Table	1. Percer	itage of	Patie	nts' U	lrine	Samples	Giving
	Higher	Values	than t	the Cu	utoff	Values*	

	Glucose	Mannose	Galactose
Liver cancer	25	50	25
Pancreatic cancer	33	33	0
Breast cancer	0	11	0
Esophageal cancer	0	40	0
Rectal cancer	0	11	0
Stomach cancer	0	33	0
Lung cancer	14	14	0
Healthy subjects	10	25	10
* The cutoff values we	re 6582, 326, a	nd 103 μ mol of	sugar (glucose,

mannose, and galactose, respectively) per gram of creatinine.

tected by this method agreed with those analyzed by the conventional glucokinase method (16). We also found high mannose concentrations in some samples; because concentrations of serum mannose are correlated to candidiasis (17), measurement of urinary mannose might give useful information.

In conclusion, our method is useful because fucose and other sugars in crude urine samples can be assayed simultaneously at the picomole level, without any cleanup procedure before labeling. Our results suggest that this method could be of use in studies of the relationship between sugars in urine and diseases, including diseases that develop because of an error in the metabolism of sugars.

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Excess Osmolal Gap in Diabetic Ketoacidosis Explained

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Even in the absence of detectable ethanol or visible lipemia, a large plasma osmolal gap is the usual finding in cases of diabetic ketoacidosis. This gap decreases to an insignificant value within 20 h of treatment. Detailed biochemical analysis of six cases showed that, on average, the gap could be almost wholly accounted for by an increase in acetone, a decrease in the plasma water fraction, and smaller increments in amino acids and glycerol. Calculated plasma osmolality can seriously underestimate the true value in diabetic ketoacidosis, and so some previously observed anomalies may be explained.

Additional Keyphrases: acetone · plasma water

Bhagat et al. (1) reported that, in patients admitted in diabetic ketoacidosis (DKA), the mean plasma osmolal gap in samples taken within 2 h of admission was 14.5 mmol/kg higher than the mean acetone concentration. However, for samples taken up to 12 h after admission, the mean osmolal gap and the mean plasma acetone concentration had become comparable (1). They further observed that, when plasma osmolality was calculated

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from sodium results obtained by direct potentiometry in samples taken within 2 h of admission, the mean unexplained gap was greatly decreased.

Various formulas have been derived to permit calculation of osmolality and are often based on comparisons with measured values (2). A formula derived from a population of samples with an average normal plasma water content of 0.933 kg/L (3) may no longer be valid in situations where plasma water content is not a constant. If C is the value for calculated osmolality, then the revised value for osmolality (R) is $R = (C \times 0.933 + U)/f$, where U is the sum of the concentrations of additional, unmeasured, net-uncharged substances having an osmotic coefficient of unity, and f is the plasma water fraction in kg/L. This equation predicts that calculation of C will tend to underestimate the true osmolality, not only in situations where there is an increase in U, but also if there is a decrease in f. The purpose of the present study was to test this hypothesis by observing the results obtained in patients admitted in DKA.

Patients and Methods

A series of plasma samples were obtained from each of six insulin-dependent diabetic patients, admitted in DKA as emergencies to Crosshouse Hospital. The two males and four females, age 12–76 years, all were treated initially with intravenous saline and insulin.

Sodium, potassium, urea, bicarbonate, and total protein were measured with an Astra 8 analyzer (Beckman Instruments Inc., Brea, CA) or a Hitachi 717 analyzer (Hitachi Ltd., Tokyo, Japan). Osmolality was measured by freezing-point depression with an Advanced Digimatic Osmometer (Model 3D II; Advanced Instruments Inc., Needham, MA). Glucose was determined with a YSI Model 23 AM Glucose Analyzer (Yellow Springs Instrument Co., Inc., Yellow Springs, OH). Acetone (4), total amino acids (5), free glycerol (6), and total plasma lipid (7) were determined colorimetrically. Lactate was assayed by an enzymatic ultraviolet technique (8) and ethanol by an enzymatic commercial kit method (Bio-Mérieux, Marcy-L'Etoile, France).

Calculated plasma osmolality, C (mmol/kg), was determined for all samples from the sodium, potassium, urea, and glucose measurements, expressed in mmol/L, and by applying the formula of Bhagat et al. (2):

$$C = 1.89Na + 1.38K + 1.03urea + 1.08glucose + 7.45$$

The plasma water fraction, f (kg/L), was calculated from measurements of total protein, P (g/L), and total lipids, L (g/L), with Waugh's formula (9):

f=(991-1.03L-0.73P)/1000

Results and Discussion

On admission, the plasma glucose results for all six patients ranged from 21.6 to 40.3 mmol/L. Each had strongly positive reactions for ketones with Ketostix™ (Miles Labs. Ltd., Slough, U.K.). [Note that Ketostix do not react with acetone itself.] Plasma bicarbonate ranged from 3 to 8 mmol/L. Mean plasma sodium concentration was 133 mmol/L. (range 129 to 139). Plasma ethanol was undetectable in all six admission specimens. None exhibited visible lipemia, and no patient was identified as having a lactic acidosis.

The resulting changes in plasma water with time after admission are shown in Figure 1 and illustrate that, in a single patient, the fraction could change from extremes of 0.899 on admission to 0.943 at 29 h afterwards. In such a case, for a plasma sodium equivalent to 140 mmol/L at a normal plasma water content of 0.933 kg/L, indirect potentiometric methods would yield an apparent sodium concentration of $140 \times 0.899/0.933 =$ 135 mmol/L, i.e., an underestimate of 5 mmol/L, on admission, due to the relative increase in protein and lipid concentrations as a result of fluid depletion. Thus subsequent osmolality coloulations will be erroneously low. This large-molecule effect on sodium and potassium concentration measurements has been shown to be greatly minimized when direct potentiometric methods are used (10, 11), and thus would contribute little to the negative error in calculated osmolality, as was observed by Bhagat et al. (1),

A summary of these findings (Table 1) shows that the values for apparently unexplained osmolal gap are similar to those reported by Bhagat et al. (1). However, taking into consideration the slight increment in amino acids and the significant decrease in plasma water fraction in these patients at admission, one finds that the revised calculation of complainty (R) accounts for all of the measured osmolality (M). Therefore, calculations of osmolality must be modified to include consideration of plasma water content in situations where this content is likely to deviate significantly from normal. This study illustrates the firsthat, in DKA, calculated

This study illustrates the firsthat, in DKA, calculated plasma osmolality can earlier underestimate the true value. This may perhaps explain the observation that coma in DKA is found at apparently lower osmolalities (calculated values) than in nonketotic patients (12).

Failure to take into account the effect of changes in plasma water fraction on the relationship between mo-



Fig. 1. Change in plasma water fraction (f) with time after admission in six patients

Table	1.	Changes	in	Compon	ents	of	Osmolal	Gap	in
Six Patients with DKA									

	Time post-admission, h				
	0-2	5-12			
Total protein, g/L	88 (2)*	73 (4)			
Total lipids, g/L	12 (3)	9 (2)			
Plasma water (f), kg/L	0.914 (0.003)	0.929 (0.007)			
Acetone (A), mmol/L	8.1 (0.7)	7.2 (1.0)			
Amino acids, mmol/L	4.0 (0.4)	2.8 (0.2)			
Giycerol, mmol/L	0.3 (0.05)	0.1 (0.05)			
Total (U), mmol/L	12.4 (0.6)	10.1 (0.9)			
Osmolality, mmol/kg					
Measured (M)	329.5 (7.5)	311.0 (7.4)			
Calculated ^b (C)	309.5 (5.2)	300.0 (5.9)			
Osmolal gap	20.0 (3.8)	11.0 (3.2)			
Apparent unexplained gap $[M - (C + A)]$	11.9 (3.6)	3.8 (2.7)			
R°	329.6 (5.9)	312.2 (6.4)			
New gap (M - R)	-0.1 (3.5)	-1.2 (2.3)			
Mean (and SEM).					

^bOsmolality calculated from formula of Bhagat et al. (1).

°(C × 0:933 + U)/f.

lality and molarity of plasma constituents, even in the absence of visible lipemia, may lead to misconceptions in the interpretation of the pathophysiological consequences of DKA. For example, a recent report (13) has suggested that increases in plasma glucose concentration in DKA may provide an osmotic stimulus to arginine vasopressin (AVP) secretion. The plasma sodium concentration at which AVP secretion was completely suppressed was decreased from about 140 mmol/L to 128 mmol/L. The present study would suggest that consideration of sodium molality, in relation to AVP secretion, might eliminate the apparently divergent responses observed.

Katz has argued (14) that the principal cause of the hyponatremia in DKA at admission is a shift of intracellular water to the extracellular space during hyperglycemia and that dilution by this water results in a decrease in the concentration of plasma sodium. This decrease, in cases of DKA with volume depletion, is reportedly as much as $0.36 \text{ mmol/L per 1 mmol/L supra$ normal increase in plasma glucose (15). Notwithstanding these arguments, I have shown here that a significant proportion of the apparent decrease in observedsodium concentration at admission is probably attributable to a decrease in plasma water fraction. Regressionof observed plasma sodium vs glucose in spontaneoushyperglycemic states does, in fact, produce a poor correlation (16).

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