Body fluid abnormalities in severe hyperglycemia in patients on chronic dialysis: theoretical analysis

Antonios H. Tzamaloukas\textsuperscript{a,b,*}, Todd S. Ing\textsuperscript{c}, Kostas C. Siamopoulos\textsuperscript{d}, Mark Rohrscieib\textsuperscript{b}, Moses S. Elisaf\textsuperscript{d}, Dominic S.C. Raj\textsuperscript{b}, Glen H. Murata\textsuperscript{a,b}

\textsuperscript{a}New Mexico VA Health Care System, Albuquerque, NM, USA
\textsuperscript{b}Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM, USA
\textsuperscript{c}Department of Internal Medicine, Hines VA/Loyola University Medical Center, Hines, IL, USA
\textsuperscript{d}Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

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Abstract

Hyperglycemic syndromes cause disturbances in the tonicity of body fluids, the distribution of body water between major body fluid compartments, and the external balance of body solute and water. The unique feature of dialysis-associated hyperglycemia (DH) is that, during its development, it can cause changes exclusively in the internal balance of body solute (hypertonicity) and fluids (intracellular volume contraction and extracellular volume expansion) without affecting the external balance of water or solute. This makes DH the proper substrate for studying predictions of the changes in tonicity and extracellular volume caused by hyperglycemia because these predictions fail, by and large, to account for changes in the external balance of sodium, potassium, and water observed in hyperglycemic syndromes occurring in patients with preserved renal function. The predictions suggest that the baseline state of extracellular volume and the degree of hyperglycemia are major factors influencing the magnitude of abnormalities in the tonicity and extracellular volume resulting from DH, while transfers of solute between the intracellular compartment and the extracellular compartment have relatively smaller effects. Edematous patients are at risk for greater hypertonicity and larger increases in their extracellular volume than euvolemic—or, even less, hypovolemic—patients with the same degree of hyperglycemia. Studies reporting the treatment of DH with only insulin therapy can be used to test these theoretical predictions and to analyze the relationship between solute and fluid abnormalities and clinical manifestations.

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1. Introduction

Hyperglycemia causes disturbances in the external balance of body water and solutes, the distribution of body water between the intracellular compartment (IC) and the extracellular compartment (EC), the serum concentrations of solutes, and the body’s acid–base balance. In patients with preserved renal function, hyperglycemia leads to profound losses of water, sodium, and potassium through osmotic diuresis (Brodney, Rappaport, & West, 1950; Gemarni & Kassirer, 1974; Seldin & Tarail, 1950). These losses may dominate the clinical picture (Daugirdas, Kronfol, Tzamaloukas, & Ing, 1989; Feig & McCurdy, 1977; Foster, 1974; Pollock & Arieff, 1980). Consequently, the importance of fluid replacement during management of hyperglycemia is well recognized (Foster & McGarry, 1983; Kitabchi et al., 2001, 2003), even when there is no clinical evidence of severe hypovolemia (Adrogue, Barrero, & Eknoyan, 1989).

Osmotic diuresis is either absent or minimal in dialysis-associated hyperglycemia (DH). Axelrod (1975) proposed that clinical manifestations of severe hyperglycemia differ between patients with preserved renal
function and patients with advanced renal failure because of the absence of osmotic diuresis in the latter group. Subsequent studies provided an understanding of the pathogenesis of the main clinical manifestations of DH and principles of treatment.

We analyzed the association between body fluid abnormalities and clinical manifestations of DH and investigated factors that could affect the development and severity of clinical manifestations. In this report, we addressed the theoretical aspects of body fluid abnormalities in DH. In a second review, which follows, we analyzed published reports on DH, and we compared the findings of these reports to the findings of studies of hyperglycemia in patients with intact renal function and to predictions of theoretical analysis.

2. Effects of hyperglycemia on internal solute–water balance

Hyperglycemia causes an increase in EC solute and a shift of water from the IC into the EC (Petersen, Khalaf, Bocker, & Kerr, 1993; Seldin & Tarail, 1950). Water shift is a consequence of the osmotic principle, which states that osmolalities in the IC and the EC are equal in steady state (Appelboom, Brodsky, Tuttle, & Diamond, 1958; Maffly & Leaf, 1959; Peters, 1944). As a result of the osmotic principle, body water is distributed between the IC and the EC in proportion to the total amount of solute present in each compartment (Darrow & Yannett, 1935). This principle of body water distribution constitutes the basis of theoretical analyses and therapeutic schemes of fluid shifts and osmolality changes under various abnormal osmotic states (Adrogue & Madias, 1997, 2000a, 2000b; Axelrod, 1975; Kurtz & Nguyen, 2005; Tzamaloukas, 1983).

In addition to the principle of body fluid distribution, body fluid changes in hyperglycemia are influenced by three other processes, namely, osmotic diuresis, water intake as a result of thirst, and acid–base disturbances that might accompany hyperglycemia. The magnitude of changes in body fluids that result from the principle of body fluid distribution can be predicted (see below). In contrast, the magnitude of changes in body fluids resulting from the other three processes present in severe hyperglycemia is, by and large, unpredictable. Since most dialysis patients have absent or negligible renal function, DH is unique in that changes in body solute and fluid during its development or its treatment with insulin administration alone can be the exclusive consequence of the principle of body fluid distribution. This particular circumstance allows us to compare changes observed and predicted by theoretical models of hyperglycemia, which are based exclusively on the principle of body fluid distribution without taking osmotic diuresis or fluid intake into consideration.

2.1. Formulas for calculating tonicity and extracellular volume changes in hyperglycemia

The following formulas represent clinically useful approximations of serum tonicity ([Ton]) and total osmolality ([Osm]):

\[ [\text{Ton}] = 2[\text{Na}] + [\text{Glu}] \]
\[ [\text{Osm}] = 2[\text{Na}] + [\text{Glu}] + [\text{Urea}] \]

where [Na] is serum sodium concentration; [Glu] is serum glucose concentration, and [Urea] is serum urea concentration (all in mmol/l) (McCurdy, 1970). The tonicity or effective osmolality formula is an indirect measure of the ability of serum to shrink or swell cells that are suspended in it. This formula provides a better approximation of the effect of DH on body fluid distribution than total osmolality because urea, often in high concentrations in dialysis patients to bring about elevated total serum osmolality values, is distributed in total body water and does not engender osmotic fluid shifts in steady state (Kapsner & Tzamaloukas, 1991).

Correction of hyperglycemia causes a reduction in tonicity. This finding was first demonstrated indirectly by balance studies in patients with intact renal function who were treated for severe hyperglycemia (Tomkins & Dormandy, 1971) and then directly in patients with DH who were treated with insulin therapy only. Predicting tonicity at the end of treatment (when serum glucose concentration is normalized) is important in fluid management. Eq. (2) is not appropriate for this prediction. In practice, the prediction is made by the formula \( \Delta[\text{Na}]/\Delta[\text{Glu}] \), where \( \Delta[\text{Na}] \) is the change in serum sodium concentration and \( \Delta[\text{Glu}] \) is the corresponding change in serum glucose concentration during the development or the correction of hyperglycemia. When glucose and sodium concentrations are both expressed in the International System of Units, the relation among changes in serum glucose concentration, serum sodium concentration, and serum tonicity level is expressed by the equation (Tzamaloukas & Avasthi, 1986):

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

During the development of hyperglycemia, a gain in EC solute (EC hypertonicity) causes an osmotic fluid shift from the IC into the EC, with resulting dilution of serum sodium concentration. Under these circumstances, the change in EC volume is derived from baseline (euglycemic) serum sodium concentration and the final (hyperglycemic) serum sodium concentration as follows (Feig & McCurdy, 1977): If \([\text{Na}]_1 \) and \([\text{Na}]_2 \) are serum sodium concentrations at the time of euglycemia and at the time of hyperglycemia, respectively; \( V_1 \) and \( V_2 \) are the corresponding EC volumes; and \( \Delta V \) is the change in volume.

\[
\Delta V = (V_1 - V_2) = \frac{[\text{Na}]_2 - [\text{Na}]_1}{[\text{Na}]_2 - [\text{Na}]_1} \times V_1
\]
EC volume during treatment (i.e., $\Delta V = V_2 - V_1$), assuming that the amount of sodium remains constant in the EC:

\[
[Na_1] V_1 = [Na_2] (V_1 + \Delta V)
\]

from which

\[
\Delta V / V_1 = [Na_1] / [Na_2] - 1.
\]  

Eq. (5) expresses the fractional increase in EC volume from euglycemic baseline value as a consequence of the development of hyperglycemia.

3. Tonicity in DH

3.1. Modeling of DH

The quantitative changes in serum tonicity and in body fluids that result from hyperglycemia can be predicted by models based on the principle of body fluid distribution. Fig. 1 shows three schematic stages of hyperglycemia developing in an anuric patient. In this figure, ordinates depict IC and EC volumes, abscissa depict osmolalities, and areas of rectangles (products of ordinates and abscissas) depict the total amounts of solute in the IC and in the EC.

Fig. 1A shows euglycemic baseline stage. Fig. 1B shows the hypothetical stage of the instantaneous addition of glucose to the EC without any change in the amount of total body water and prior to any osmotic movement of fluid. Fig. 1C illustrates the final steady-state stage after the net movement of water from the IC into the EC has ceased because IC and EC tonicities have now become equal.

The model depicted in Fig. 1 is based on the assumptions that: total IC solute is the same in (A), (B), and (C); total EC solute is the same in (B) and (C); and the principle of body fluid distribution is the sole determinant of the final body fluid distribution in (C). Under these assumptions, which are necessary and sufficient for characterizing the body as a “perfect” osmometer (Tzamaloukas, 1983), IC and EC solute conservation equations between (B) and (C) can be derived with $\Delta[\text{Ton}]$ and $\Delta V / V_1$ as dependent variables.

Fig. 1 is consistent with published models of body fluid changes brought about by hyperglycemia (Axelrod, 1975; Crandall, 1974; Jenkins & Larmore, 1974; Katz, 1973; Robin et al., 1979; Tzamaloukas, Kyner, & Galley, 1987). A critical value for this model is the amount of solute (glucose) added to the EC in Fig. 1B. The total solute added is equal to $\Delta[\text{Glu}] V_1$. The relation between $\Delta[\text{Glu}]$ and $\Delta[\text{Glu}]$ is as follows:

\[
\Delta[\text{Glu}] = \Delta[\text{Glu}](1 + \Delta V / V_1).
\]  

In comparison to the euglycemic stage (A), hyperglycemia developing in an anuric patient causes (C) an increase in tonicity ($\Delta[\text{Ton}]$), a rise in EC volume ($\Delta V$), and a corresponding fall in IC volume in steady state. The clinical question raised is whether these changes in tonicity and body water distribution lead to any clinical manifestations. Intuitively, the magnitude of $\Delta[\text{Ton}]$ and $\Delta V$ should be among the determinants of clinical manifestations. Quantitative predictions of $\Delta[\text{Ton}]$ and $\Delta V$ follow.

3.2. Prediction of the change in tonicity caused by DH

The expression $\Delta[\text{Na}] / \Delta[\text{Glu}]$ has a negative sign because the directions of changes in serum sodium and glucose concentrations are opposite during the development or the correction of hyperglycemia (Eq. (3)). A $\Delta[\text{Na}] / \Delta[\text{Glu}]$ value of $-2.8$ mmol/l per 100 mg/dl (or $-0.5$ mmol/mmol) was initially proposed (Welt, 1959). This value implies no change in tonicity from hyperglycemia because osmolalities in a 0.5-mmol/kg H2O monovalent sodium salt solution (with complete dissociation) and a 1-mmol/kg H2O glucose solution are equal. Arithmetic values of $\Delta[\text{Na}] / \Delta[\text{Glu}]$ higher than 2.8, reported in certain clinical studies, cannot be attributed to the osmotic translocation of intracellular fluid into the EC because they indicate decreases in tonicity as hyperglycemia develops. Changes in the external...
balance of body solutes and water resulting in relative water excess cause, in most probability, these high $\Delta[Na]/\Delta[Glu]$ values (Tzamaloukas, 1982).

The main contribution of the Katz (1973) formula is the recognition that the numerical value of the ratio $\Delta[Na]/\Delta[Glu]$ must be lower than 2.8 to reflect the rise in tonicity as a result of hyperglycemia. Katz proposed a $\Delta[Na]/\Delta[Glu]$ value of $-1.6$ mmol/l per 100 mg/dl ($-0.29$ mmol/mmol). The predicted value from this formula rise of rate in tonicity (Eq. (3)) is 2.2 mOsm/kg per 100-mg/dl increase in serum glucose concentration. The Katz formula assumes normal baseline EC volume and a serum glucose concentration approximately equal to 56 mmol/l (1000 mg/dl). This formula and its modifications (Crandall, 1974; Jenkins & Larmore, 1974; Moran & Jamison, 1985; Robin et al., 1979; Roscoe, Halperin, Rolleston, & Goldstein, 1975; Tzamaloukas et al., 1987) do not take into account the contributions of osmotic diuresis and water intake to changes in serum tonicity in hyperglycemia.

Modifications of the Katz formula either express deviations from perfect osmometric behavior or are consequences of the perfect osmometer hypothesis. Deviations from perfect osmometric behavior address exchanges of solute between the IC and the EC during the development of hyperglycemia. One modification of the Katz formula estimated a $\Delta[Na]/\Delta[Glu]$ value between $-1.35$ and $-1.50$ mmol/l per 100 mg/dl by analyzing the entry of solute (glucose) during the development of hyperglycemia into the IC of tissues, such as the brain, that do not depend on insulin for glucose uptake (Roscoe et al., 1975). A second modification of the Katz formula computed the effects on the ratio $\Delta[Na]/\Delta[Glu]$ of potassium exit from the IC into the EC during the development of hyperglycemia (Moran & Jamison, 1985). In addition to being relatively small (Tzamaloukas, Moran, & Jamison, 1986), solute movements in these two modifications of the Katz formula have offsetting effects on the net fluid shift between the IC and the EC.

Unlike the influences discussed, consequences of the perfect osmometer hypothesis can have pronounced effects on the change in tonicity in DH. This category of factors affecting the degree of hypertonicity in anuric hyperglycemia includes the baseline state of the EC volume and the degree of hyperglycemia. The ratio of IC volume to EC volume in euglycemia is the most powerful determinant of the ratio $\Delta[Na]/\Delta[Glu]$ (Moran & Jamison, 1985; Tzamaloukas et al., 1987). Hyponatremia develops in hyperglycemia because of the osmotic translocation of IC fluid into the EC. If the IC did not exist, serum sodium concentration would not change during hyperglycemia ($\Delta[Na]/\Delta[Glu]=0$), and the rise in serum tonicity would attain a theoretical maximum that would be equal to the rise in serum glucose concentration expressed in millimoles per kilogram (Eq. (3)). The transfer of fluid from the IC into the EC attenuates the effect of hyperglycemia on EC tonicity. Attenuation is large (the value of the ratio $\Delta[Na]/\Delta[Glu]$ approaches $-2.8$ mmol/l per 100 mg/dl) in EC volume depletion, when the IC is large in relation to the EC, and small (the value of the ratio $\Delta[Na]/\Delta[Glu]$ approaches zero) in markedly edematous states, when the IC is less large in relation to the EC.

Progressive hyperglycemia has an effect on the relationship $\Delta[Na]/\Delta[Glu]$ similar to the effect of edema (Robin et al., 1979; Tzamaloukas et al., 1987) because the IC becomes progressively smaller and the EC becomes progressively larger as hyperglycemia progresses. However, the effect of progressive hyperglycemia becomes noticeable only at extremely high blood glucose concentrations (Robin et al., 1979).

Finally, a recent analysis calculated the effect of hyperglycemia on serum sodium using the Katz formula plus potential changes in total exchangeable sodium, potassium, and water; Gibbs–Donnan equilibrium; osmotic coefficients of sodium salts; osmotically inactive sodium and potassium salts; and body solutes other than sodium or potassium salts (Kurtz & Nguyen, 2005). In summary, the ratio $\Delta[Na]/\Delta[Glu]$, and therefore the change in tonicity caused by hyperglycemia, cannot be represented by a single value in DH, but should be expected to vary considerably according to the underlying state of the EC volume, degree of hyperglycemia, and changes in other body solutes.

Fig. 2 shows the effects of different states of EC volume on the ratio $\Delta[Na]/\Delta[Glu]$ (Tzamaloukas et al., 1987) in hypotensive patients with varying euglycemic EC volumes but with the same IC volume. In these models, a rise in serum glucose concentration from 5.6 mmol/l (100 mg/dl) to 20 mmol/l (360 mg/dl) produces $\Delta[Na]/\Delta[Glu]$ values of $-0.41$ mmol/mmol ($-2.30$ mmol/l per

![Fig. 2. Prediction of the ratio $\Delta[Na]/\Delta[Glu]$ in progressive hyperglycemia in hypotensive anuric patients with the same euglycemic intracellular volume (28 l) and euglycemic extracellular volume: 14 l in euglycemia, 7 l in severe volume deficit, 28 l in edema, 42 l in anasarca, and 56 l in extreme anasarca (Tzamaloukas et al., 1987). $\Delta[Na]/\Delta[Glu]$ values of $-1$ mmol/mmol and $-5.6$ mmol/l per 100 mg/dl are equivalent.](image)
100 mg/dl) in volume depletion and $-0.08 \text{ mmol/mmol}$ ($-0.45 \text{ mmol/l per 100 mg/dl}$) in extreme anasarca.

Fig. 3, drafted from Eq. (3), shows the effect of different states of EC volume and of the degree of hyperglycemia on tonicity in the hypothetical subjects depicted in Fig. 2. The low numerical values of the ratio $\frac{\Delta \text{Na}}{\Delta \text{Glu}}$ in patients with edematous states (Fig. 2) are translated into high values of the corresponding $\Delta \text{[Ton]}$ (Fig. 3).

4. Internal volume shifts in DH

Eq. (5) allows the calculation of the fractional increase in EC volume ($\Delta V / V_1$) during the development of hyperglycemia. The corresponding fractional decrease in IC volume can also be calculated (Tzamaloukas et al., 1987). Fig. 4 shows the fractional changes in EC and IC volumes in hypothetical patients depicted in Figs. 2 and 3.

The change in tonicity from the euglycemic stage to the hyperglycemic stage (from A to C in Fig. 1) is determined by the fractional change in IC volume because the IC solute remains constant during the development of hyperglycemia. The greater is the fractional dehydration of the IC, the greater will be the rise in tonicity. The same change in tonicity is alternatively determined by the fractional dilution of the EC volume. The greater is the fractional dilution of the EC, the greater is the attenuation of tonicity from Fig. 1B to Fig. 1C (the lower is the rise in tonicity from Fig. 1A to Fig. 1C). Thus, fractional changes in IC and EC volumes have opposite effects on the rise in tonicity during the development of hyperglycemia.

Fig. 4 shows that for the same degree of hyperglycemia, the fractional increase in EC volume is highest in states of EC volume depletion and lowest in situations of extreme anasarca, while the corresponding fractional reduction in IC volume is highest in states of extreme edema and lowest in states of EC volume depletion. These fractional volume changes in body fluid compartments are consistent with the changes in tonicity shown in Fig. 3.

The magnitude of total EC volume expansion caused by a given degree of hyperglycemia can be found by multiplying fractional EC volume increase, calculated by Eq. (5),...
by euglycemic EC volume when the value of the latter is known. Euglycemic EC volumes differed greatly among the states shown in Figs. 2–4, while euglycemic IC volume was the same for all hypothetical patients. Fig. 4 predicts that the magnitude of osmotic volume shift from the IC to the EC must be greatest in patients with extreme anasarca and lowest in those with EC volume depletion to cause the depicted fractional changes in IC volume, even though the fractional increase in EC volume is lowest in states of extreme anasarca.

Fig. 5 shows the magnitude of EC volume gains, calculated by multiplying the fractional rises in EC volume shown in Fig. 4 by the euglycemic EC volume of each hypothetical hyperglycemic patient depicted in Figs. 2–4. The findings of Fig. 5 confirm the predictions from the fractional IC and EC volume changes depicted in Fig. 4. For the same degree of hyperglycemia, the increase in EC volume is substantially larger in volume-expanded states than in volume-contracted states. In a euvoletic patient with an EC volume of 14 l and an IC volume of 28 l at the time of euglycemia (5.6 mmol/l or 100 mg/dl), the predicted increase in EC volume for a rise in blood glucose concentration equal to 66.7 mmol/l (1200 mg/dl) and a final serum glucose value of 72.3 mmol/l (1300 mg/dl) is 2.3 l.

Note that Figs. 2–5 compare the different EC volume states with the same degree of hyperglycemia. The amount of glucose required to raise serum glucose concentration to a given level (Δ[Glu]1 V1 in Fig. 1) is progressively larger as baseline EC volume (V1) increases progressively from a state of EC volume depletion to one of extreme anasarca (Figs. 2–5). The differences shown in Figs. 2–5 are caused by the different amounts of glucose required to generate the same level of hyperglycemia. The results would be different if the same amount of glucose were added to the EC in each of the volume states. For example, if the amount of glucose required to raise serum glucose concentration by 66.7 mmol/l (1200 mg/dl) in a euvoletic patient were added to the EC of the patient with extreme anasarca in Figs. 2–5, Δ[Glu] would amount to only 8.3 mmol/l (150 mg/dl).

5. Conclusions

This theoretical analysis concluded that DH causes hypertonicity and EC volume expansion. The magnitudes of the increases in tonicity and in EC volume in DH depend on the degree of hyperglycemia and on states of EC volume at the time of euglycemia. When subjected to the same degree of hyperglycemia, edematous patients are at higher risk for severe hypertonicity and larger EC volume expansion than euvoletic patients and, all the more so, than volume-depleted patients. Edematous patients are, therefore, at a higher risk of developing clinical manifestations caused by hyperglycemia-induced fluid abnormalities.

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References


