Hyperglycemia-induced hyponatremia: metabolic considerations in calculation of serum sodium depression

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Summary: Hyperglycemia is associated with a decrease in serum sodium concentration. Previous methods of estimating the degree of decrease have not considered the fact that glucose will enter certain cells despite relative insulin deficiency; thus, glucose will not contribute directly to the osmotic gradient responsible for water shifts into or out of these tissues. The expected decrease in serum sodium concentration is 1.35 meq/l for every 100 mg/dl increase in blood glucose concentration — the metabolic correction factor. Although the numerical difference between this factor and that calculated by others is small, the metabolic implications could be critical. In the hyperglycemic state the water content of tissues not requiring insulin for glucose transport could increase, and where tissue swelling is physically restricted (for example, in the brain) this expansion could seriously affect organ function.

Résumé: *Hyponatrémie déclenchée par hyperglycémie: considérations métaboliques au sujet du calcul de la diminution de la valeur de sodium au sérum*

L'hyperglycémie est associée d'une diminution de la concentration du sodium au sérum. Les méthodes utilisées antérieurement pour évaluer le degré de cette réduction ne considéraient pas le fait que le glucose pénètre dans certaines cellules malgré une relative insuffisance d'insuline, de sorte que le glucose ne contribue pas directement au gradient osmotique qui provoque les transferts d'eau en dehors de ces tissus ou vers ces tissus. La diminution probable de la concentration de sodium au sérum est de 1.35 meq/l pour chaque 100 mg/dl d'augmentation de la concentration de glucose au sérum — facteur métabolique de correction. En dépit du fait que la différence numérique entre ce facteur et celui qui a été calculé par d'autres soit minime, il n'empêche que les conséquences métaboliques peuvent être critiques. Au cours de l'état d'hyperglycémie la teneur en eau des tissus qui n'exigent pas d'insuline pour le transport d'eau risque d'augmenter et, dans le cas où l'expansion tissulaire est physiquement restreinte (dans le cerveau, par exemple), cette expansion risque de compromettre sérieusement la fonction de l'organe.

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It is well known that hyperglycemia is associated with a decrease in serum sodium concentration. Because glucose is not free to enter all cells, in hyperglycemia water moves from the intracellular fluid (ICF) to the extracellular fluid (ECF) along the osmotic gradient. Until recently the predicted decrease in serum sodium concentration was 2.8 meq/l for every 100 mg/dl increase in blood glucose concentration above normal. Katz[1] demonstrated the inaccuracy of this assumption, for water will move into the ECF only until osmotic equilibrium is reached, rather than until the ECF osmolality has returned to normal — the basis for the original prediction.

This approach of Katz, however, fails to consider a metabolic component of hyperglycemia. Not all tissues of the body depend on insulin for the entry of glucose into cells. In hyperglycemia the increase in the concentration of glucose in the ICF of some cells will alter substantially their ICF osmolality. We have therefore modified further the calculation, taking into account both the physicochemical and the metabolic alterations in hyperglycemic states. A small numerical change is produced. The importance of this concept lies in understanding that differences will exist in not only the quantity of water movement but also its direction (into or out of individual organs), particularly for the brain.

With relative insulin deficiency, only certain "insulin-sensitive" organs will maintain the concentration gradient for glucose of several orders of magnitude from ECF to ICF.[2] The mass of these "insulin-sensitive" tissues is approximately 83% of body weight (Table I). This represents an ICF water volume of about 22 l (ICF^s). This large dysequilibrium of glucose concentration between ICF and ECF is not found in the "insulin-insensitive" tissues (ICF^i),[2] which contain 4 to 5 l of intracellular water (Table I). Therefore, in diabetes mellitus with hyperglycemia, glucose concentrations should be similar in the ECF (total volume, 14 l) and in the ICF of the "insulin-insensitive" tissues (volume, 4.41 l). The ICF^i is small in volume, but changes affecting it have important consequences for the whole organism because the "insulin-insensitive" tissues include the brain.

For the sake of comparison we shall use the same figures as Katz[1] and add 1000 mOsm of glucose to a 70-kg person (total body water 42 l, ICF 28 l and ECF 14 l) who has normal values for blood glucose and serum osmolarity (285 mOsm/l). The total osmolar content of the body is thus 11 970 mOsm (285 mOsm/l × 42 l). After the addition of 1000 mOsm of glucose this value increases to 12 970

mOsm. The new serum osmolarity is then 308.8 mOsm/l (12 970 mOsm ÷ 42 l). Before addition of the glucose the osmolar content of the ICF^s was 6167 mOsm (285 mOsm/l x 21.64 l, the volume of ICF^s derived from Table I). After addition of the glucose this 6167 mOsm must be dispersed with an osmolarity of 308.8 mOsm/l and the new ICF^s volume will become 19.97 l (6167 mOsm ÷ 308.8 mOsm/l). Therefore the fluid shift is 1.67 l (21.64 l − 19.97 l). If we assume that the glucose concentration of the ICF^s is negligible compared with that of the ECF and ICF^i, then 1.67 l of fluid shifted from the ICF^s will be equilibrated together with the glucose, throughout the ECF and the ICF^i (4.44 l), and will increase the total of ICF^i and ECF to 20.08 l. The proportion of the fluid shift remaining in the ECF will be 1.27 l (ECF ÷ [ECF + ICF^i] × 1.67 l). Therefore, the new ECF volume after the fluid shift will be 15.27 l.

Since the ECF contains 1960 meq of sodium (140 meq/l × 14 l) and glucose addition causes the ECF volume to increase to 15.27 l, the new serum sodium concentration will be 128 meq/l. Before glucose addition the ECF contained 77 mOsm of glucose (14 l × 5.5 mOsm/l) and the ICF^i 24.3 mOsm of glucose (4.1 × 5.5 mOsm/l), a total of 101.3 mOsm. After the glucose addition the 1101.3 mOsm of glucose will be distributed in 20.08 l, giving a final concentration of 54.8 mOsm/l (1101.3 mOsm ÷ 20.08 l). When expressed in mg/dl the final glucose concentration is 986. Thus, an increase of blood glucose concentration from 100 to 986 mg/dl causes a decrease in serum sodium concentration of 12 meq/l. Proportionately, an increase in blood glucose concentration of 100 mg/dl will cause a decrease in serum sodium concentration of 1.35 meq/l. We have therefore calculated the metabolic correction factor to be −1.35 meq/l sodium•100 mg•dl glucose (this figure is independent of the amount of added glucose).

These calculations were made with the oversimplification that the glucose concentrations in the ECF and ICF^i were equal. In the complicated clinical setting true equilibrium probably does not exist and the glucose concentration in the ICF^i will be less than in the ECF. Therefore, the expected correction factor could range from the equilibrium value of 1.35 to Katz's value of 1.6, determined when the glucose concentration in the ICF^i is considered negligible.[1]

Table I—Tissue weights and water content of a 70-kg person[3]

Tissue	Weight: % body weight	Weight: Water % wet weight	Water content (l): Total	Water content (l): ICF*
Major "insulin-sensitive" tissues[2]				
Muscle				
Skeletal	43.0	79.2	23.8	15.94
Cardiac	0.4	82.7	0.2	0.16
Skin	7.0	69.4	3.4	2.28
Adipose tissue†[5]	14.2	15.1	1.5	0.22
Skeleton[6]	18.0	36.0	4.5	3.04
Total	82.6		33.4	21.64
Major "insulin-insensitive" tissues[2]				
Brain	2.3	77.4	1.25	0.83
Liver	2.0	71.1	1.00	0.67
Kidneys	0.5	81.1	0.28	0.19
Lungs	1.6	78.7	0.88	0.59
Spleen	0.2	79.0	0.11	0.07
GI tract (mucosal cells)‡[7]	—	80.0	0.66	0.66
Erythrocytes§	25 ml/kg	80.0	1.40	1.40
Total			5.58	4.41

*ICF = 67% of total water of all tissues except adipose tissue and erythrocytes.
†ICF = 22 μl/g.
‡GI tract mucosal cell volume = surface area (33×10^3 cm^2) × height (0.025 cm) = 825 cm^3 — 80% of volume assumed to be ICF.
§Volume of erythrocytes = 25 ml/kg (average value) — 80% of volume assumed to be ICF.

Although numerically this new (metabolic) correction factor (1.35) does not differ much from Katz's factor of 1.6, the metabolic implications are very important, in that the degree and even the direction of water movement will differ in the ICF^s and ICF^i. Elevation of blood glucose concentration and a subsequent increase in ECF osmolarity would result in a shift of water out of the ICF of "insulin-sensitive" tissues. In contrast, the ICF of "insulin-insensitive" tissues would have an increased glucose concentration and thereby an increased osmolarity. As a result there would be little, if any, water shift out of these tissues, for the osmolar gradient induced by elevated glucose concentration would be small. In fact, water might even shift *into* these cells as a result of the dilution of the ECF (hyponatremia) produced by the water shift out of the ICF^s. This could result in opposite effects in the two tissue types, with shrinkage of the large mass of ICF^s and expansion of the smaller but critical ICF^i. This expansion of "insulin-insensitive" cells, particularly those within the confines of the cranium, have very significant implications for the patient.

In the absence of hyperlipemia and hyperproteinemia, a deviation of the predicted hyperglycemia-induced decrease in serum sodium (1.35 to 1.6 meq/l•100 mg•dl increase in glucose) should suggest disproportions in sodium and water losses, appreciation of which is fundamental in the selection of early intravenous therapy in these patients. It is obvious that proper evaluation of any case requires integration of the findings from the history, the physical and laboratory examinations in each clinical circumstance.

Rapid correction of the hyperosmolar ECF by abruptly decreasing the glucose concentration with insulin will result in a decreased ECF osmolarity, although the relatively high ICF^i osmolarity (and glucose concentration) might still persist. Therefore, a further fluid shift from the ECF to the ICF^i would result in more swelling of the cerebral cells. These important consequences must be recognized during therapy. The immediate aim of fluid therapy should be rapid restoration of ECF volume with isotonic saline, which, by increasing renal perfusion, will itself result in renal glucose excretion. This, even in the absence of exogenous insulin, will cause a significant decrease in the blood glucose concentration. Note should, of course, be taken of the concurrent fluid and electrolyte losses in the urine. Later, hypoosmolar fluids will probably be necessary to restore the water lost by osmotic diuresis.

This outline of principles of management is applicable to patients in both the nonketotic hyperosmolar state and typical diabetic ketoacidosis. Because fat mobilization and ketosis are not prominent in the nonketotic hyperosmolar state, and because therepy might cause an excessively rapid decrease in blood glucose concentration,[8] it might be argued that this syndrome should be treated initially without insulin, or at least with smaller doses than are presently recommended. This, of course, could not be argued for the case of ketoacidosis, in which insulin suppression of fat mobilization and ketogenesis is an essential component of therapy.

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