ineffective with advanced CKD, leading to an increased risk of hyponatremia (6).

In PD patients, hyponatremia is mainly mediated by inadequate regulation of water excretion and positive electrolyte-free water balance. In this situation, hyponatremia is the consequence of free water intakes exceeding free water clearance capacity. This phenomenon is more predominant in PD patients without residual renal filtration capacity (6,20–22). These patients have therefore a limited range of water intake allowing a normal natremia. A positive electrolyte-free water balance is accompanied by an increase in extracellular volume (ECV) and/or weight gain which is proportional to the amount of water ingested (18).

Some conditions are associated with non-osmotic ADH secretion leading to hyponatremia. However, this mechanism is less effective in PD patients because of isosthenuria (6). Indeed, in clinical states characterized by a reduced effective circulating volume (e.g. cardiac failure, liver cirrhosis), non-osmotic secretion of ADH leads to hyponatremia in the setting of increased extracellular volume. Inflammation has also been associated with hyponatremia due to non-osmotic secretion of ADH (23).

Clinicians could perform the following investigations in order to assess extracellular volume overload (6,24):

- Anamnesis: fluid intake, review of the patient's medication and the renal replacement therapy modality and prescription.
- Physical examination: assessment of extracellular fluid volume (overload, total body water), weight gain, urine outflow evaluation, external balances of water)
- Biologically: serum osmolality, sodium and potassium, urinary osmolality, NT ProBNP, blood glucose, lipids, protein, albumin, and inflammation markers.
- Imaging, and other exams:
  - o Chest radiography, transthoracic echocardiography
  - o Lung ultrasound (LUS)
  - o Bioimpedancemetry (bioimpedance-based studies in PD population confirm the overall overhydration status of PD patients).

Electrolyte-free water shift from intracellular to extracellular compartment – hypertonic hyponatremia

Hypertonic hyponatremia is also seen in PD patients. It is due to an excess of solutes in the extracellular fluid, mostly exogenous. Dextrose-based fluid used in PD is a well-known cause of hyperglycemia. Severe hyperglycemia may increase serum tonicity and lead to a shift of electrolyte-free water from the intracellular to extracellular fluid and therefore to hyponatremia (25). Some authors proposed formulas allowing clinicians to adequately estimate natremia according to serum glucose concentration (26).

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Icodextrin or polyglucose-based solutions are also associated with hypertonic hyponatremia after initiation of PD (8,18). The latter hyponatremia is secondary to extracellular accumulation of icodextrin metabolites (e.g., maltotriose and maltotetraose), osmotically active solutes (22).

Isotonic hyponatremia (pseudo-hyponatremia)

The presence of an additional abnormal solute (e.g. hyperlipidemia, hyperproteinemia), may affect the laboratory assessment of natremia and cause the so-called pseudohyponatremia in the setting of normal serum osmolality, and normal intracellular volume. As PD is associated with dyslipidemia, because of a combination of carbohydrate absorption and peritoneal protein loss (27), isotonic hyponatremia may be experienced by some PD patients.

Negative sodium balance

Hyponatremia may be the result of a negative sodium balance in PD patients, because of insufficient sodium intakes or excessive losses.

Insufficient sodium intakes (e.g., malnutrition, low sodium diet) are associated with hyponatremia in the setting of hypovolemia. Indeed, sodium balance is one of the main determinants of extracellular volume. Malnutrition is frequently observed in PD and is associated with decreased sodium chloride intake as well as decreased potassium intake (see section "*other pathophysiology*").

Low dietary solute intake beer drinker's potomania, tea and toast diet may also be seen in PD patients.

More occasionally, hyponatremia can be related to sodium loss either because of diuretics or laxatives agents intake, both common situations in PD patients, or because of sodium loss in PD fluid in the setting of excessive ultrafiltration with sodium extraction (8,28). Sodium removal in PD patients is more likely to occur in the setting of high ultrafiltration rate, continuous ambulatory rather than automated PD and with the exposure to icodextrin (22).

Other pathophysiological aspects

In case of potassium chloride deficiency, the loss of potassium in the intracellular compartment will lead to the passage of sodium from the extracellular to the intracellular compartment in order to ensure electro-neutrality. This situation is characterized by a normal extracellular volume hypoosmolar hyponatremia. This situation is accompanied by metabolic alkalosis. The intracellular potassium deficiency will also cause hypoosmolality of the intracellular compartment and therefore free water osmotic shift to the extracellular compartment. This will also favor hyponatremia (21,28). In PD patients, the latter mechanism is induced by 1) malnutrition and insufficient potassium intake; 2) hyperinsulinemia caused by dextrose-based fluid (25); 3) laxative use and diarrhea; 4) potassium loss in peritoneal effluent.

Rarely, changes in the set point of serum osmolality can be seen in PD patients. This so-called osmostat reset should be a diagnosis of exclusion (22,28).

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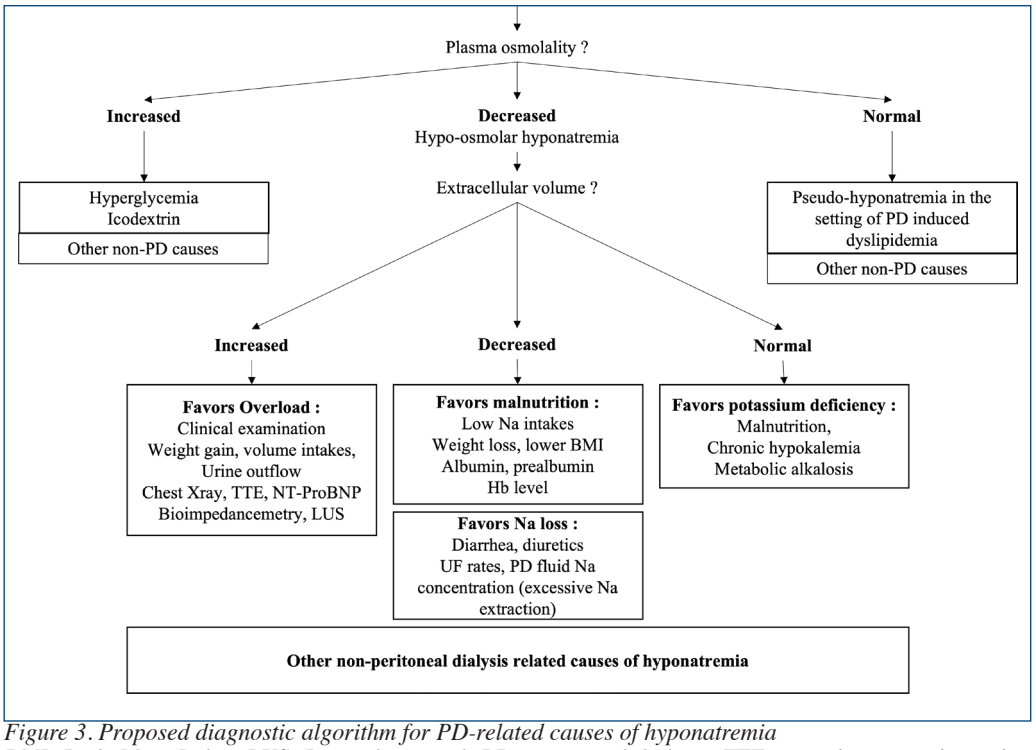

Figure 3. Proposed diagnostic algorithm for PD-related causes of hyponatremia
BMI: Body Mass Index; LUS: Lung ultrasound; PD: peritoneal dialysis; TTE: transthoracic echocardiography; UF: ultrafiltration.

CONCLUSIONS

Hyponatremia is a common electrolyte disorder in PD patients that should not be overlooked. Indeed, even mild hyponatremia is correlated to serious short- and long-term complications. Its epidemiology, pathophysiology and etiology are often different from the general population. Here we proposed a PD-related diagnostic algorithm of hyponatremia.

DISCLOSURE

Author declared no conflict of interest

AUTHORS CONTRIBUTIONS

Maxime Taghavi and Lucas Jacobs wrote the article jointly, Max Dratwa reviewed the article and suggested changes, Joelle Nortier designed the project, reviewed the article and made corrections.

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