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HYPONATREMIA IN DIABETES

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***Abstract:** Diabetes Mellitus (DM) is rapidly emerging as an important cause of mortality and morbidity in developing countries.[1] It is an established risk factor for coronary heart disease (CHD), stroke and end-stage renal disease (ESRD). Diabetic nephropathy is one of the complications of diabetes mellitus, which ultimately leads to renal failure and renal failure is a cause of electrolyte imbalance among hospitalized diabetic patients; other causes are diarrhea, vomiting, diuretic use and chronic laxative use. The most common electrolyte imbalance is hyponatremia – others are hypokalemia, hypomagnesemia and hyperkalemia. This review presents to the reader an in depth coverage of the condition, its pathophysiology, clinical features and management aspects.*

Introduction

Hyponatremia is defined as a plasma sodium concentration <130 mmol/L. It usually reflects a hypotonic state. However, plasma osmolality may be normal or increased in some cases of hyponatremia. Hypertonic hyponatremia is usually due to hyperglycemia.

Pathophysiology

Relative insulin deficiency causes myocytes to become impermeable to glucose. Therefore, during poorly controlled diabetes mellitus, glucose is an effective osmole and draws water from muscle cells resulting in hyponatremia. Isotonic hyponatremia may occur in conditions like hyperlipidemia and hyperproteinemia. In general, hypotonic hyponatremia occurs either due to a primary Na^+ loss (secondary water gain) like sweating, burns, gastrointestinal loss (vomiting, diarrhea),renal loss (diuretics, hypoaldosteronism, salt wasting nephropathy) or due to a primary water gain (secondary Na^+ loss) like SIADH, hypothyroidism, primary polydipsia or due to a primary Na^+ gain (exceeded by secondary water gain) like heart failure, hepatic cirrhosis, nephritic syndrome. It is important to note that diuretic-induced hyponatremia is almost always due to thiazide diuretics and cerebral salt wasting after neurosurgery is also the cause of hyponatremia.[2]

The mechanisms of fluid and solute abnormalities that should be considered in any patient with severe hyperglycemia include changes in the total amount of extracellular solute, osmotic diuresis, intake of water driven by thirst, and influences from associated conditions. The absence of osmotic diuresis distinguishes dialysis-associated hyperglycemia (DH) from hyperglycemia with preserved renal function (HPRF). Mainly because of this absence, comparable degrees of hyperglycemia tend to produce less hypertonicity and less severe intracellular volume contraction in DH than in HPRF, while extracellular volume is expanded in DH but contracted in HPRF. Ketoacidosis can develop in both DH and HPRF. Mechanisms causing fluid and solute abnormalities in hyperglycemia are shown in Table 1.

The qualitative changes in body fluid and electrolytes caused by each one of these mechanisms are predictable.

Table 1 | Mechanisms causing fluid and solute abnormalities in hyperglycemia

- Gain in extracellular solute
- Osmotic diuresis
- Water intake secondary to thirst
- Ketoacidosis
- Concomitant diseases

Prior estimation of the corresponding quantitative changes and the amount of fluid and solute needed to correct the abnormalities are far more difficult. This is the case for HPRF because the required fluid and solute replacement can potentially be enormous, as well as DH, because the margin of error is limited by severe renal dysfunction.

The gain in extracellular solute (glucose) is the fundamental hyperglycemic disturbance that causes the other fluid and electrolyte abnormalities. This solute gain causes hypertonicity[3] and secondary changes in intracellular and extracellular volume in both HPRF and DH. In HPRF, in addition to hypertonicity osmotic diuresis has profound effects on extracellular and intracellular volume.

Tonicity in Hyperglycemia

The distinction between tonicity and osmolality is important in understanding hyperglycemic changes in body fluid and solutes. Tonicity is the property of a solution to induce, through osmotic fluid transfers, steady state changes in the volume of cells suspended in it. Osmolality is a reflection of the total number of solutes dissolved in the water of the solution. Solutes restricted from entering cells contribute to tonicity and osmolality. Solutes crossing cell membranes with ease contribute to osmolality, but not tonicity.[4] In the setting of hyperglycemia, tonicity is more important than osmolality because the former is the cause of intracellular and extracellular volume changes and of clinical manifestations.

The initial accumulation of solute (glucose) elevates both tonicity and osmolality in any type of hyperglycemia. The total body solute gain from hyperglycemia is the product of the increase in glucose concentration times the extracellular volume. Estimation of the total solute gain in hemodialysis requires accounting for the change in extracellular volume during development of hyperglycemia.[5] The gain in body solute resulting from hyperglycemia is the cause of both fluid and electrolyte abnormalities and clinical manifestations.

During development of hyperglycemia, the initial extracellular hypertonicity causes an osmotic fluid shift from the intracellular into the extracellular compartment resulting in dilution of the extracellular solutes and hypertonic hyponatremia.[6] At presentation with hyperglycemia, serum tonicity (Ton) is approximated by the following formula:[7]

$$Ton = 2 \times Na + Glu/18$$

Where serum sodium concentration ([Na]) is in mmol/l and glucose concentration ([Glu]) is in mg/dl. Correction of hyperglycemia without any changes in the external balance of water, sodium and potassium leads to an increase in serum sodium concentration, but decrease in tonicity.[8]

Clinical Features of Hyponatremia

Hyponatremia induces generalized cellular swelling, a consequence of water movement down the osmotic gradient from the hypotonic ECF to the ICF. The symptoms are primarily neurologic, reflecting the development of cerebral edema within a rigid skull.

The initial CNS response to acute hyponatremia is an increase in interstitial pressure, leading to shunting of ECF and solutes from the interstitial space into the cerebrospinal fluid and then into the systemic circulation. This is accompanied by an efflux of the major intracellular ions, Na^+, K^+, and Cl^-, from brain cells. Acute hyponatremic encephalopathy ensues when these volume regulatory mechanisms are overwhelmed by a rapid decrease in tonicity, resulting in acute cerebral edema.

The development of cerebral edema largely depends on the cerebral adaptations to hypotonicity. The water channel AQP4 appears to play a key role in the movement of water across the blood-brain barrier, as knockout mice for AQP4 are protected from hyponatremic brain swelling.[9]

Early symptoms can include nausea, headache, and vomiting. However, severe complications can evolve rapidly, including seizure activity, brainstem herniation, coma, and death.

A key complication of acute hyponatremia is normocapnic or hypercapnic respiratory failure; the associated hypoxemia may amplify the neurologic injury. Normocapnic respiratory failure in this setting typically is due to noncardiogenic, neurogenic pulmonary edema, with a normal pulmonary capillary wedge pressure. Risk factors for neurologic complications in hyponatremic patients are shown in Table 2 and 3.[10]

Association of Hyponatremia with Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is the most feared and life-threatening hyperglycemic emergencies in diabetes, associated with uncontrolled diabetes mellitus and may lead to significant neurologic morbidity and death. Early diagnosis and management in an emergency department is paramount to improve patient outcomes. The mainstay of treatment in DKA is aggressive rehydration, insulin therapy, electrolyte management, and discovery and treatment of any underlying precipitating events.

Table 2 | Risk factors for acute cerebral edema

- Postoperative menstruating female
- Elderly women taking thiazides
- Children
- Polydipsia secondary to psychiatric disorders
- Hypoxemic patients

Table 3 | Risk factors for osmotic demyelination (central pontine myelinolysis)

- Liver transplant recipient
- Alcoholics
- Malnourished patients
- Hypokalemic patients
- Burn victims
- Na: <105 mmol/lit

Pathophysiology of DKA

Diabetic ketoacidosis is characterized by hyperglycemia, which stems from insulin resistance or deficiency of insulin secretion from the pancreas. In DKA, the driving force is insulin insufficiency and a subsequent increase in insulin counterregulatory hormones (ICRHs), which prevents the body from metabolizing carbohydrates.[11,12] Insulin normally stimulates the transfer of glucose from the bloodstream into tissues of the body, where it is needed for energy, glycogen storage, and lipogenesis. Insulin also inhibits hepatic gluconeogenesis, preventing further glucose production by the body.[13] When insulin is absent, hepatic gluconeogenesis continues, yet glucose cannot move into the cells and instead builds up in the bloodstream. This elevated glucose leads to osmotic diuresis and dehydration.

Diabetic ketoacidosis occurs more frequently in type 1 diabetes mellitus; however, it can also occur in type 2 diabetes mellitus. It is growing increasingly common in type 2 diabetes mellitus, which is thought to be due to an acute halt of insulin secretion by temporary pancreatic beta islet cell dysfunction, and temporary insulin resistance.

Hyponatremia in DKA

Glucose-induced hyponatremia is another side effect of hyperglycemic crisis. Corrected serum sodium in hyperglycemia is routinely calculated with the correction factor of 1.6.[14] Hillier and colleagues,[15] in 1999, however, found more accurate mean correction factor of 2.4, particularly in glucose levels greater than 400. The standard correction factor of 1.6 may still remain accurate for blood glucose up to 400 mg/dl and calculation of serum sodium in DKA are as follows:

- Measured Na (mEq/L) +0.016 X [Glucose (mg/dL) -100] for Glucose < 400 mg/dL
- Measured Na (mEq/L) +0.024 X [Glucose (mg/dL) -100] for Glucose > 400 mg/dL

Association of Hyponatremia with Sepsis

Diabetes mellitus is a well-known immune-compromised state, predisposing admitted patients to develop hospital acquired infections and subsequent sepsis easily. Most cases of severe sepsis are triggered by bacteria or fungi that do not ordinarily cause systemic disease in immunocompetent hosts. To survive within the human body, these microbes often exploit deficiencies in host defenses, indwelling catheters or other foreign matter, or obstructed fluid drainage conduits. Microbial pathogens, in contrast, can circumvent innate defenses because they either:

1. lack molecules that can be recognized by host receptors or
2. have elaborate toxins or other virulence factors.

In either cases, the body can mount a vigorous inflammatory reaction that results in severe sepsis yet fails to kill the invaders. The septic response may also be induced by microbial exotoxins that act as superantigens as well as by many pathogenic viruses.

Sepsis leads to metabolic acidosis and electrolyte imbalances, of which hyponatremia is the commonest. Adrenal insufficiency is usually associated with hyponatremia in cases of severe sepsis.

Table 4. shows the algorithm of initial evaluation of hyponatremia currently in practice.

Laboratory Assessment of Hyponatremia

Serum osmolality is determined as low value (<275 mosm/kg H_2O) confirms true hypo-osmolality. Osmolal gap <10 rules out pseudo-hyponatremia.

Urine osmolality is determined as appropriate response to hyponatremia is maximally diluted urine (<100mosm/kg H_2O)

Urine sodium is determined as spot value from fresh urine is usually< 20 (mEq/L) in low effective circulating blood volume states.

Usually urinary sodium is> 20–40 in euvolemic patients, without decreased effective circulating blood volume.

Plasma glucose is determined as serum sodium will decrease 1.6–2.4 mmol/L for every 100 mg/dL increase in glucose over 100 mg/dL

Tests of Thyroid and Adrenal Function

Hypothyroidism can also impair free water excretion. Although the mechanisms are not fully understood, giving thyroid hormone can correct the low plasma sodium concentration.[16]Pure glucocorticoid deficiency due to adrenocorticotropic hormone deficiency or anterior hypopituitarism can cause hyponatremia in the presence of preserved mineralocorticoid function. These patients are usually euvolemic. Cortisol replacement suppresses ADH release from the hypothalamus and promotes free water release at the level of the kidney.[17]

Association of thyroid diseases both hyper- and hypo- function are very common with diabetes mellitus. Secondary diabetes after thyrotoxicosis can occur. Diabetic process may also be unmasked by the stress on carbohydrate

Table 4 | Initial evaluation of hyponatremia- make an algorithm of the bullets in the box here

- Examine the patient for signs of acute neurologic changes
- Confirm that the blood draw was accurate (verify result)
- Clinically determine his or her extracellular fluid volume status
- Rule out hyperglycemia
- Determine rate of development of hyponatremia (hours to weeks)
- Review all recent and current intravenous fluid orders
- Review all intravenous medications for free water content (eg, antibiotics mixed with dextrose and water)
- Review all medications (especially use of diuretics)
- Confirm true hypo-osmolality
- Review and order appropriate laboratory tests

metabolism due to thyrotoxicosis. The contributory factors are increased glucose absorption from the gut, increased glucose metabolism, insulin resistance, pancreatic damage, hepatic degeneration etc. Genetic association between thyrotoxicosis and diabetes is also reported.

Co-occurrence of hypothyroidism and diabetes mellitus is also frequent. Autoimmune etiology might be one of the causes but it is not the case in all occurrences. Hypothyroidism lowers the degree of hyperglycemia and potentiates hypoglycemia in diabetic patients. Thyroxine replacement raises the blood sugar, which can be controlled by titrating antidiabetic drugs. In uncontrolled diabetic state, thyroid function is altered and Sick Euthyroid Syndrome can occur. Altered metabolism of thyroid hormone is also seen in diabetic ketoacidosis. T4 levels usually remain normal and this is due to impaired 51-monodeiodination of T¬4 and rT3 in peripheral tissues, the state so called as "Sick Euthyroid Syndrome".

Thyroid-stimulating hormone, Free Thyroxine (T4), Adrenocorticotropic hormone (ACTH), ACTH stimulation tests should be done

- when there is a clinical suspicion of thyroid or adrenal hypofunction
- to establish a diagnosis of SIADH (document normal thyroid and adrenal function)when careful evaluation does not provide clear etiology

Serum Uric acid and Blood Urea Nitrogen level

Estimation of Serum Uric acid and Blood Urea Nitrogen level are helpful in differentiating euvolemic SIADH from hypovolemic causes of hyponatremia.

SIADH = syndrome of inappropriate antidiuretic hormone secretion

In patients with hyponatremia, euvolemia, and true hypo-osmolality, the continued release of ADH is inappropriate. However, release can continue in SIADH. Most cases of SIADH are associated with tumors, pulmonary and central nervous system disease, or various drugs, although the cause is not always evident when hyponatremia is detected.[18] While most cases of SIADH appear to be associated with abnormal and inappropriate levels of ADH (relative to plasma osmolality), 10–20% of patients do not have measurable levels of the hormone in their serum, despite continued renal-free water reabsorption.[19]

Treatment of Hyponatremia

Treatment of hyponatremia depends on the stage whether it is acute onset or chronic.

Acute Symptomatic Hyponatremia

Emergency correction needed

- hypertonic saline (3%) at 1–2 ml/kg/hour
- co-administration of furosemide

Chronic Symptomatic Hyponatremia

Some emergency correction needed

- hypertonic saline at 1–2 ml/kg/hour (if seizures), otherwise isotonic saline.
- coadministration of furosemide (20 mg IV)
- change to water restriction upon 10% increase of [Na^+], or if symptoms resolve.

Perform frequent measurement of serum and urine electrolytes. Do not correct serum [Na^+] >12 mmol/lit/day.

Asymptomatic

No immediate correction needed

Long Term Management

Long term management consists of the following:

- Identification and treatment of reversible etiologies
- Water restriction
- Demeclocycline 300–600 mg bid (allow 2 weeks for full effect)
- Vasopressin receptor antagonist (not to be used with severe liver dysfunction)

Conclusion

One primary problem with diabetes is that the amount of glucose in the blood can offset the proportion of serum electrolytes. The association between blood glucose and serum electrolytes is a complex one and is related to a number of other factors such as age and associated conditions. Serum electrolyte imbalance in type 1 diabetes is primarily a result of elevated blood glucose. With hyperglycemia, the body tries to rid itself of the excess blood glucose by increasing urinary output. Increased urination produces water and electrolyte loss, which then upsets the body's balance of electrolytes. The balance is especially disturbed between sodium and potassium.

We sometimes see people in the hospital or in various settings who may have "asymptomatic hyponatremia," the vast majority of patients who have significant hyponatremia, although appearing to be asymptomatic, really are not and probably have subtle clinical abnormalities. These may be gait disturbances, a tendency to fall, decreased ability to concentrate, cognitive defects, and so forth. We are all aware of the association between hyponatremia and death, but on the milder end of the spectrum, there are a variety of abnormalities that we are not able to detect regularly in people who have mild to moderate hyponatremia in terms of the serum sodium concentration.

Hyponatremia may be a cause of confusion in diabetic patients and must be kept in mind while evaluating this group of patients. It is therefore prudent to monitor sodium levels in all diabetic patients regularly particularly during DKA, sepsis and long continued use of diuretic and heart

failure and gross hyperglycemia without ketosis or having concomitant thyroid dysfunction.

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