Pathophysiology and Management of Fluid and Electrolyte Disturbances in Patients on Chronic Dialysis with Severe Hyperglycemia

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ABSTRACT

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. Among DH patients, hyperkalemia appears to be more frequent when ketoacidosis is present than when nonketotic hyperglycemia is present. Among HPRF patients, the frequency of hyperkalemia appears to be similar whether ketoacidosis or nonketotic hyperglycemia is present. Usually patients with severe DH have no symptoms or may exhibit a thirst. Infrequent clinical manifestations of DH include coma and seizures from hypertonicity or ketoacidosis and pulmonary edema from extracellular expansion. Insulin infusion is usually the only treatment required to correct the biochemical abnormalities and reverse the clinical manifestations of DH. Monitoring of the clinical manifestations and biochemical parameters during treatment of DH with insulin is needed to determine whether additional measures, such as administration of saline, free water, or potassium salts, as well as emergency hemodialysis (HD) are needed. Emergency HD carries the risk of excessively rapid decline in tonicity; its benefits in the treatment of DH have not been established.

Severe hyperglycemia causes profound imbalances in body fluids and electrolytes in patients with preserved renal function (HPRF) (1,2). Management of these imbalances is a critical part of the treatment of the hyperglycemic syndromes (3,4). The hyperglycemic fluid and electrolyte abnormalities in patients with greatly diminished or absent renal function, exemplified by patients on chronic dialysis, have similarities with, but also quantitative, and even qualitative, differences from the abnormalities in patients with HPRF (5,6). The clinical manifestations that result from fluid and electrolyte abnormalities and their treatment may differ between dialysis-associated hyperglycemia (DH) and hyperglycemia occurring in patients with HPRF. Understanding the differences in pathophysiology between DH and HPRF is important for preventing management errors.

This report reviews the management of fluid and electrolyte abnormalities in severe DH and its rationale. The underlying fluid and electrolyte pathophysiologic mechanisms and their relationship to the clinical presentations of DH are reviewed first. Subsequently, the management of abnormalities in body water and solute, acid–base balance, and potassium balance is presented. Finally, the indications for and potential pitfalls of emergency hemodialysis (HD) are discussed.

Pathophysiology of Fluid and Electrolyte Abnormalities in Hyperglycemia

Table 1 shows the mechanisms of fluid and electrolyte abnormalities that should be considered in every patient presenting with hyperglycemia. The qualitative changes in body fluid and electrolytes caused by each one of these mechanisms are predictable. Estimating a priori the corresponding quantitative changes—and the amount of fluid and solute needed to correct the abnormalities—is 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. Ways to predict the
magnitude of some of the fluid and electrolyte abnormalities in DH will be discussed.

The gain in extracellular solute (glucose) is the fundamental hyperglycemic disturbance that causes the other fluid and electrolyte abnormalities. This solute gain causes hypertonicity (7) 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.

The qualitative effects of osmotic diuresis on body fluid and electrolyte balance are predictable and consist of losses of body water, sodium, and potassium. The concentration of sodium is typically lower in the urine than in the serum of patients with HPRF (8). Thus the loss in body water is proportionally larger than the loss in sodium resulting in further increase in tonicity in severe cases of hyperglycemia (9). The average potassium concentration in the urine of patients with osmotic diuresis is fourfold higher than in the serum; these losses result in total body potassium deficits regardless of the serum potassium concentration (8). The quantitative effects of osmotic diuresis vary from patient to patient. Clinical monitoring guiding the adjustments in rate and composition of the infused fluids is the optimal way of addressing the clinical consequences of osmotic diuresis in HPRF.

Hypertonicity causes thirst and fluid consumption. Following infusion of hypertonic solutions in nephrectomized animals, Fitzsimons observed intense drinking which stopped when tonicity returned to normal (10). There is evidence linking hypertonicity in hyperglycemia and fluid consumption in humans. In spontaneous (11) or induced (12) HPRF, tonicity approached normal values, suggesting fluid intake. Similarly, patients on HD with DH had fluid gains leaving them only with modest hypertonicity (13–15).

In HPRF, water is lost from the body through osmotic diuresis and gained through fluid consumption, while body solute is gained through the development of hyperglycemia and lost through osmotic diuresis. Water losses and severe hypertonicity dominate the picture in severe HPRF (9). In anuric DH, the fluid gain secondary to thirst moderates the hypertonicity and affects both tonicity and intracellular and extracellular volumes after correction of hyperglycemia. Estimates of the amount of fluid consumed are useful for the management of patients with DH.

When ketoacidosis occurs during the course of hyperglycemia, both clinical presentation and electrolyte balance are affected. These will be discussed later. Finally, patients may have body fluid and solute abnormalities secondary to disease processes unrelated to hyperglycemia. Large losses of solute and fluid through the gastrointestinal tract (diarrhea, vomiting) or the skin (excessive sweating, burns, exudative dermatologic diseases) can affect body water and solute in patients with either DH or HPRF. Although these abnormalities are unpredictable, they can have profound effects on the management and outcome of hyperglycemic patients. For this reason, the management of DH should be guided by a careful history, physical examination, and monitoring of the patients during treatment.

### Fluid and Electrolyte Abnormalities at Presentation with Hyperglycemia

The effects of all the mechanisms shown in Table 1 should be evaluated at presentation with severe hyperglycemia. We will consider hyperglycemia-induced changes in tonicity and extracellular and intracellular volume, changes caused by ketoacidosis, and potassium balance.

### 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. The serum (or the interstitial fluid) can contain excesses in both categories of solutes in some instances, such as DH, in which there are increases in the serum concentration of both glucose, which has extracellular distribution, and urea, which has total body water distribution (16). 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. Consequently, the management of DH addresses issues related to tonicity, not to osmolality.

The initial accumulation of solute (glucose) elevates both tonicity and osmolality in any type of hyperglycemia. The concept that hyperglycemia per se changes total body solute was demonstrated first indirectly by water and solute balance studies in HPRF (17) and then directly by measurement of serum osmolality during development or treatment of DH (18). 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 HD requires accounting for the change in extracellular volume during development of hyperglycemia (5,7). The gain in body solute resulting from hyperglycemia is the cause of both fluid and electrolyte abnormalities and clinical manifestations. However, with DH, secondary changes in external fluid and solute balance may be absent; when this solute gain dissipates by correction of hyperglycemia, body solute and water balance return to their baseline levels.
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 (19). At presentation with hyperglycemia, serum tonicity (Ton) is approximated by the formula (20):

\[ \text{Ton} = 2 \times \left[ \frac{[\text{Na}] + [\text{Glu}]}{18} \right] \]

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 (18). At euglycemia the only determinant of tonicity is the serum sodium concentration. Prediction of the serum sodium concentration at euglycemia (the “corrected” serum sodium concentration or \([\text{Na}]_{\text{Cor}}\)) allows timely diagnosis and management of water deficits or excesses. \([\text{Na}]_{\text{Cor}}\) is calculated by the formula (21):

\[ [\text{Na}]_{\text{Cor}} = [\text{Na}] + 0.16 \times ([\text{Glu}] - 100) \]

where [Na] and [Glu] are the values at hyperglycemia. Formula 2 uses Katz’s theoretical calculation that serum sodium concentration increases by 1.6 mmol/l for every 100 mg/dl decrement in serum glucose concentration (22). The corrected sodium is not applicable in HPRF because the external balances of water, sodium, and potassium change during treatment of this condition. In DH, which is routinely treated without any substantial changes in the external balances, formula 2 predicts the euglycemic serum sodium concentration with considerable accuracy (6).

Figs. 1 and 2 show, respectively, tonicity and serum sodium concentration at baseline, at hyperglycemia (serum glucose 1250 mg/dl), and after its correction in two hypothetical subjects, one with HPRF and one with anuric DH, both with normal tonicity and volume status at baseline. At presentation with hyperglycemia, the patient with HPRF was considered to have a net loss of body water, sodium, and potassium equal to their respective average losses in one study of severe HPRF (9), while the patient with DH was considered to have consumed an amount of water comparable to the average estimate from a study in DH patients (23). Tonicity values after correction of both HPRF and DH were calculated assuming no changes in the external balance of fluid or solute during correction of hyperglycemia. Comparable degrees of hyperglycemia result in substantially higher tonicity in HPRF than DH. Serum sodium concentration reflects these differences in tonicity at presentation with hyperglycemia and particularly after its correction without fluid replacement or loss (6). The presence of edema affects the hypertonicity of DH. For the same degree of hyperglycemia, tonicity is higher in DH patients with edema than in those without it (5,6,18).

In addition to insulin, correction of hypertonicity in severe HPRF requires infusions of large amounts of hypertonic solutions. In DH, infusion of insulin alone leads to correction of hypertonicity (23). To avoid neurologic complications from rapid changes in brain cell volume, current guidelines suggest that the decline in serum tonicity during treatment of severe hyperglycemia should not exceed 3 mOsm/kg/hour (24). Serum glucose and sodium concentrations should be monitored during treatment of DH to ensure an acceptable rate of decline in tonicity (\(\Delta[\text{Ton}]\)), which is the result of the decline in serum glucose concentration (\(\Delta[\text{Glu}]\)) expressed in mmol/l (one mmol/l is equivalent to 18 mg/dl) and the increase in serum sodium concentration (\(\Delta[\text{Na}]\)). \(\Delta[\text{Ton}]\) is expressed by the formula (18):

\[ \Delta[\text{Ton}] = \Delta[\text{Glu}] + 2 \times \Delta[\text{Na}] \]

where \(\Delta[\text{Glu}]\) has a negative sign. The average \(\Delta[\text{Ton}]\) derived from a number of studies in DH patients treated with insulin was 2.4 mOsm/kg per 100 mg/dl \(\Delta[\text{Glu}]\) (6), a value equal to Katz’s prediction (22). Therefore, the preferred rate of decline in serum glucose during treatment of DH is 100–125 mg/dl/hour.
Changes in Extracellular and Intracellular Volume and Total Body Water in Hyperglycemia

Figs. 3 and 4 show percent changes in extracellular and intracellular volume respectively in the two hypothetical patients depicted in Figs. 1 and 2. The baseline extracellular-to-intracellular volume ratio of both subjects was 1.67, a value which is within the range of volume ratios calculated for patients with DH who were euvolemic at the time of euglycemia (25). The volume changes in each major body fluid compartment at hyperglycemia and after its correction were calculated by applying the principle of body water distribution, which states that in the steady state body water is distributed between the intracellular and the extracellular compartments in proportion to the amount of solute in each compartment (26). Sodium was considered an extracellular solute and potassium an intracellular solute.

Extracellular volume is greatly reduced from the baseline state at presentation with HPRF and will be further reduced after correction of the HPRF without saline administration even if there is no further salt and water loss during treatment (Fig. 3). Intracellular volume is also greatly contracted in HPRF, in which large urinary potassium losses compound the intracellular dehydration resulting from hypertonicity; this contraction will only be partially corrected after treatment (Fig. 4). The contraction of the intracellular volume is the source of severe neurologic manifestations. However, the fluid transferred out of the cells in severe HPRF tends to stabilize the extracellular volume at the peak of hyperglycemia despite the large volume loss in the urine; this allows many patients to maintain adequate cardiac output and blood pressure. The decline in serum glucose concentration during the treatment of severe HPRF with insulin can unmask the severity of extracellular volume depletion. As a result, the need for volume repletion becomes urgent during correction of HPRF. Continuous losses of salt and water through diuresis during the treatment of HPRF further increases the need for volume replacement.

In DH, extracellular volume is expanded from baseline at presentation and will remain slightly expanded after its correction because of the extracellular distribution of a portion of the fluid consumed during the development of hyperglycemia (Fig. 3). Intracellular volume is contracted during hyperglycemia in DH and becomes slightly expanded after its correction (also from the fluid consumed during its development) (Fig. 4).

During correction of anuric DH with insulin infusion, the fractional (or percent) change in extracellular volume between presentation with hyperglycemia and the final euglycemic state can be estimated from the change in serum sodium concentration during treatment as follows (7):

$$\Delta V/V_1 = \frac{[Na]_2}{[Na]_1} - 1$$

where $\Delta V$ is the change in extracellular volume during correction of hyperglycemia, $V_1$ is the euglycemic extracellular volume, and $[Na]_1$ and $[Na]_2$ are the serum sodium concentrations at euglycemia and hyperglycemia, respectively. Formula 3 applied to a number of studies of DH corrected with insulin infusion resulted in a mean $\Delta V/V_1$ value of 13 ml/l of euglycemic extracellular volume for each 100 mg/dl change in serum glucose concentration (6).

An estimate of the total increase in extracellular volume from baseline to DH can be obtained from equation 3 if the euglycemic extracellular volume is known. For example, the estimated total extracellular expansion at hyperglycemia was 2.2 L in the hypothetical patient with DH in Figs. 1–4. This patient had a euglycemic extracellular volume equal to 15 L. For the same degree of hyperglycemia, DH patients with edema have larger extracellular volume expansion—and intracellular volume contraction—than patients without edema (6). Total body water is greatly reduced from baseline in a typical patient with severe HPRF and either unchanged or slightly increased from baseline in a typical patient with DH.
Acid–Base Balance Abnormalities in Hyperglycemia

In addition to ketoacidosis, patients with DH can develop several other abnormalities including lactic acidosis, respiratory alkalosis, respiratory acidosis from either severe pulmonary edema or hyperkalemia-induced muscle weakness, and metabolic alkalosis from vomiting (27,28). Patients tend to suffer from ketoacidosis less frequently after starting chronic dialysis than prior to it (28). Prolonged half-life of insulin in advanced renal failure and frequent follow-up of patients on chronic dialysis have been identified as reasons for the decreased frequency of ketoacidosis in the dialysis population. However, individual patients on dialysis may exhibit an unduly high frequency of diabetic ketoacidosis. The usual course leading to ketoacidosis is omission of one or more insulin doses, often due to an intercurrent illness. This is important because evidence of underlying disease should be sought at presentation with ketoacidosis.

Patients with HPRF and ketoacidosis present with ketonuria and metabolic acidosis, typically the high anion gap variety, but also the hyperchloremic type. Ketoacidosis in DH presents with a low serum bicarbonate concentration, a large serum anion gap, and the presence of ketone bodies in the serum (29). The ratio of the change in anion gap from the baseline value to the corresponding change in serum bicarbonate concentration is useful in the diagnosis of mixed acid–base abnormalities, such as combined ketoacidosis and metabolic alkalosis (30). Hyperchloremic acidosis is not often encountered in patients with DH and ketoacidosis because the excretion of keto-anions along with a cation (usually sodium) in the urine is required for the generation of this type of acidosis (31). Needless to say, such excretion is either poor or nonexistent in patients with DH.

In patients with DH and elevated serum anion gap, serum lactate level should be measured in all instances, while testing for exogenous substances causing anion gap acidosis (methanol, ethylene glycol, salicylates, etc.) should be performed if there is clinical suspicion. The measurement of arterial blood gases is not necessary for establishing the diagnosis of ketoacidosis. It is, however, necessary for determining the appropriateness of the respiratory compensation for the degree of metabolic acidosis (32). Inappropriate compensation (arterial pCO₂ either too high or too low) points to an associated disorder that needs to be addressed. In this instance, the investigation should include search for diseases of the respiratory system, the neurologic system, and the muscular-skeletal system, as well as for intake of drugs affecting the respiration. In common with HPRF, ketoacidosis in DH responds to insulin infusion.

Serum Potassium Concentration in Hyperglycemia

Fig. 5 shows mean serum potassium concentration at differing levels of serum glucose concentration in an HD patient with multiple episodes of DH (33). Progressively higher levels of serum glucose were associated with progressively (and significantly) higher levels in serum potassium. Given the multiplicity of the influences on serum potassium concentration in the setting of DH, a clear relationship between serum levels of potassium and glucose may not be found in all diabetics treated with chronic dialysis. Nevertheless, the potential of DH to cause hyperkalemia with occasionally lethal consequences (34,35) has been recognized.

Hyperglycemia has multiple effects on the serum potassium concentration. Lack of insulin causes translocation of intracellular potassium to the extracellular compartment (36,37). (The serum level of insulin that is required to promote potassium entry into cells is lower than that required for cellular carbohydrate uptake) (38). A second hyperkalemic effect of hyperglycemia is a consequence of the associated hypertonicity, which also leads to egress of potassium from the cells into the extracellular compartment (39) and has been implicated as the cause of hyperkalemia in instances of rapid rise in serum glucose concentration (40). In HPRF, contraction of the extracellular volume (Fig. 3) and reduction in the renal function (9) have also potential hyperkalemic influences. Conditions not directly related to hyperglycemia, such as the presence of hyporeninemic hypoaldosteronism, intake of medications that promote hyperkalemia (e.g., angiotensin-converting enzyme inhibitors) or hypokalemia (e.g., diuretics), hypercatabolic states, and dietary intake of potassium may also affect serum potassium concentration in hyperglycemic patients (41).

Whether diabetic ketoacidosis causes hyperkalemia independently of insulin deficiency or hypertonicity is not clear. Based on the inability of intravenous infusion of beta-hydroxybutyric acid to cause hyperkalemia in anesthetized dogs (42), the absence of hyperkalemia in alcoholic ketoacidosis, and the free movement of ketoacids through cell membranes, current thinking is that diabetic ketoacidosis per se does not cause hyperkalemia (43). In HPRF including ketoacidosis, loss of potassium through osmotic diuresis counterbalances the hyperkalemic effects of hyperglycemia. A small number of
HPRF patients present with hypokalemia. In anuric DH, serum potassium concentration reflects only the internal potassium shifts and offers a good opportunity for studying the effects of diabetic ketoacidosis on internal potassium balance.

Fig. 6 shows the frequency of moderate ($\geq 5.5 \text{ mmol} / \text{l}$) and severe ($\geq 6.0 \text{ mmol} / \text{l}$) hyperkalemia in one study of HPRF with ketoacidosis (44), one study of HPRF with nonketotic hyperosmolar coma (9) and one study of DH with either ketoacidosis or nonketotic hyperglycemia in HD patients (45). The frequency of hyperkalemia did not differ between patients with ketoacidosis and those with nonketotic hyperglycemia in HPRF studies. However, the HPRF study of nonketotic hyperglycemia (9) reported substantially higher mean serum glucose concentration (1170 vs. 558 mg/dl) and tonicity (353 vs. 328 mOsm/kg) than the HPRF study of ketoacidosis (43). In HD DH, the frequency of hyperkalemia was higher when ketoacidosis was present. However, the episodes of ketoacidosis were associated with higher mean serum glucose concentration (934 vs. 682 mg/dl) and tonicity (307 vs. 297 mOsm/kg) than the episodes of nonketotic hyperglycemia (45).

Serum potassium values differ between peritoneal dialysis and HD. Fig. 7 shows the frequency of moderate and severe hyperkalemia in DH occurring in patients on peritoneal dialysis and HD (45). The frequencies of hyperkalemia were lower in peritoneal dialysis DH than HD DH. However, the frequency of hyperkalemia was higher in ketoacidosis than in nonketotic hyperglycemia in both dialysis modalities. Akin to the situation in HD, the episodes of ketoacidosis in peritoneal dialysis were associated with higher serum glucose concentration and tonicity than the episodes of nonketotic hyperglycemia. In addition, the number of episodes of ketoacidosis was small (less than 10) among the peritoneal dialysis patients studied. A greater number of observations are needed to establish the frequency of hyperkalemia in peritoneal dialysis patients with diabetic ketoacidosis.

Although it appears that among patients with DH the frequency of hyperkalemia is higher in the presence of ketoacidosis than in its absence, differing serum glucose concentration and tonicity values encountered in the two categories of DH make it difficult to establish firmly the association. Insulin administration is usually the only treatment needed to correct the hyperkalemia of DH (29). Serum potassium concentration should be monitored during correction of DH.

**Clinical Manifestations of Dialysis-Associated Hyperglycemia**

It is important to distinguish whether the clinical manifestations in patients with DH are the consequences of DH or of an intercurrent illness. Clinical manifestations specific to DH are linked to specific fluid and solute disturbances. Most patients with DH have no symptoms even at levels of extreme hyperglycemia (14,21). The absence of severe hypertonicity or volume depletion is largely responsible for the relative paucity of symptoms. The most frequent clinical manifestation of DH is thirst with fluid consumption (14,23). It is relatively rare for DH to cause severe nervous and circulatory system manifestations.

Hypertonicity is an infrequent cause of coma and an even more infrequent cause of seizures in DH (18,23). Tonicity levels exceeding 320 mOsm/kg increase the risk of severe neurologic manifestations in all types of hyperglycemia (46). In the absence of other causes, neurologic manifestations are exceedingly rare in DH patients with tonicity less than 320 mOsm/kg (23). Ketoacidosis is the second DH-specific cause of coma (23). In addition to DH-specific conditions, the differential diagnosis in patients with DH and coma includes diseases of the central nervous system, infections, and ingestion of consciousness-modifying drugs.

Another infrequent manifestation of DH is pulmonary edema that resolves with the use of insulin infusion alone (18,47). This clinical picture has been attributed to...
expansion of the extracellular volume during development of hyperglycemia and reversal of the extracellular expansion during correction of hyperglycemia (48). Although the magnitude of the internal fluid shift in extreme DH is large enough to be the only cause of the circulatory overload (Fig. 3), pre-existing cardiac disease and adverse effects of insulin’s absence on myocardial contractility or pulmonary capillary permeability may contribute to the clinical picture (6).

Management of Dialysis-Associated Hyperglycemia

Table 2 summarizes the typical fluid and solute abnormalities in HPRF and DH. Treatment should address rectification of all these abnormalities. Replacement of fluid and electrolytes, in addition to insulin infusion, plays a prominent part in the management of HPRF (24). The management of DH consists of two essential measures—insulin infusion and monitoring of clinical manifestations and pertinent laboratory tests. Additional measures may be needed depending on the clinical and laboratory picture. Infusion of insulin corrects all the abnormalities listed in Table 2 in the majority of the cases of DH.

**TABLE 2. Typical fluid and electrolyte changes resulting from severe hyperglycemia**

<table>
<thead>
<tr>
<th>In preserved renal function</th>
<th>In dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body water</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Tonicity</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Intracellular volume</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Extracellular volume</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Total body sodium</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Extracellular [Na]</td>
<td>↓, → , or ↑</td>
</tr>
<tr>
<td>Total body potassium</td>
<td>↓</td>
</tr>
<tr>
<td>Extracellular [K]</td>
<td>↓, → , or ↑</td>
</tr>
</tbody>
</table>

[Na], sodium concentration; [K], potassium concentration.

There are no studies of insulin infusion rates in DH. The guidelines for managing HPRF recommend an initial intravenous bolus dose of regular insulin of 0.15 units per kg followed by continuous infusion of 0.1 units hourly (4). This regimen should be followed for the initial management of DH. During treatment of DH with insulin, serum glucose concentration and tonicity decrease, while serum sodium concentration increases (18). The rate of insulin infusion should be adjusted to obtain a rate of decline in serum glucose concentration equal to 100–125 mg/dl/hour. Serum sodium and glucose levels should be monitored every 2–4 hours early in the course of severe DH.

One question that should be addressed when treatment of DH is started is whether there is an associated water deficit or excess. Calculation of the “corrected” serum sodium concentration provides the information needed. In DH, “corrected” serum sodium concentration is rarely above the normal range (6). The volume of water needed to correct the water deficit in this instance should be calculated using standard principles (49) and assuming that the “corrected” sodium represents the euglycemic serum sodium level. Hyponatremia after correction of DH with insulin therapy is frequent (6) but modest and usually needs no specific treatment. Correction of DH with insulin leads to corresponding correction of the intracellular contraction.

The great majority of patients with DH exhibit no symptoms from the associated extracellular volume expansion, while the pulmonary edema seen in a few cases with DH is routinely rectified with insulin infusion. Rare patients with DH and severe pulmonary edema (18,23) may require emergency dialysis. Blood volume contraction in DH has three potential sources—substantial residual renal function with osmotic diuresis, extrarenal fluid and solute or blood losses, and loss of fluid from the vascular into the interstitial compartment. When signs of extracellular volume deficit are present in patients with DH, the origin of this deficit should be investigated by careful history, physical examination,

**TABLE 3. Approach to patients with severe dialysis-associated hyperglycemia**

**Diagnosis**
- History: Associated conditions, with emphasis on those leading to hyperglycemia
- Physical examination: Emphasis on circulatory and neurologic systems
- Initial laboratory tests: Measured: Serum electrolytes. Calculated: Serum tonicity, “corrected” serum sodium concentration. In addition, if serum anion gap is unusually large and serum TCO2 is unusually low, serum ketones and lactate concentration plus arterial blood gases. Toxicology screen for mental changes and anion gap acidosis without ketones
- ECG for hyperkalemia. Chest X-ray, brain, or other imaging for appropriate clinical indications

**Treatment**
- Infuse regular insulin as a bolus of 0.15 U/kg followed by continuous infusion at a rate of 0.10 U/kg hourly. Modify insulin infusion rate to achieve a 100–125 mg/dl hourly rate of decline in serum glucose concentration. Monitor serum glucose and electrolytes every 2–4 hours
- Infuse saline in small boluses (250 ml) for history of external fluid losses and in larger boluses for clinical signs of volume deficit.
- Monitor circulatory status after each saline bolus
- Calculate the water deficit from body weight and “corrected” serum sodium concentration, if this last variable is elevated. Infuse this amount of water in the form of 5% dextrose in water (D5W) after serum glucose has reached levels below 400 mg/dl or of hypotonic saline if volume deficit is also diagnosed
- Manage severe hyperkalemia with ECG manifestations by additional means (infusion of calcium salts, inhalation of beta-adrenergic compounds and ingestion or enemas of cationic exchange resins). Consider emergency hemodialysis in cases of extreme hyperkalemia
- Administer intravenous potassium salts in small increments (10–20 mmol) if serum potassium drops below 3.3 mmol/l. Measure serum potassium after each infusion
- Consider ultrafiltration in cases of severe pulmonary edema
- Manage associated conditions
and ancillary measures (imaging, laboratory tests). If the decision to replace volume is taken, the rate of volume replacement should be low, for example in 250 ml boluses of isotonic saline with evaluation of the need for further volume replacement after each bolus. If there are ongoing large fluid losses or severe hypotension is present, the rate of fluid infusion should be high and the monitoring for signs of volume deficit or excess should be intense.

During insulin treatment of ketoacidosis in the case of DH, the serum anion gap decreases proportionally to the increase in the serum bicarbonate concentration \((28,29)\). Monitoring of serum bicarbonate and anion gap during treatment of presumed diabetic ketoacidosis may lead to a search for other causes of high anion gap acidosis if the anion gap acidosis remains unchanged or worsens as the serum glucose concentration declines.

Serum potassium concentration typically falls during treatment of DH with insulin. The rate of decline in serum potassium level early in the course of treatment is higher than the rate of decline in serum glucose concentration \((29)\). Typically the hyperkalemia accompanying DH is corrected prior to the correction of the hyperglycemia. Emergency dialysis may be considered if hyperkalemia is severe and associated with electrocardiographic abnormalities. In some instances, hypokalemia develops during treatment of DH with insulin. If serum potassium decreases below 3.3 mmol/L, infusion of modest amounts (10–20 mmol) of potassium salts is indicated. Every dose of intravenous potassium should be followed by measurement of the serum potassium concentration.

**Indications and Risks of Emergency Hemodialysis in Dialysis-Associated Hyperglycemia**

There are two instances when emergency HD may be considered in DH, namely severe pulmonary edema and severe hyperkalemia. During HD in a patient with a high serum glucose concentration and a low serum sodium value, glucose diffuses from the blood into the dialysate and sodium diffuses from the dialysate into the blood. The rate of change in serum tonicity depends on the transfer coefficients and the concentration gradients for glucose and sodium across the dialysis membrane. In patients with extreme hyperglycemia, the rate of change in tonicity may be quite high during HD. In one instance of DH treated with emergency HD for severe hyperkalemia, we estimated a rate of decline in tonicity equal to \(14.5\ mOsm/kg\ per hour\) \((33)\), a value almost five times higher than the rate of change in tonicity that is considered safe \((24)\). Although the effects of rapid decline in serum tonicity during treatment of DH have not been studied, it would seem prudent to avoid rapid declines if possible. Unfortunately, current options are limited in this regard. Sodium and glucose modeling is neither practical nor studied as a means of preventing rapid changes in tonicity during HD.

If ketoacidosis is present in a patient with DH, emergency HD using bicarbonate dialysate can lead to a rapid rise in serum bicarbonate and blood pH. Whether there are any adverse effects of rapid correction of metabolic acidosis by dialysis also has not been studied adequately.

We suggest that conventional HD is best avoided in treating patients with DH. Severe symptomatic extracellular volume excess in DH can be treated with ultrafiltration alone (rather than HD), in addition to insulin infusion. Hyperkalemia can be addressed in the usual nondialytic fashion with the use of intravenous calcium salt infusion, beta-adrenergic agonist inhalation and sodium polystyrene sulfonate (orally or rectally) while insulin-driven potassium shifts are proceeding. Peritoneal dialysis has lower solute transfer rates than HD and can be continued during treatment of severe DH. Table 3 summarizes the diagnosis and management of DH.

**Conclusions**

Although the absence of renal function moderates its clinical manifestations and simplifies its treatment, severe hyperglycemia occurring in patients on chronic dialysis requires understanding of the underlying solute and fluid disturbances and careful monitoring of the patients during treatment. Insulin infusion is the only treatment required in the majority of the patients. Administration of saline, free water, or potassium may be needed in some patients. Emergency HD carries potential risks and its usefulness has not been established.

**References**

DIALYSIS-ASSOCIATED HYPERGLYCEMIA


