The Variable Hyponatremic Response to Hyperglycemia

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Hyperglycemia may lower the plasma sodium concentration. Theoretical analyses have suggested that elevations in glucose concentration produce an invariant hyponatremic response. We propose, however, that change in plasma sodium concentration in response to hyperglycemia is variable and depends on (1) the distribution of total body water and solute, (2) the relationship between the gain of extracellular glucose and the loss of intracellular solute and (3) the intake and loss of solute and water. These factors are incorporated into a formulation of the relationship between the plasma sodium and glucose concentrations.

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Because hyperglycemia may notably reduce plasma sodium concentration, a clinician often must decide whether the reduction is appropriate for the elevation in glucose concentration of the plasma.[1-6] More than 20 years ago it was suggested that sodium concentration would decline approximately 2.8 mEq per liter for each 100 mg per dl rise in glucose concentration above 100 mg per dl.[1,2] Katz rejected this "classic" figure and suggested that the change in sodium concentration varied linearly with the increment in glucose concentration. He calculated the decrement in sodium concentration to be 1.6 mEq per liter per 100 mg per dl rise in glucose concentration.[3] This figure and the analysis from which it was derived are widely accepted.[4-7] In assessing the relationship between hyperglycemia and hyponatremia, however, the answers to several questions will largely determine the correct decrement in sodium concentration. What is the distribution of body solute and water? What is the source of the extracellular glucose that produces hyperglycemia? What other conditions apply? Understanding the limitations inherent in earlier approaches enables us to formulate a more broadly applicable relationship.

Classic Solution

The classic analysis included these assumptions: (1) total body water is 60% of body weight and is distributed two thirds as intracellular fluid (ICF) and one third as extracellular fluid (ECF), (2) glucose and sodium are essentially restricted to the extracellular space, (3) water freely crosses cellular membranes, (4) glucose is "added to" the extracellular space, (5) intracellular solute remains constant, (6) extracellular, and therefore intracellular, osmolality ultimately returns to *normal*—that is, an elevated glucose and a coincidentally depressed sodium concentration[1-3]—and (7) the classic solution does not specify that the increase in extracellular fluid space that occurs in hyperglycemia must be supplied by a positive water balance. It follows that if osmolality is to remain unaltered and intracellular solute is constant, intracellular volume must be static.

Because water traverses cellular membranes easily, the following relationship obtains:

$$\frac{\text{ICF solute (osmole)}}{\text{ICF volume (liter)}} = \frac{\text{ECF solute (osmole)}}{\text{ECF volume (liter)}}. \quad (1)$$

For purposes of calculation and to illustrate the classic solution, the following plasma values will be defined as normal for a 70-kg man: sodium, 140 mEq per liter; glucose, 100 mg per dl (5.5 mosm per liter); osmolality, 285 mosm per kg. Total body water is 42 liters. The ICF has a volume of 28 liters and contains 7,980 mosm. The ECF has a volume of 14 liters and contains 3,990 mosm.

Inserting these values into equation 1, the effect of adding glucose to the extracellular fluid may be expressed as:

$$\frac{7{,}980 \text{ mosm}}{28 \text{ liters}} = \frac{(3{,}990 + G) \text{ mosm}}{(14 + X) \text{ liters}}, \quad (2)$$

where G = milliosmoles of added glucose and X = the additional water (in liters) needed to reestablish normal osmolality. Solving for X (in liters) in terms of G (in milliosmoles),

$$X = 0.0035G.$$

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ABBREVIATIONS USED IN TEXT
ECF = extracellular fluid
ICF = intracellular fluid

The new sodium concentration, P_{Na}, is

$$P_{Na} = 140\left[\frac{14}{(14+X)}\right]\text{mEq/liter.}$$

The new glucose concentration, P_G, is

$$P_G = \left[\frac{G + (5.5)\cdot(14)}{(14+X)}\right]\text{mosm/liter.}$$

The fall in sodium concentration, ΔP_{Na}, is

$$\Delta P_{Na} = [140 - P_{Na}]\text{ mEq/liter.}$$

The increment in glucose concentration, ΔP_G, is

$$\Delta P_G = [P_G - 5.5]\text{ mosm/liter.}$$

The relationship between ΔP_{Na} and ΔP_G may then be calculated. The sodium concentration is reduced 2.75 mEq per liter per 100 mg per dl increase in glucose concentration.

Solution of Katz

Katz correctly observed that simple addition of solute to the body would necessarily produce at equilibrium an osmolality greater than normal. A redistribution of body water from intracellular to extracellular fluid space would not suffice to return osmolality to its original value.[3] In his analysis, Katz assumes the same conditions as for the classic solution with the following exceptions: (1) it is no longer assumed that osmolality remains normal and (2) intake and output are specifically excluded. Solute as glucose is "added to" the extracellular fluid, raising total body solute content. Intracellular water moves to the extracellular compartment until intracellular and extracellular osmolality equilibrate at some higher value. Intracellular solute is still assumed to be fixed, however. The relationship is

$$\frac{\text{ICF solute (osmole)}}{\text{ICF volume} - Y} = \frac{\text{ECF solute (osmole)} + G}{\text{ECF volume} + Y}, \quad (3)$$

where Y represents the volume of intracellular water moving to the extracellular space, and G is the added glucose.

Employing the same normal values as in the classic solution and inserting these into equation 3, Katz's solution may be expressed as

$$\frac{7{,}980}{28 - Y} = \frac{3{,}990 + G}{14 + Y}. \quad (4)$$

Solving for Y in terms of G,

$$Y = \frac{28G}{11{,}970 + G}.$$

While sodium concentration declines approximately 1.6 mEq per liter with each 100 mg per dl increase in glucose concentration, it is apparent that Y, the volume of intracellular water added to extracellular fluid, cannot vary linearly with the increment in glucose concentration and therefore that ΔP_{Na} cannot vary linearly with ΔP_G.

General Solution

We must identify the source of glucose in the extracellular fluid. This is particularly important in the case of an insulinopenic diabetic patient who has ketoacidosis and is unable to eat, and in whom the plasma glucose is often markedly elevated. Glucose is produced *intracellularly*—it is not "added to" the extracellular fluid from an exogenous source. A variety of intracellular substances are consumed or transformed in the production of the glucose that ultimately enters the extracellular space.[8] This represents the movement of intracellular solute to the extracellular aqueous compartment, and it is incorrect to assume that the quantity of intracellular solute remains fixed. A general analysis of the relationship between glucose concentration and sodium concentration should account for volume changes in both intracellular and extracellular solute and water, as well as accommodating the special conditions assumed for both the classic and Katz's solutions. Finally it should be applicable to the clinical setting of diabetic ketoacidosis where knowledge of the sodium-glucose relationship could be of great benefit.

The general expression is

$$\frac{(\text{ICF solute} - G_1)}{(\text{ICF volume} - Y_1)} = \frac{(\text{ECF solute} + G_2)}{(\text{ECF volume} + Y_2)} \quad (5)$$

where

Y_1 = water lost from the ICF (in liters),
Y_2 = water gained by the ECF (in liters),
G_1 = ICF solute loss (in milliosmoles),
G_2 = ECF gain in glucose (in milliosmoles).

(If intake and output are excluded, ECF volume gain equals ICF loss, that is, $Y_1 = Y_2$; G_1 does not equal G_2, however.)

It is more nearly correct to assume in normal humans that 55% of body water (and solute) is intracellular and 45% is extracellular.[9] Using this assumption, Katz's solution would have predicted a decline of 1.4 mEq per liter in sodium concentration for a 100 mg per dl increase in glucose rather than the 1.6 mEq per liter originally calculated. In the 70-kg man used as our example, ICF volume equals 23.1 liters, containing 6,584 mosm; ECF volume equals 18.9 liters and contains 5,386 mosm. Substituting these values into equation 6,

$$\frac{6{,}584 - G_1}{23.1 - Y_1} = \frac{5{,}386 + G_2}{18.9 + Y_2}. \quad (6)$$

Equation 1 and equation 3 may be derived as special cases of equation 5. In the classic solution, ICF solute and water are assumed to be constant—that is, $G_1 = 0$ and $Y_1 = 0$. Applying these values to equation 5 and allowing for the difference in body fluid distribution, equation 2 is derived from equation 5. Katz assumed that there is no intracellular solute loss, or $G_1 = 0$. However, in Katz's solution, water was allowed to shift from the intracellular compartment, $Y_1 \neq 0$. Because intake and output are excluded as factors in Katz's solution, $Y_1 = Y_2$. Applying these conditions to equation 5 while using Katz's assumed body fluid distribution, equation 3 is derived from equation 5.

Osmotic Equivalence of Glucose Precursors

In the absence of glucose intake, extracellular glucose is produced from gluconeogenesis or glycogenolysis.[8,10,11] The major precursors of glucose are amino acids (derived from proteolysis and transamination); lactate and pyruvate (primarily from glycolysis); and glycerol (from lipolysis).[8,10-12] Acetone may also be a precursor of glucose.[13] Although proteins and glycogen are large molecules, their osmotic activity cannot safely be neglected.[8,14] Some (obligate) intracellular water is retained by the osmotic activity of glycogen or protein. One gram of glycogen obligates osmotically approximately 1.6 grams of water.[8,14] Assume that 1 gram of glycogen per 1.6 grams of water is isosmotic—that is, 1 gram of glycogen per 1.6 grams of H_2O is "osmotically equivalent"

to 285 mosm per kg H_2O. Thus 1 gram of glycogen is equivalent to approximately 0.5 mosm. After glycogenolysis, 1 gram (0.5 mosm) of glycogen forms 5.5 mosm of glucose.[11]

Similarly, each gram of intracellular protein obligates approximately 3.3 grams of water.[8,14] Assume that 1 gram of protein per 3.3 grams of H_2O is osmotically equivalent to 285 mosm per kg of H_2O. A gram of protein is equivalent to approximately 1 mosm. When metabolized, protein yields both glucogenic and ketogenic substrates, providing eight amino acid residues per gram of protein, substrates that can be used to generate approximately three milliosmoles of glucose.[11]

If there is no coexistent lactic acidosis, the concentrations of lactate and pyruvate in the diabetic are not much different from normal values.[12,15] Hepatic extraction of these substrates may be more efficient, particularly during ketoacidosis, but there is little evidence to suggest that a major transcellular shift of these metabolites occurs.[8,12,15]

Fat is stored in a milieu that is almost perfectly water-free.[8] Because intracellular fat obligates no water, it has an osmotic equivalence of zero.

Relationship Between the Loss of Intracellular Solute and the Gain of Extracellular Glucose

From the foregoing considerations, the sources of glucose may be estimated in a diabetic patient with ketoacidosis. Assume that no fluids or solids are consumed. Biochemically the patient resembles to some extent a normal person who is fasting except that the rate of glycogenolysis is elevated, not depressed.[12] During ketoacidosis, glucose output from glycogenolysis may equal that from gluconeogenesis.[12,15] For an extracellular glucose gain of 400 mosm, for example, glycogenolysis and gluconeogenesis will each provide approximately 200 mosm. Using determinations of portal vein and hepatic artery blood flow rates and gluconeogenic substrate concentrations, studies of transhepatic substrate fluxes suggest that about half of gluconeogenic glucose is derived from lactate and pyruvate (100 mosm), a sixth from glycerol (33 mosm) and the remaining third (67 mosm) from amino acid residues.[12,13,15-18]

For glycogenolysis to provide 200 mosm of extracellular glucose, the *intracellular solute loss* is

$$\left[\frac{200\text{ mosm glucose}}{5.5\text{ mosm glucose/gram glycogen}}\right]\cdot\left[\frac{0.5\text{ mosm}}{\text{gram glycogen}}\right]=18\text{ mosm}.$$

For glycerol, lactate and pyruvate, the intracellular osmotic loss is nil. For proteolysis to provide amino acid residues adequate to produce 67 mosm of extracellular glucose, the intracellular solute loss is

$$\left[\frac{67\text{ mosm glucose}}{3\text{ mosm glucose/gram protein}}\right]\cdot\left[\frac{1\text{ mosm}}{\text{gram protein}}\right]=22\text{ mosm}.$$

Thus the production of 400 mosm of extracellular glucose (G_2) entails the loss of approximately (18 + 22) = 40 mosm of intracellular solute (G_1). Hence, G_1 is approximately one tenth of G_2. It is important to realize that the relationship between G_1 and G_2 depends little on the assumptions regarding the amounts of extracellular glucose derived from each intracellular source. If one source generates less glucose, more will be supplied by a second source, leaving the net intracellular solute loss substantially unchanged. Substituting these values into equation 6,

$$\left[\frac{6{,}584-(G_2/10)}{23.1-Y_1}\right]=\left[\frac{5{,}386+G_2}{18.9+Y_2}\right].$$

Again $Y_1 = Y_2$. Expressing G_2 now simply as G, the ECF gain in glucose, and solving for Y, the volume of water that shifts from the intracellular to the extracellular compartment,

$$Y=\frac{24.9G}{11{,}970+0.9G}. \qquad (7)$$

Equation 7 is nonlinear, as is the expression for the decrement in plasma sodium concentration. Table 1 shows calculations for the change in plasma sodium concentration for several values of plasma glucose concentration in a 70-kg man. The general solution indicates that the plasma sodium concentration will decline in a nonlinear manner, 1.5 to 1.6 mEq per liter for each 100 mg per dl rise in plasma glucose concentration in a 70-kg man.

TABLE 1.—*Demonstration of the Variable Decrement in Sodium Concentration in Response to Hyperglycemia in a 70-kg Man*

Values		*Plasma Sodium Concentrations*		
G (mosm)	100	300	700	1,000
Y (liter)	0.21	0.61	1.38	1.93
ECF volume (liter)	19.1	19.5	20.3	20.8
P_{Na} (mEq/liter)	138.5	135.6	130.5	127
ΔP_{Na} (mEq/liter)	1.5	4.4	9.5	13
P_G (mg/dl)	193	378	721	963
ΔP_G (100 mg/dl)	0.93	2.78	6.21	8.63
ΔP_{Na} to ΔP_G (mEq/liter per 100 mg/dl)	1.61	1.58	1.53	1.51

G = total glucose added to the ECF (see equation 7)
Y = volume of intracellular water shifting to extracellular compartment
ECF = extracellular fluid
P_{Na} = plasma sodium concentration
ΔP_{Na} = decrease in plasma sodium concentration
P_G = plasma glucose concentration
ΔP_G = increase in plasma glucose concentration
Assumptions: Initial values: Total body water, 42 liters; ECF, 18.9 liters; ICF, 23.1 liters, P_{Na}, 140 mEq/liters; P_G, 100 mg/dl (5.5 mosm/kg)

Effect of Intake by Mouth

The assumption that diabetic ketoacidosis develops when nothing is taken in by mouth is not valid for every case. If intake of water and glucose is considered, the general expression of equation 5 still applies, but the gain in ECF volume no longer necessarily equals the loss in ICF volume. The relationship between ICF solute loss and ECF glucose gain also changes. For a given increment in extracellular glucose concentration, exogenous glucose intake reduces the requirement for generating glucose from intracellular sources. Compared to results predicted when water and glucose taken by mouth are excluded, glucose consumption without water results in a diminished loss of ICF solute, less of a reduction in ICF volume and a smaller gain in ECF volume. Consequently, dilution of extracellular sodium is lessened, and the range of values for ΔP_{Na} to ΔP_G ratio is below 1.5 to 1.6 mEq per liter per 100 mg per dl rise in glucose concentration. In contrast, water intake without glucose means a net increase in the gain of ECF volume. Dilution of extracellular sodium is increased, and values for ΔP_{Na} to ΔP_G ratio exceed 1.5 to 1.6 mEq per liter. Intake of *both* glucose and water affects ΔP_{Na} to ΔP_G ratio as a function of tonicity of the fluid added: hypertonic solutions diminish and hypotonic solutions increase the ratio of ΔP_{Na} to ΔP_G.

Effect of Distribution of Body Water and Solute

The distribution of body water before the development of hyperglycemia is also an important variable in the determination of the ratio of ΔP_{Na} to ΔP_G. While equation 7 satisfactorily describes the relationship between an elevated glucose concentration and a depressed sodium concentration because it accounts for the source of extracellular glucose, it assumes a distribution of body water that is initially 55% intracellular and 45% extracellular. There are instances, however, when this assumption is incorrect: for example, in a patient with edema or one who develops ketoacidosis with a diminished extracellular fluid volume. Whatever the distribution of total body water and solute at the onset of diabetic ketoacidosis, the fundamental considerations regarding the shifts of solute and water still apply and may be used to derive a unique curve relating ΔP_{Na} to ΔP_G for each ICF to ECF ratio. In an edematous patient having excess extracellular fluid equal to 15% of body weight, the ΔP_{Na} to ΔP_G ratio would vary from 1.25 to 1.35 mEq per liter per 100 mg per dl of glucose elevation over a range of glucose values. For a hypovolemic patient with a deficiency of extracellular fluid equal to 10% of body weight, the ratio would be 1.8 to 1.9 mEq per liter. The plasma sodium concentration in a hypovolemic patient may be as much as 8 mEq per liter less than that of the edematous patient for the same plasma glucose level, a clinically significant difference. Hence, because of the dependence of ΔP_{Na} to ΔP_G ratio on the prehyperglycemic partitioning of solute and water between ICF and ECF, there is clearly not a *single* decremental sodium value for a given glucose increment. A nomogram that takes these variables into account is depicted in Figure 1.

Whether the losses of extracellular fluid occur before or during the development of hyperglycemia does not affect the applicability of the nomogram in Figure 1. Urinary solute lost during the osmotic diuresis caused by glucosuria has less sodium and more glucose than the same volume of solute in extrarenal losses.[19-21] For a given gain in extracellular glucose, the effect of urinary losses of solute is to elevate the ratio of ΔP_{Na} to ΔP_G between 1% and 10%, a change which can be neglected in the use of the nomogram.

Although the nomogram defines precisely the varying relationship between the plasma concentrations of sodium and glucose, we suggest that clinical application include the following simple guidelines:

1. If the patient in the ketoacidosis is euvolemic, then the original correction factor of Katz may be used for the ratio of ΔP_{Na} to ΔP_G, which is 1.6 mEq per liter sodium concentration per 100 mg per dl glucose concentration.
2. If, as is more likely to be the case, the patient has a depletion in volume, then a value of 2 mEq per liter

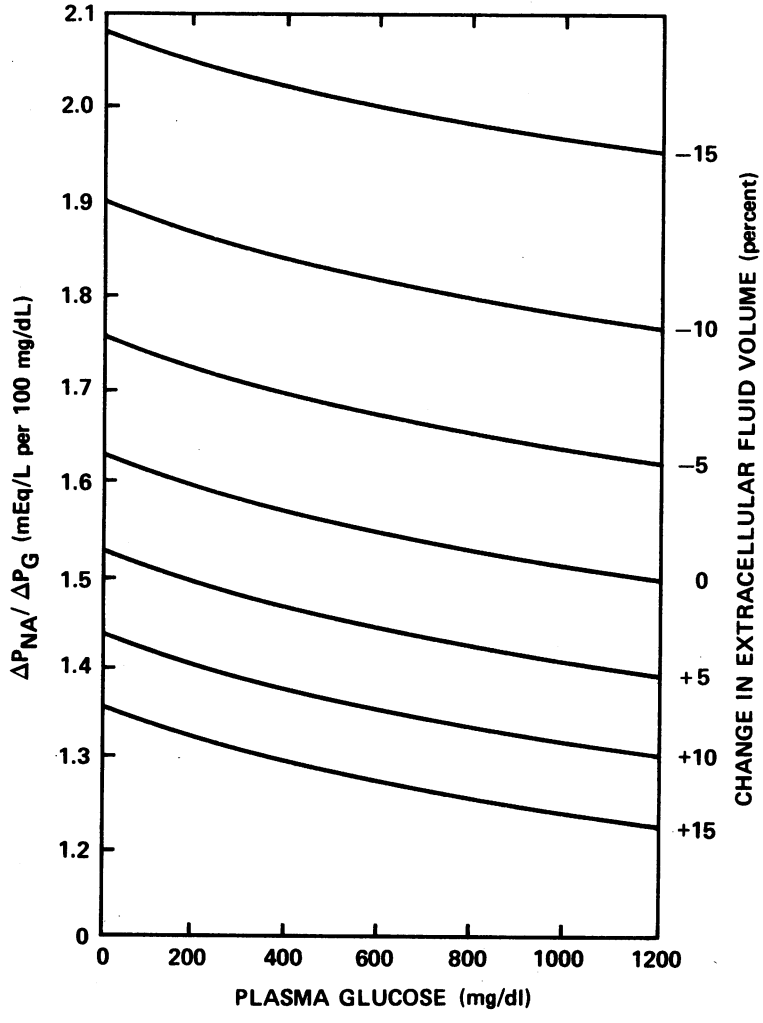

Figure 1.—The decline in plasma sodium concentration ΔP_{Na} (mEq/liter) per increment in glucose concentration ΔP_G (100 mg/dl) is plotted as a function of the glucose concentration and the change from normal in extracellular fluid volume. The abscissa is the plasma glucose concentration. Excess plasma glucose equals this plasma glucose concentration minus 100 mg/dl. The left ordinate is $\Delta P_{Na}/\Delta P_G$. The right ordinate is the estimated change in ECF volume associated with changes in *total body weight* (in percent). To determine $\Delta P_{Na}/\Delta P_G$, locate the intersection of the vertical line determined by the plasma glucose concentration and the curved line determined by the estimate of the change in ECF volume. A horizontal line from the point of intersection to the left ordinate determines the ratio of $\Delta P_{Na}/\Delta P_G$. Multiplying the ratio of $\Delta P_{Na}/\Delta P_G$ by the excess glucose concentration yields the reduction in sodium concentration due to hyperglycemia.

sodium concentration per 100 mg per dl glucose elevation above normal is preferable.

3. Should the patient with ketoacidosis have expanded volume—for example, if the patient has congestive heart failure—a value of 1.2 mEq per liter sodium concentration per 100 mg per dl glucose concentration is a more reasonable correction factor.
4. Finally, it may also be useful to keep these guidelines in mind when confronted by patients with nonketotic hyperglycemic states, although quantitative glucose production has not been studied as thoroughly as glucose production in diabetic ketoacidosis.

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Information Needed for Psoriasis Study

What factors are involved in the origin and course of psoriasis? Researchers in the Department of Dermatology, Stanford University School of Medicine, are examining this question and seek to enlist physicians in an extension of their epidemiologic studies. Physicians are best able to assess certain questions, such as appearance of psoriasis with β-blockers, exacerbation with mental or physical stress, occurrence with arthritis and so forth.

If the journal's readers or family members who have psoriasis will write to Psoriasis, Post Office Box V, Stanford, CA 94305, a short questionnaire will be sent. Responses will be used in the study and the researchers will be pleased to send a report of their findings.