Development of Indices for Determining Extracellular Fluid Sodium and Water Status in Acute Diabetic Ketoacidosis: Possible Tools for Clinical Audit

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The limitation of plasma sodium concentration as an indicator of extracellular hydration status in cases of acute diabetes is well recognized and could lead to individually inappropriate fluid therapy. However, in view of the small analytical and biological variations exhibited by plasma concentrations of protein, water, and sodium in health, we have developed simple laboratory indices that may better describe the extracellular environment. Preliminary data presented here for 20 patients with acute diabetic ketoacidosis admitted as emergencies to Crosshouse Hospital suggest that the type of approach we describe has the potential to supply meaningful therapeutic data to the managing physician and, therefore, merits further study in a clinical setting.

Indexing Terms: hydration status/monitoring therapy

Clinical assessment of extracellular fluid (ECF) volume, in some situations, can be highly unreliable (1–5). In diabetic ketoacidosis (DKA), estimation of the degree of dehydration is an important assessment for successful therapy (6). Overhydration during treatment represents a potentially avoidable cause of death (7), but undertreatment also carries a high mortality (6). Hematological variables can be unhelpful (8) or even misleading in the assessment of hydration state (9).

In addition, it is virtually impossible to accurately establish the degree of sodium depletion in an individual patient in DKA (10). Plasma sodium concentration indicates only the ratio of total ECF sodium to ECF volume and gives little information on the absolute values of either (3). The best choice of optimal fluid replacement therapy, in individual circumstances, remains controversial (6).

The plasma concentration of total protein in health exhibits relatively small within- and between-subject biological variations when specimens are collected with minimal stasis (11, 12). This variation may be further reduced after 30 min of supine posture (13), and current assays for total protein are generally capable of achieving their analytical goals for intralaboratory imprecision (14). Short-term changes in protein concentrations are largely due to alterations in the volume of the plasma compartment as a result of fluid shifts (e.g., in acute dehydration) rather than to changes in synthetic or catabolic rate (15, 16). Additionally, plasma sodium concentration and water content are the most tightly controlled characteristics in health and exhibit very small biological variations (11).

In view of these physiological and analytical considerations, it may be possible to develop indices that, at least in theory, allow quantitative assessment of the degree of depletion of both water and sodium from the ECF in DKA, and of the subsequent changes encountered as rehydration therapy proceeds. Our purpose in the present study, therefore, was to investigate some of the variables required for the development of such theoretical indices, and then to attempt an initial assessment of their likely value during subsequent monitoring of treatment. For this we observed the changes that took place in 20 randomly selected patients in DKA admitted as emergencies to Crosshouse Hospital.

Theory

For a given individual, the amount of protein in plasma \( n_{\text{protein}} \) is assumed to remain constant:

\[
n_{\text{protein}} = c_0 \times u_0 = c \times u.
\]

The plasma protein concentration is \( c \) \((g/L)\), \( u \) is the plasma volume \((L)\), and subscript "0" denotes the normal situation. Plasma water and interstitial water are assumed to change proportionally. Plasma volume equals mass of water, \( W \) \((kg)\), divided by mass concentration of water, \( f \) \((kg/L)\): \( u = W/f \). Therefore, in individuals who have acutely lost or gained water, the percent fraction of ECF water remaining is equal to the percent fraction of mass of water in plasma remaining, \( W/W_0 \), and equals:

\[
100 \times (u/u_0) \times (f/f_0) = 100 \times (c_0/c_0) \times (f/f_0)
\]

The amount of sodium in plasma, \( S \) \((mmol)\), equals the concentration of sodium, \( s \) \((mmol/L)\), times the plasma volume \((S = s \times u)\). Changes in ECF sodium status are similarly assumed to be proportional to changes in plasma sodium status. Hence, when both the amount of water and sodium in the ECF have changed,

\[
\% (S/S_0) = 100 \times (s/s_0) \times (u/u_0) = 100 \times (c_0/c_0) \times (s/c)
\]

The constant terms \( 100 \times (c_0/f_0) \) and \( 100 \times (c_0/s_0) \) can be assigned values derived from the mean results of normal population studies; thus, ECF water and sodium status may be calculated from the relatively simple measurements of \((f/c)\) and \((s/c)\), respectively.
Subjects and Methods

A series of plasma samples was obtained from each of 20 insulin-dependent diabetic patients admitted in DKA as emergencies to Crosshouse Hospital. They comprised 10 males and 10 females, ages 6–77 years. Plasma glucose was determined with a YSI Model 23 AM Glucose Analyzer (Yellow Springs Instrument Co., Yellow Springs, OH). Plasma sodium (by indirect ion-selective electrodes), total protein (biuret method), albumin (bromcresol green), and bicarbonate (phosphoenolpyruvate carboxylase) were measured on a Hitachi 717 analyzer (Hitachi, Tokyo, Japan). Total plasma lipid was determined colorimetrically (17), and plasma water was calculated from Waugh’s formula (18), as described recently (19, 20). Admission samples were tested for ketones with Ketostix (Miles Labs., Slough, UK).

In addition, to assign values to the constant terms 100 × (c/c0) and 100 × (c/s0) above, we collected 10 mL of venous blood from each of 21 healthy laboratory staff, ages 25–50 (mean 36) years, 11 men and 10 women. These healthy, ambulant subjects were fasted overnight and were seated just before collection of the first 10-mL blood specimen, which was taken without tourniquet between 0900 and 0930. Subjects then assumed a recumbent position, which they maintained for 30 min before collection of a second specimen. All plasma samples were obtained without delay, by centrifugation, and then stored frozen until subsequent single-batch analyses for each of the test analytes (21).

To afford some assessment of the equivalence of the constant terms determined from a healthy population with those from diabetic patients in stable metabolic control, we also obtained blood samples from each of 18 insulin-dependent diabetics who attended the diabetic outpatient clinic: 6 men and 12 women, ages 25–47 (mean 34) years. Each was ambulant and then seated before blood was collected into heparin-containing tubes. This time, because of the significant effect of posture on ECF fluid distribution (21), subsequent calculations of the constant terms in these stable, diabetic individuals were compared with the values obtained from the healthy population in upright posture. Similarly, the values for the constant terms to be applied to the acute diabetic patients admitted as emergencies were based on the mean plasma results obtained from the healthy subjects in the recumbent posture.

Results

On admission, the plasma glucose results for all 20 acutely admitted diabetic patients ranged from 24.9 to 78.1 mmol/L (mean 39.9). Each had strongly positive reactions for ketones. Plasma bicarbonate ranged from 4 to 13 mmol/L (mean 7), and plasma sodium ranged from 121 to 139 mmol/L (mean 131). Plasma total protein progressively decreased from a mean (SEM) of 84.6 (1.3) g/L at admission to 64.8 (1.7) g/L at an average of 12 h (range 8–15) later. Similarly, over the same period, plasma albumin decreased from 53.2 (1.0) to 40.5 (1.3) g/L, and calculated plasma water increased from 0.915 (0.0013) to 0.937 (0.0014) kg/L. The total protein/albumin ratio showed no significant difference between the two time periods (by paired t-test).

For the 21 healthy volunteers, mean (SEM) results in recumbent posture were: sodium 139.3 (0.37) mmol/L, total protein 70 (0.9) g/L, total lipid 7.9 (0.37) g/L, and plasma water 0.932 (0.0008) kg/L. The results obtained in upright posture were: sodium 139.6 (0.36) mmol/L, total protein 76 (0.8) g/L, total lipid 8.5 (0.40) g/L, and plasma water 0.927 (0.0008) kg/L.

For the 18 stable diabetic outpatients, mean (SEM) plasma glucose was 11.3 (1.1) mmol/L with an absolute range of 4.0–19.7 mmol/L. The other results were sodium 139.1 (0.54) mmol/L, total protein 74 (0.7) g/L, total lipid 9.4 (0.5) g/L, and plasma water 0.927 (0.0009) kg/L.

Statistical comparison by F-test of the variances for the constant terms between the healthy population in upright posture and the diabetic clinic patients revealed no significant difference. Similarly, there was no significant difference between the mean values for the two groups, for either of the constant terms, by unpaired t-tests.

The final expressions adopted, which we applied to our DKA patients, were: percent of normal ECF water, % (W/W0) = 7500 × f/c; and percent of normal ECF sodium, % (S/S0) = 50 × s/c, where f, c, and s are plasma water, total protein, and sodium concentrations, respectively. For each index, these yielded means of 100% and all-subject total standard deviations of 6%.

The values for % (W/W0) and % (S/S0) for all 20 acute diabetic patients are plotted against time after admission (Fig. 1). These preliminary findings suggest that by 24 h after admission, about one-fourth of the patients could be significantly overhydrated, when compared with the range of values obtained from a healthy population in recumbent posture.

For individual cases in clinical practice, the data obtained from these indices can be presented in a variety of ways. Any graphical representation, however, should reflect the dynamic quality of the data. For one of the 20 patients admitted in DKA, Fig. 2 illustrates results of the estimates of ECF sodium and water and of measured plasma sodium concentration plotted against time since admission. Fig. 2 also indicates the limitations of reliance on plasma sodium concentration alone to assess ECF status.

Another way of presenting these data is to plot % (S/S0) vs % (W/W0) as shown in Fig. 3 for the same patient. In this format, the dynamic nature is illustrated by connecting the points from consecutive time sequences, and is similar to the recently described C-plot of Carpenter (22).

Discussion

The indices we have described give no indication of the fluid status of the intracellular environment. However, for these measurements to accurately reflect the extracellular environment, it is essential that the blood-
collection procedures in future clinical studies be rigidly standardized to take account of the effects of posture (21), venestasis, and type of blood specimen. In addition, any specimen contamination from intravenous infusion fluid must be avoided (23).

Plasma water concentration, $f_w$, reportedly exhibits a negligibly small between-subject biological variation in health (11, 24). One quoted value for $f_w$ in plasma is 0.933 kg/L (25), the residual volume being occupied by lipid and protein. This quantity may be determined (e.g.) by Waugh's formula (18–20) or by gravimetry (26), but not by osmometry (20). The plasma sodium concentration, $s_w$, like plasma water, is among the most tightly controlled variables in health.

During quiescent periods, the mean plasma concentration of total protein, or any other candidate protein molecule, in stable diabetics should not be significantly different from that for a healthy population. For total protein this condition is generally met (27). However, it is inappropriate in, e.g., children younger than 6 years (28), or in subjects with preexisting situations that are likely to affect the underlying plasma protein concentration—such as acute blood loss, nephrotic syndrome, severe liver disease, malnutrition, protein-losing enteropathy, hyper- and hypogammaglobulinemia, or myeloma.

Clearly, our approach is based on some major assumptions. Foremost is that changes in plasma water are reflected throughout the ECF. No account is taken of the Gibbs–Donnan distribution of sodium molalities between plasma and interstitial fluid (29, 30). In the absence of available data, we must assume that the effects of this distribution are unimportant to any relative changes observed in these indices as rehydration therapy proceeds. Moreover, short-term changes in protein concentration should be due entirely to fluid shifts into and out of the vascular compartment, not to movement of protein itself. Increases in the transcapillary escape rate of albumin have been carefully observed in patients with septic shock or after cardiac surgery (31). Simi-

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**Fig. 1.** Change in estimate of percent of normal ECF water remaining, %W/Wo (top) and of percent of normal ECF sodium remaining, %S/So (bottom), with time after admission, for 20 patients admitted in diabetic ketoacidosis.
trusive indices described here might yield in terms of improving the outcome in particular individuals, the way is open for a careful and wide-ranging audit of this approach in a properly controlled clinical, rather than laboratory, setting.

References
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In conclusion, we note that the validity of these proposed indices of ECF status are practically impossible to verify in a preliminary study. Improved methods of illustrating acute changes in ECF status are needed that are practical and applicable to individual patients (22). In view of the potential benefit that the simple, non-

daughter, in studies involving a euglycemic glucose clamp, intravenous infusion of insulin may also result in modest increases in this escape rate (32). However, we argue that the consistency with which the total protein/albunmin ratio was maintained during treatment in each of the 20 patients admitted as emergencies in DKA suggests that changing plasma protein concentrations do indeed reflect changes in ECF fluid status.

Fig. 2. Example of the changes in ECF sodium, ECF water, and plasma sodium concentration with time after admission for one of the patients admitted in diabetic ketoacidosis.

Fig. 3. Example of the change in ECF sodium with ECF water for the same patient as in Fig. 2.