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Review

Plasma sodium changes in the hyperglycaemic state: Clinical aspects of pathophysiology and management

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Abstract

Plasma sodium changes are commonly encountered in hospitalised patients, including diabetics. Nonketotic hyperglycaemic hyperosmolar syndrome (HHS) is mostly found in uncontrolled type 2 diabetes mellitus. This condition represents a metabolic emergency carrying a high mortality. HHS is characterised by extreme dehydration and neurological symptoms. Plasma sodium changes play a significant role in the presentation and prognosis of HHS, making their effective management mandatory. In this review, we consider the pathophysiology of HHS-related sodium abnormalities together with the relevant clinical presentation. We also describe the diagnostic approach and therapeutic strategies.

Key words: *Hyperglycaemic hyperosmolar syndrome, Hypernatraemia, Hypertonicity, Hyponatraemia, Water deficit*

Introduction

Plasma sodium changes are commonly encountered in electrolyte disturbances occurring in a broad spectrum of patients (including diabetic patients).[1,2] The high prevalence and the potential neurological sequelae associated with hypo- or hypernatraemia necessitate a systematic and rigorous differential diagnosis before correct treatment is administered.[3] Patients with uncontrolled diabetes mellitus may present with two major symptomatic hyperglycaemic syndromes: diabetic ketoacidosis (DKA) and non-ketotic hyperglycaemic hyperosmotic syndrome (HHS).[4-6]

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Sodium changes play a significant role in the symptomatology of both DKA and HHS, thus making their effective management mandatory.[4-7] In this review, we consider the plasma sodium abnormalities in patients with HHS with a special focus on the pathophysiology and the relevant clinical presentation. We also describe the appropriate intervention strategies.

Pathophysiology of sodium changes in patients with hyperglycaemia

Hyperglycaemia in patients with poorly controlled diabetes mellitus is a common clinical problem, in which variable changes in the plasma sodium concentration [Na^+]

occur.[4,5] Since glucose penetrates slowly into cells, increased levels of plasma glucose raise the effective plasma osmolality (measured plasma osmolality minus the blood urea nitrogen divided by 2.8, since urea is not an effective osmole) and cause water to move outwards, i.e. from the cells into the extracellular fluid.[4] This results in a decrease in plasma [Na^+] by dilution. The serum sodium concentration tends to rise during the hypotonic osmotic diuresis induced by glycosuria, and tends to fall during the shift of water from the intracellular to the extracellular fluid induced by hyperglycaemia. In this setting, the corrected plasma sodium concentration ([Na^+] corrected) is calculated by increasing [Na^+] by 1.6 mmol/L for every 100 mg/dL increment in the serum glucose levels above normal.[8] If the corrected [Na^+] is above normal, then hypotonic fluid loss has occurred (i.e. water and electrolytes have been lost; water loss has been greater than electrolyte loss). In fact, if the "uncorrected" [Na^+] is normal or elevated in the presence of hyperglycaemia, then relatively large water losses have taken place. In such circumstances, the magnitude of the hypertonic ("hypernatraemic") state can be "unmasked" by calculating the corrected [Na^+].[4-8] If the corrected [Na^+] is normal, the fluid losses, on the average, have been isotonic rather than hypotonic. Proper treatment depends heavily on the determination of the magnitude of fluid loss.[5-7] Recent data suggest that the hyperglycaemia-induced decrease in sodium concentration is considerably higher than the "standard" *correction factor* of 1.6 mmol/L Na^+ per 100 mg/dL [5.6mmol/L] glucose), especially when glucose levels are greater than 400 mg/dL (22.4 mmol/L).[9] Moreover, it has been proposed that a correction factor of a 2.4 mmol/L decrease in [Na^+] per 100 mg/dL (5.6 mmol/L) increase in glucose concentration represents a better overall estimate of this association than the "*usual*" correction factor of 1.6.[9]

The direct effect of hyperglycaemia on sodium levels is counterbalanced by the osmotic diuresis related to glucosuria. Indeed, osmotic diuresis causes water loss in excess of sodium and produces a rise in serum [Na^+] and plasma osmolality.[4,7,10] Furthermore, decreased water intake and increased insensible losses through the skin and the respiratory tract (e.g. in association with an underlying infection) can aggravate this metabolic disturbance. [4,10] The final serum [Na^+] reflects the balance between these factors. Although, most patients with uncontrolled diabetes mellitus are mildly hyponatraemic, a number of patients with nonketotic hyperglycaemia exhibit hypernatraemia due to excessive free water loss. In such cases, the profound osmotic diuresis-induced water loss counteracts the hyperglycaemic-induced decrease in serum sodium levels.[4,5] Hypernatraemia can also be observed during treatment when the rapid decrease in serum glucose levels and consequently in serum osmolality facilitates water entry into dehydrated cells thereby causing an elevation in extracellular sodium concentration.[11]

Apparent changes in plasma osmolality can also result from errors in the measurement of [Na^+].[12] A form of pseudohyponatraemia may be noted in patients with uncontrolled diabetes mellitus who exhibit marked hyperlipidaemia (particularly hypertriglyceridaemia) and lactescent serum.[12] In this context, lipids occupy space in the volume of plasma, thus leading to lower readings in the concentrations of sodium and free water per litre of plasma. However, the physiologically significant plasma water sodium and plasma osmolality remain unaffected.[2] Newer methods using ion-selective electrodes for the

measurement of plasma electrolytes obviate this problem.[12]

Table 1. Diagnostic criteria for nonketotic hyperglycaemic hyperosmotic syndrome (HHS)

✓ Profound dehydration (decreased skin turgor, postural changes in blood pressure and pulse rate)
✓ Neurological symptoms (ranging from mental confusion to coma)
✓ Plasma glucose levels > 600 mg/dL (36 mmol/L)
✓ Plasma osmolality (Posm) >310 mOsm/kg
✓ Arterial pH > 7.3
✓ Plasma bicarbonate levels > 15 mmol/L
✓ Normal anion gap (< 14 mEq/L)
✓ Absence of ketosis

Table 2. Predisposing factors for HHS

Infections
Acute myocardial infarction
Stroke
Burns
Drugs (e.g. phenytoin, glucocorticoids, immunosuppressive agents, diuretics)
Peritoneal dialysis

Pathophysiology of non ketotic hyperglycemic hyperosmolar syndrome

HHS is a major complication of uncontrolled Type 2 diabetes mellitus.[5,6,10,13,14] The characteristic clinical features on presentation are dehydration and stupor or coma (Table 1).[10] It may result from extreme hyperglycaemia-induced diuresis under circumstances in which the patient is unable to drink enough water to keep up with urinary fluid losses. Common precipitating factors include the consumption of glucose-rich fluids, concurrent medication such as thiazide diuretics or steroids, and intercurrent illness (e.g. infections) (Table 2).[4,10] Diagnosis and effective treatment (Tables 1 and 3) of this condition is mandatory since it is associated with a high mortality (as high as 20-30%).[7,10] Commonly, HHS develops in elderly patients (with mild or even previously undiagnosed diabetes) presenting with a stroke or infection, which worsens hyperglycaemia and prevents adequate water intake.[1,4,7,10] Several drugs, such as phenytoin, glucocorticoids, immunosuppressive agents and diuretics, have also been reported to trigger HHS in Type 2 diabetic patients.[1,4,10]

Patients present with extreme hyperglycaemia, hyperosmolality, volume depletion and central nervous system (CNS) signs ranging from a clouded sensorium to coma.[15,16] Symptoms related to diabetic complications may be masked by the clinical picture of the acute illness responsible for the precipitation of the hyperglycaemic state (e.g. infection).[4,10] The earliest complaints associated with hyperglycaemia are polyuria, polydypsia, and weight loss due to the combination of osmotic diuresis and hypovolaemia. The severity of these symptoms is generally proportional to both the extent and duration of hyperglycaemia. Onset may be insidious over a period of days or weeks, with progressive weakness, polyuria, and polydipsia.[4,5,10] Hypovolaemia is invariably found in association with marked hyperglycaemia and is primarily induced by the associated glucosuria. As the filtered load of glucose rises, it eventually exceeds tubular reabsorptive capacity. As a result,

glucose remains in the tubular lumen and acts as an osmotic diuretic, increasing the urinary loss of electrolytes and water. In severe cases, fluid losses may be as much as 8 to 10 litres and result in circulatory collapse.[4,5] In patients with a profound decrease in extracellular volume, symptoms and signs produced by hypovolaemia are evident, such as postural hypotension, muscle cramps, symptoms related to coronary or cerebral ischaemia, decreased skin turgor, hypotension and tachycardia.[4,5,17,18]

In more severely affected patients neurological abnormalities may be seen.[16] The level of consciousness generally correlates with the severity and duration of hyperosmolality.[18] Only about 10% of patients present with coma, and an equal number show no signs of changes in the level of consciousness. A variety of often reversible neurological abnormalities may exist, including grand mal or focal seizures (about 10% of cases), extensor plantar reflexes, aphasia, hemisensory or motor deficits, delirium, and exacerbation of a preexisting organic mental syndrome, such as prior stroke or dementia.[10,17,18] The neurologic symptomatology is related to the increase in plasma osmolality, which is initially responsible for the water movement out of the cells, thus resulting in brain cell dehydration.[19,20] However, within a few hours, brain cell volume begins to rise towards normal owing to the generation of new osmoles (initially potassium, sodium and chloride and later inositol and the aminoacids glutamine and glutamate known as *osmolytes* or *idiogenic osmoles*.[21] Initially, there is movement of sodium and potassium into the brain, in part from newly formed cerebrospinal fluid.[4] However, if this was the only adaptation, the alteration on brain cell cation concentration could have deleterious effects on the activity of cell proteins. This is prevented by the generation of the so-called osmolytes, which are newly formed solutes that do not interfere with protein function as their concentration rises. Within the brain, inositol and the aminoacids glutamine and glutamate appear to constitute a major part of the protective response to an elevation in plasma sodium concentration.[19-21] Despite the relative preservation of brain cell volume, the severity of neurological symptoms in hyperglycaemic conditions is roughly proportional to the degree of hyperosmolality.[20] Thus, lethargy and confusion develop when the effective plasma osmolality exceeds 310 mosm/kg, and coma can occur when plasma osmolality is greater than 320-330 mosm/kg.[5]

The role of hypernatraemia in the symptomatology of nonketotic hyperosmolar syndrome

There is evidence that hyperglycaemic patients with hypertonicity are symptomatic only if hypernatraemia is present.[5,20] Hypernatraemia can sometimes be disclosed only when the corrected sodium concentration for the dilutional effect of hyperglycaemia is determined.[6-8] A number of studies demonstrated that neurological symptoms may be absent in cases of severe gradually developing hyperglycaemia.[4,20] This could be due to the capacity of the brain tissue to restore intracellular water by accumulating electrolytes and the so-called idiogenic osmoles.[21] Furthermore, the brain cells are relatively permeable to glucose even in the absence of insulin.[19] Therefore, hyperglycaemia *per se* does not produce severe hypertonicity in the CNS.[20] By contrast, hypernatraemia itself causes severe cellular dehydration in the CNS. In addition, this state is associated with a rather slow compensatory accumulation of brain osmolar content. Thus, not only the serum osmolality level, but also the serum

sodium concentration in particular, should be measured when

Table 3. Management of HHS

- ✓ Supportive care and intensive monitoring
- ✓ Fluid administration (see text)
- ✓ Correction of hyperglycaemia by giving small doses of insulin intravenously via a pump
- ✓ Correction and prevention of electrolyte abnormalities
- ✓ Management of predisposing/aggravating factors
- ✓ Thromboembolism prevention (such as deep venous thrombosis and pulmonary embolism) preferably by using a low molecular weight heparin

evaluating a patient with extreme hyperglycaemia.[6,20] A normal or elevated serum sodium value implies that substantial cellular dehydration has taken place and that the risk of coma or other neurologic abnormalities is high. In contrast, hyponatraemia suggests that cellular dehydration has not occurred or has occurred only to a limited extent.[20] It has been suggested that, in cases of hyperglycaemic hyperosmolar syndrome, altered mental status is best predicted by serum sodium levels; serum glucose levels alone are considered a poor indicator.[16,17,20] In all cases, the corrected serum sodium level should be calculated, because a mild hyponatraemia in the face of an extremely high serum glucose concentration may represent a corrected hypernatraemic value.[16,17,20]

Treatment: Basic principles (Table 3)

Fluid replacement is of paramount importance in treating HHS.[7,22] If hypovolaemia is present, as evidenced by hypotension and oliguria, fluid therapy should be initiated with isotonic saline to expand the extracellular volume.[7,22] The strategy in fluid administration aims *first* at restoring blood pressure and thus vital organ perfusion. An initial infusion of 0.9% saline should be administered in order to expand extracellular volume. As hypotension is attributed mainly to fluid losses, the patient's volume deficit is grossly estimated to be at least 10% to 15% of body weight.[22] Saline infusion

will eventually lower tonicity, as its osmolarity is hypotonic to the patient's serum. In addition, the expansion of extracellular volume will promote glycosuria. Close monitoring of ongoing fluid and solute losses is mandatory at this stage. Potassium supplementation should be started soon after urine output is restored because insulin drives glucose and potassium back into cells. [5,7] At a *second* stage, the patient's water deficit is calculated by the following formula: (0.6 x Body Weight) x {($[Na^+]_{corrected}$ ÷ 140 mmol/L) - 1} (7,22). Half-isotonic saline can be used after the phase of rapid fluid repletion to replace the free water loss induced by the osmotic diuresis. It must be emphasised that potassium ions are as osmotically active as sodium ions. Therefore, the addition of potassium chloride (KCl) in the hypotonic solutions can significantly raise the osmolality of intravenously administered fluids.[22]

Diabetic patients presenting with HHS are very sensitive to the hypoglycaemic action of insulin.[4,7,10,22] In these patients, hypotonic fluid and insulin administration may be followed by cerebral oedema from an overly rapid decrement in plasma osmolality related to a precipitous fall in both glucose and sodium levels.[4,7,10,22] Thus, it is suggested that the abrupt decrease in serum glucose should be avoided, while insulin

administration should either be stopped or reduced when the plasma glucose levels decline to approximately 250-300 mg/dL (14.0-16.8 mmol/L), while a glucose containing solution is usually began at this time.[7]. At the same time, although the optimal rate of correction of hypernatremia remains to be defined precisely, the general rule not to lower the serum sodium level more rapidly than 0.5 mmol/L/h seems reasonable.[7,20] However, in these cases the fluid administration-induced decrease in serum sodium may be counterbalanced by an increase in serum sodium levels due to the progressive decrease in serum glucose and eventually in serum osmolality leading to water entry into cells.[7,22] Thus, it is pointed out that the corrected serum sodium levels after adjustment for the dilutional effect of hyperglycaemia should be closely monitored during treatment.[17]

Conclusion

The diagnosis of HHS is typically made in an elderly (> 60 years) patient with mild diabetes mellitus manageable with diet and/or oral hypoglycaemic agents. A history of an intercurrent illness or a similar stress usually precedes this complication. The physical findings are strongly determined by the degree of fluid and electrolyte loss, and therefore depend on the length of the hyperglycaemic state. Plasma sodium changes play a significant role in the presentation and prognosis of HHS. Diagnostic evaluation and treatment should be commenced urgently. Fluid and electrolyte replenishment together with insulin administration are the cornerstones in the management of this life-threatening condition.

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