EVALUATION OF HYDRATION STATUS OF PATIENTS WITH HYPERGLYCEMIA

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ABSTRACT

Background: Acute hyperglycemia increases serum osmolality which leads to a rapid decline in serum sodium levels. Consequently, assessment of hydration status in individuals with hyperglycemia remains difficult. The goal of this study was to compare common equations that estimate osmolality to measured serum osmolality in patients hospitalized with hyperglycemia.

Methods: In this cross-sectional study, data was collected from adult patients with serum glucose levels greater than 200 mg/dL. Serum osmolality was measured directly and compared to osmolality estimates using the Dorwart equation and the Rasouli equation. Sodium correction factors for hyperglycemia of 1.6 and 2.4 were also utilized for each equation, yielding six total equations. Patients greater than 18 years of age with measured serum osmolality $\geq$ 295 mOsm/L were included in the analysis. Regression analysis was performed in order to determine the best equation to predict hydration status of patients with hyperglycemia.

Results: A total of 195 hospitalized adults with hyperglycemia were evaluated for inclusion in the study. Twelve of 195 hyperglycemic patients had normal hydration (serum osmolality 280-294 mOsm/L), and thus were excluded from the analysis. Among the equations utilized, the Rasouli equation utilizing a sodium correction factor of 2.4 was the most accurate predictor of dehydration, correctly identifying 94% of those patients.

Conclusions: The two commonly used equations to estimate osmolality consistently underestimated the actual measured osmolality level of patients with hyperglycemia. The Rasouli equation utilizing a sodium correction factor of 2.4 was the most accurate equation for predicting measured osmolality; however, it still tended to underestimate osmolality. In order to determine the hydration status of patients with hyperglycemia rapidly, we recommend direct measurement of serum osmolality.

KEY WORDS: Hyperglycemia, Osmolality, Sodium, Hyponatremia

INTRODUCTION

According to the American Diabetes Association, "Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two most serious acute complications of diabetes."[1] The incidence of HHS has been estimated to be less than 1 case per 1000 patient years

of diabetes, while DKA is more commonly seen at approximately 2 cases per 100 patient years.[2,3] Since the development of guidelines for the management of these disorders, which includes early administration of intravenous (IV) fluids, the mortality rates have decreased to approximately 2% per episode of DKA and 10 – 20% per episode of HHS.[1-3] While these conditions are relatively rare, it is important for clinicians to recognize and treat them early in order to decrease the mortality associated with them.

Patients that present with hyperglycemic crises will often have associated hyponatremia. Because of this low sodium level, the calculated osmolality, provided as part of routine chemistry panels, underestimates the true level of dehydration of these patients. Early research of this topic demonstrated that for every 100 mg/dL increase in serum glucose above 100 mg/dL, the serum sodium level should decrease by 2.8 mEq/L.[4] In 1973, however, it was determined that movement of water out of cells ceased before normal extracellular osmolality was restored, leading to equilibrium in both the intracellular and extracellular spaces.[5] This discovery suggested the serum sodium correction factor of 2.8 mEq/L should in fact be changed to 1.6 mEq/L.[5] Since this discovery, clinicians have used the correction factor of 1.6 mEq/L to estimate the corrected serum sodium in patients with hyperglycemia. To further confuse clinicians, Hillier and colleagues studied the response of serum sodium to an acute hyperglycemic episode in 6 healthy volunteers.[4] The results of this study suggested the correction factor of 1.6 mEq/L only held true when serum glucose levels were less than 400 mg/dL. When the serum glucose was greater than 400 mg/dL, it was suggested to utilize a correction factor of 4 mEq/L. Overall, the authors concluded in patients with hyperglycemia, for every 100 mg/dL increase in serum glucose above 100 mg/dL, the serum sodium level should decrease by 2.4 mEq/L.

While sodium is the major ion that maintains the serum osmolality, increasing levels of glucose can alter this significantly.[6] The relationship between serum sodium, glucose and osmolality is more complex than that previously described. Changes induced by hyperglycemia can be described in three phases. In the initial, acute phase, hyperglycemia induces increased serum osmolality, leading to water movement from the intracellular to extracellular compartment.[6] During this phase, patients experience the rapid reduction in serum sodium levels described by Hillier and colleagues.[4,6] In the second, diuretic phase, patients experience an osmotic diuresis, often leading to dehydration. This diuretic phase complicates the relationship between serum glucose and serum sodium and the degree of hydration may make serum sodium estimation inaccurate. In the third, equilibrium phase, patients develop balance between intracellular and extracellular compartments as the body attempts to minimize the effect of salt and water loss. As a result, dehydration ensues unless enough water and salt, to replace these losses, are consumed. Serum sodium and other electrolytes may be decreased, normal, or elevated, as described above. Therefore, serum sodium and calculated serum osmolality may not be good indicators of the patient's hydration status.

The goal of this study was to compare two commonly used equations to calculate osmolality to the actual measured serum osmolality in patients hospitalized with hyperglycemia, in order to evaluate their true hydration status.

MATERIALS

This was an Institutional Review Board approved cross-sectional study at an 881-bed regional referral hospital in Huntsville, Alabama, USA. Data was collected from patients, aged 19 years or greater, who presented with serum glucose levels greater than 200 mg/dL. Serum osmolality was measured directly and compared to osmolality estimates using the Dorwart and Chalmers (Equation 1) and the Rasouli and Kalantari (Equation 2) equations.[7,8] Additionally, sodium correction factors of 1.6 (Equation 1a and 2a) and 2.4 (Equation 1b and 2b) for hyperglycemia were also utilized for each equation, yielding a total of six equations that were compared to the measured osmolality, Table 1. Patients with a measured serum osmolality greater than or equal to 295 mOsm/L were included in the analysis. Regression analysis was performed in order to determine the best possible linear equation to predict hydration status of patients with hyperglycemia in our population. All statistical analyses were performed using SPSS version 15.[9]

RESULTS

In this study, 195 consecutive hospitalized adult hyperglycemic patients admitted to our institution with a blood glucose greater than 200 mg/dL were evaluated for inclusion in the study. Twelve of 195 hyperglycemic patients had normal hydration (serum osmolality 280-294

mOsm/L), and thus were excluded, leaving a total of 183 patients available for analysis. For our population, the average age was 51 years (19 – 93 years), average serum glucose level was 466 mg/dL (209 – 1602 mg/dL), average sodium level was 134 mEq/L (109 – 161 mEq/L), and average blood urea nitrogen was 29 mg/dL (30 – 126 mg/dL). Approximately half the patients had a glucose level greater than 400 mg/dL. Males accounted for 56% of the sample.

Comparison of calculated osmolality to measured osmolality was accomplished utilizing six equations, and a new equation derived from this data, Tables 2 and 3. In our population, the measured osmolality ranged from 296 to 417 mOsm/L, with a mean ± SD of 319 ± 22.00 mOsm/L. Equations 1, 1a, 1b, 2, and 2a were all significantly lower than the actual measured osmolality with a mean osmolal gap ranging from 4.88 ± 14.10 mOsm/L to 25.44 ± 14.12 mOsm/L, $p < 0.0001$. Equation 2b was the closest to the actual measured osmolality with a mean osmolal gap of -0.68 ± 15.35 mOs/L, $p = 0.55$. Regression analysis conducted to determine a new equation where no gap would be seen in the mean value of calculated and measured osmolality rendered Equation 3. This equation gave a mean osmolal gap of 0 ± 13.67 mOsm/L.

When assessing the ability of the selected equations to predict the dehydration of patients, Equation 1 performed the worst, Table 4. This equation was only able to accurately predict 40% of patients who were dehydrated, with the largest error coming in those patients who were less severely dehydrated. In patients with measured osmolality levels ranging from 296 to 310 mOsm/L, Equation 1

accurately predicted 8% of patients as being dehydrated. Equation 2b performed the best of the six selected equations, accurately predicted 94% of patients who were dehydrated, though at the lower severity level of 296 to 310 mOsm/L, it lost precision, accurately predicting 87% of patients. Equation 3, derived from this study, performed the best, accurately predicting 96% of patients who were dehydrated, though it too lost precision at an osmolality level of 296 to 310 mOsm/L, accurately predicting 91% of patients.

DISCUSSION

Among patients who present to institutions with hyperglycemia or hyperglycemic crises, assessment and improvement of hydration status is the most crucial step in improving their outcomes. Early and adequate rehydration is the first step in the treatment of these deadly conditions. In addition to the clinical assessment of these patients, it is important to have a tool which can provide quick determination of level of dehydration, in order to select appropriate rehydration techniques. The equations used by institutions and individuals to calculate the osmolality of patients who are hyperglycemic are less than adequate.

Dorwart and Chalmers derived an equation for calculating osmolality in 1975, Equation 1.[7] This equation, which is still used today at our institution, was determined through the use of 715 blood samples. In their methods and evaluation of the study, the authors failed to note glucose levels in the population. Therefore it is unclear whether patients with hyperglycemia were actually included in the derivation of the equation.

Given the standard deviation of 6 mOsm/L between this equation and the measured osmolality, it is unlikely that many patients had greatly elevated glucose levels.

In 2005, Rasouli and Kalantari derived a different equation to calculate osmolality on 210 blood samples.[8] In this study, the authors noted that only 15 patients with diabetes (defined as a blood glucose greater than 140 mg/dL) were included, though actual glucose values were not disclosed. This equation calculated a standard deviation of 15.2 mOsm/L from the measured osmolality, more closely resembling the standard deviations exhibited in the present study. However, without having a large population of patients with hyperglycemia in their trial, support for its use in this population cannot be offered.

The argument can be made however, that in patients with hyperglycemia, glucose will cause a shift of water from the intracellular to the extracellular fluid, leading to a decline in sodium levels; therefore, a correction factor needs to be utilized to reveal the true sodium. Once the true sodium is revealed, it can be utilized in the afore mentioned equations in order to determine the true osmolality. In 1973, Katz published a column in The New England Journal of Medicine, where he used a hypothetical patient model to derive a correction factor of 1.6 for sodium in light of hyperglycemia.[5] Though this hypothetical correction factor is widely used, there is little clinical support for its use.[4] Therefore, in 1999 Hillier and colleagues decided to test this sodium correction factor in six healthy individuals in whom acute hyperglycemia was induced. Through this experiment, a new sodium correction factor of 2.4 was

derived. While the investigators had good intentions, the acute induction of hyperglycemia in otherwise healthy patients may not in fact mimic the general population of patients with diabetes who may have hyperglycemia for varying lengths of time before actually seeking medical intervention. Thus, this study is lacking in external validity.

Our study demonstrated that the equations derived by Dorwart and Chalmers and Rasouli and Kalantari, are less than ideal in this population of patients with hyperglycemia. The Dorwart and Chalmers equation had an osmolal gap of 25.44 ± 14.12 mOsm/L and an overall ability to predict dehydration of only 40%. When the sodium correction factors of 1.6 and 2.4 were used, this equation could predict dehydration only 75% of the time. Though the Rasouli and Kalantari equation performed slightly better, demonstrating an osmolal gap of 15.99 ± 14.16, it too could predict dehydration only 74% of the time. Not until a sodium correction factor of 2.4 was used in this equation was it able to perform at a level that was not significantly different from the measured osmolality, though the standard deviation was 15.35 mOsm/L.

Through regression analysis we were able to derive a new equation (Equation 3) for the calculation of osmolality in patients with hyperglycemia. While our equation was able to eliminate any osmolal gap, it still had a standard deviation of 13.67 mOsm/L. The standard deviation of the osmolal gaps ranged from $13.67 - 15.35$ mOsm/L. This suggests that a linear formula using sodium, glucose, and BUN is not likely not capable to make better predictions of osmolality in patients with hyperglycemia. In a clinical setting, rather than a controlled experimental setting, a number of confounding variables could have contributed to this increased osmolal gap. The most common variable for an increased gap in our patients, that was not controlled, would have been ethanol intoxication.

Equation 3 is a good match mathematically, but because it was designed based on our data set, it may not be accurate in other settings. The important thing to consider is that it sets a standard for how good an equation of its nature can be for predicting osmolality. All the formulas had large osmolal gaps so in order to accurately determine the level of dehydration for patients with hyperglycemia, we recommend directly measuring serum osmolality

This study is not without limitations. As mentioned we did not control for other variables which could increase the osmolal gap such as ethanol, methanol, ethylene glycol, and mannitol, to name a few. In addition, Equation 3 was built using linear regression of our limited dataset and may not be useful in other settings. Finally, the study only considered hyperglycemic patients, thus its utilization in other populations may not be as effective as the others.

CONCLUSION

Hyperglycemia leads to a state of dehydration through the loss of free water from osmotic diuresis. In hyperglycemic patients, the level of dehydration can oftentimes be overlooked by clinicians because the current formulas to predict serum osmolality underestimate actual serum osmolality. Since ordering measured serum osmolality is an uncommon practice, important information to evaluate free water

requirements and to choose appropriate intravenous fluids may be missed. This study demonstrates the clear inadequacies of two commonly used equations to estimate osmolality and therefore assess the degree of dehydration in patients with hyperglycemia. Additionally, the study shows that no linear formula using just sodium, glucose, and BUN are likely to be more accurate. In order to truly determine the hydration status of patients with hyperglycemia we recommend direct measurement of osmolality **(Table 1,2,3,4).**

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Table 1- Equations used to calculate serum osmolality

Equation 1[7]:   Osmolality = $1.86[Na^+]$ + (glucose/18) + (BUN/2.8) + 9

Equation 1a: Osmolality = Equation 1 using a correction factor of 1.6 for the sodium

Equation 1b: Osmolality = Equation 1 using a correction factor of 2.4 for the sodium

Equation 2[8]:   Osmolality = $1.897[Na^+]$ + (glucose/18) + (BUN/2.8) + 13.5

Equation 2a: Osmolality = Equation 2 using a correction factor of 1.6 for the sodium

Equation 2b: Osmolality = Equation 2 using a correction factor of 2.4 for the sodium

Equation 3:   Osmolality = $1.898[Na^+]$ + 0.071[glucose] + 0.362[BUN] + 21.92

Table 2- Measured and calculated serum osmolality values (n = 183)

	Minimum Level (mOsm/L)	Maximum Level (mOsm/L)	Mean Level (mOsm/L)	Standard Deviation
MOsm	296	417	319	22.00
$cOsm_1$	266	356	294	15.04
$cOsm_{1a}$	271	385	305	19.44
$cOsm_{1b}$	274	408	310	22.11
$cOsm_2$	275	366	303	15.15
$cOsm_{2a}$	280	395	315	19.56
$cOsm_{2b}$	289	418	320	22.28
$cOsm_3$	288	385	319	17.24

MOsm =   Measured serum osmolality

$cOsm_1$ =   Calculated osmolality using Equation 1

$cOsm_{1a}$ =   Calculated osmolality using Equation 1a

$cOsm_{1b}$ =   Calculated osmolality using Equation 1b

$cOsm_2$ =   Calculated osmolality using Equation 2

$cOsm_{2a}$ =   Calculated osmolality using Equation 2a

$cOsm_{2b}$ =   Calculated osmolality using Equation 2b

$cOsm_3$ =   Calculated osmolality using Equation 3

Table 3- Osmolal gaps for the study population (n = 183)

	Minimum	**Maximum**	**Mean**	**Standard deviation**	**p**
MOsm – cOsm$_1$	6.70	111.39	25.44	14.12	< 0.0001
MOsm – cOsm$_{1a}$	-5.40	98.30	14.54	14.10	< 0.0001
MOsm – cOsm$_{1b}$	-26.61	91.75	9.09	15.32	< 0.0001
MOsm – cOsm$_2$	-2.76	101.83	15.99	14.16	< 0.0001
MOsm – cOsm$_{2a}$	-15.21	88.47	4.88	14.10	< 0.0001
MOsm – cOsm$_{2b}$	-36.92	81.79	-0.68	15.35	0.55
MOsm – cOsm$_3$	-18.08	84.66	0	13.67	N/A

MOsm =   Measured serum osmolality

cOsm$_1$ =   Calculated osmolality using Equation 1

cOsm$_{1a}$ =   Calculated osmolality using Equation 1a

cOsm$_{1b}$ =   Calculated osmolality using Equation 1b

cOsm$_2$ =   Calculated osmolality using Equation 2

cOsm$_{2a}$ =   Calculated osmolality using Equation 2a

cOsm$_{2b}$ =   Calculated osmolality using Equation 2b

cOsm$_3$ =   Calculated osmolality using Equation 3

Table 4- Percentage of patients with accurately diagnosed levels of dehydration based on various equations to estimate osmolality

MOsm (mOsm/L)	n	$cOsm_1$	$cOsm_{1a}$	$cOsm_{1b}$	$cOsm_2$	$cOsm_{2a}$	$cOsm_{2b}$	$cOsm_3$
296-310	79	8	38	52	56	81	87	91
311-325	60	50	85	90	85	95	100	100
326-340	17	94	100	100	94	100	100	100
>340	27	78	90	93	89	96	100	100
Total	183	40	67	75	74	90	94	96

MOsm =   Measured Osmolality

$cOsm_1$ =   Calculated osmolality using Equation 1

$cOsm_{1a}$ =   Calculated osmolality using Equation 1a

$cOsm_{1b}$ =   Calculated osmolality using Equation 1b

$cOsm_2$ =   Calculated osmolality using Equation 2

$cOsm_{2a}$ =   Calculated osmolality using Equation 2a

$cOsm_{2b}$ =   Calculated osmolality using Equation 2b

$cOsm_3$ =   Calculated osmolality using Equation 3