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Evaluation of 36 formulas for calculating plasma osmolality

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Abstract *Purpose:* Measuring or calculating plasma osmolality is of interest in critical care medicine. Moreover, the osmolal gap (i.e. the difference between the measured and calculated osmolality) helps in the differentiation of metabolic acidosis. A variety of formulas for calculating osmolality have been published, most of them relying on sodium, urea and glucose. A novel formula developed by Zander has recently been published, which also takes into account the effects of potassium, chloride, lactate and bicarbonate on osmolality. We evaluate the previously published formulas including the novel formula by comparing calculated and measured osmolality. *Methods:* Arterial or venous blood samples from 41 outpatients and 195 acutely ill inpatients (total 236 subjects) were used to compare measured osmolality with calculated osmolality as obtained from 36 published formulas including the new formula. The performance of the formulas was statistically evaluated using the method of Bland and Altman. *Results:* Mean differences up to 35 mosmol/kg H_2O were observed between measured and calculated osmolality using the previously published formulas. In contrast, the novel formula had a negligible mean difference of 0.5 mosmol/kg H_2O. The novel formula also had the closest 95 % limits of agreement ranging from −6.5 to 7.5 mosmol/kg H_2O. *Conclusion:* Only 4 out of the 36 evaluated formulas gave mean differences between measured and calculated osmolality of less than 1 mosmol/kg H_2O. Zander's novel formula showed excellent concordance with measured osmolality and facilitates a more precise diagnosis based on blood gas analysers. The new equation has the potential to replace separate measurements of osmolality in many cases.

Keywords Calculated osmolality · Measured osmolality · Point-of-care · Blood gas analysis · Critical care

Introduction

Osmolality is a measure of solute concentration, defined as the number of osmotically active particles (osmoles) per kilogram of water [1]. Osmolality of human plasma is tightly regulated and averages at 288 ± 5 mosmol/kg H_2O [2]. Serum or plasma osmolality can be measured by freezing point depression or, as is done in clinical routine, can be calculated using formulas including the common osmotically active constituents of serum/plasma (sodium, chloride, glucose and urea) [3]. A difference between measured and calculated osmolality exceeding 5 mosmol/kg H_2O is commonly referred to as the "osmolal gap", indicating the presence of unmeasured osmotically active

compounds (e.g. methanol, ethylene glycol, isopropyl alcohol, propylene glycol, mannitol etc.), thus guiding clinical diagnosis and therapy [4, 5].

Most of the published formulas are based on sodium, urea and glucose (see Table 1). A novel formula developed by Zander has recently been published. The formula is based on all the components contributing to osmolality (i.e. sodium, potassium, chloride, glucose, urea, lactate and bicarbonate; the development of Zander's formula is described in the appendix) [6]. In this study we evaluated this novel formula and the previously published formulas by comparing calculated and measured osmolality.

Methods

Study population

The study was prospective and observational in nature. Patients under the age of 17 years were excluded. No additional interventions were undertaken and the analysis was performed on anonymized left-over samples obtained during clinical routine. The local ethics committee confirmed in writing that due to the nature of the study ethics approval did not have to be sought. A patient mix was chosen to reflect the clinical areas where measuring serum osmolality is of the greatest clinical relevance.

Table 1 Overview of the equations for the calculation of osmolality. For each formula the units for the plasma constituents are millimoles per litre.

Number	Formula	References
1	$1.75 \times Na^+ + glucose + 0.5 \times urea + 10.1$	[9]
2	$2.63 \times Na^+ - 65.4$	[9]
3	$1.86 \times Na^+ + glucose + 0.5 \times urea$	[10]
4	$2 \times (Na^+ + K^+) + glucose + 0.5 \times urea$	[11]
5	$1.85 \times Na^+ + 1.84 \times K^+ + 1.15 \times iCa + 1.17 \times Mg^{++} + glucose + 0.5 \times urea$	[12]
6	$2 \times Na^+$	[13]
7	$2 \times Na^+ + glucose + 0.5 \times urea$	[14]
8	$2 \times Na^+ + 7$	[15]
9	$2 \times Na^+ + 10$	[16]
10	$2 \times Na^+ + glucose$	[17]
11	$2.1 \times Na^+$	[18]
12	$2 \times Na^+ + glucose + 0.93 \times 0.5 \times urea$	[19]
13	$(2 \times (Na^+ + K^+) + glucose + 0.5 \times urea) \times 0.985$	[20]
14	$1.86 \times Na^+ + glucose + 0.5 \times urea + 5$	[21]
15	$2 \times Na^+ + 0.9 \times glucose + 0.93 \times urea \times 0.5$	[22]
16	$2 \times Na^+ + 0.5 \times urea$	[22]
17	$(1.86 \times Na^+ + glucose + 0.5 \times urea)/0.93$	[4]
18	$1.9 \times (Na^+ + K^+) + glucose + 0.5 \times urea$	[23]
19	$1.8 \times (Na^+ + K^+ + iCa) + glucose + 0.47 \times 0.5 \times urea$	[24]
20	$1.85 \times Na^+ + glucose + 0.5 \times urea + 8.55$	[25]
21a	$1.86 \times Na^+ + glucose + 0.5 \times urea + 9$	[26]
21b[a]	$1.86 \times Na^+ + glucose + urea + 9$	[26]
22	$2 \times (Na^+ + K^+) + glucose + 0.93 \times 0.5 \times urea$	[27]
23	$1.89 \times Na^+ + 1.38 \times K^+ + 1.08 \times glucose + 1.03 \times urea + 7.47$	[28]
24	$1.86 \times (Na^+ + K^+) + glucose + urea + 10$	[28]
25	$2 \times Na^+ + 0.9 \times glucose + 0.93 \times 0.5 \times urea + 8$	[29]
26	$(1.86 \times Na^+ + 1.03 \times glucose + 1.28 \times 0.5 \times urea) \times 0.985$	[30]
27	$1.36 \times Na^+ + 1.6 \times glucose + 0.45 \times urea + 91.75$	[31]
28	$(2 \times Na^+ + glucose + urea + 35.2) \times 0.985$	[32]
29	$1.897 \times Na^+ + glucose + urea \times 0.5 + 13.5$	[3]
30	$1.9 \times (Na^+ + K^+) + glucose + urea \times 0.5 + 5$	[3]
31	$1.86 \times (Na^+ + K^+) + glucose + urea$	[33]
32	$2 \times Na^+ + 1.15 \times glucose + urea$	[34]
33	$1.86 \times (Na^+ + K^+) + 1.15 \times glucose + urea + 14$	[34]
34	$1.09 \times 1.86 \times Na^+ + glucose + urea$	[35]
35	$(Na^+ + K^+ + Cl^- + lactate^- + glucose + HCO_3^- + urea + 6.5) \times 0.985$	[6]

iCa ionized calcium

[a] Also refer to the instruction manual for the Roche cobas b 221. According to the original publications, formulas 13, 26 and 28 calculate osmolarity (mosmol/l) instead of osmolality; therefore, we introduced a correction coefficient of 0.985 (0.926/0.94) to obtain osmolality (mosmol/kg H_2O). In some other cases (e.g. formulas 6, 7, 10 and 16), however, the authors deliberately describe calculation of osmolality (mosmol/kg H_2O) regardless of the fact that these formulas are actually calculating osmolarity (mosmol/l)—no correction was introduced for these formulas

Data collection

Results from point of care analysers and laboratory assays were automatically downloaded into a computerized clinical information system. Sample and patient data were irreversibly anonymized.

Laboratory assays

Arterial or venous whole blood samples were obtained from each subject on a single occasion. Plasma values of sodium, potassium, calcium, chloride, glucose, lactate, urea, pH and carbon dioxide (pCO_2) were measured using a cobas b 221 system (formerly Roche OMNI S). Base excess and actual bicarbonate (HCO_3^-) were automatically calculated from pH and pCO_2. Serum osmolality was measured with an osmo station OM-6050 (AKRAY) by means of freezing point depression after centrifugation. A daily reference fluid (standard 290 mosmol/kg H_2O) was used for calibration. Results of the reference fluid had to lie in the range 284–296 mosmol/kg H_2O (±2 %). The mean reference measure obtained with all 236 samples was 292.0 ± 2.4 mosmol/kg H_2O.

Data analysis

Data are presented as medians and interquartile ranges or as means and standard deviations. The methodological framework of Bland and Altman was used to evaluate each formula [7]. To obtain a gold standard for osmolality, which is independent of regression to the mean, we computed the average between the measured osmolality and the calculated osmolality for each observation.

Consecutively three types of bias were tested for:

1. In order to assess whether the calculated osmolality differed systematically from the measured value, we computed the difference between calculated and measured osmolality for each observation and consecutively the mean and standard deviation of the difference. Upper and lower 95 % limits of agreement were computed by adding and subtracting the standard deviation times 1.96, respectively.
2. In order to assess whether the difference between the measured and the calculated osmolality depended on the magnitude of the osmolality, we regressed the difference between the two osmolalities on the average of the two osmolalities. The regression coefficient and its p value indicate the magnitude and significance of this relationship, respectively.
3. In order to assess whether the variance of the difference between measured and calculated osmolality depended on the magnitude of the osmolality, we regressed the variance on the average of the two osmolalities. The regression coefficient and its p value indicate the magnitude and significance of this relationship, respectively.

Biases 1 and 2 were plotted with the average of the measured osmolality and the calculated osmolality on the abscissa and the difference between the measured osmolality and the calculated osmolality on the ordinate. Figure 1 shows example Bland-Altman plots for formulas 1 and 35.

For all analyses, statistical significance was defined by a two-sided $p < 0.05$. Statistical tests and mathematical modelling were performed using SPSS v17. Figures were constructed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA; www.graphpad.com).

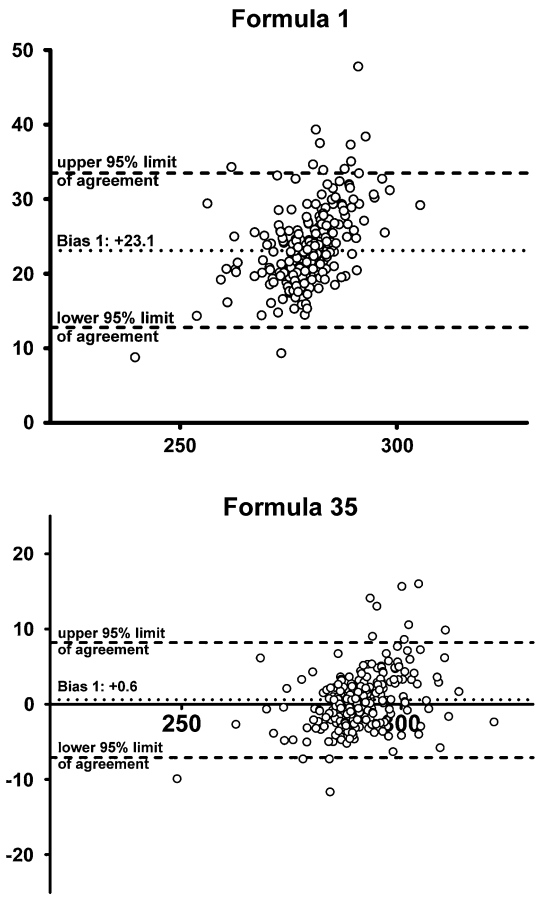

Fig. 1 Example Bland-Altman plots for formulas 1 and 35. The averages of the measured osmolality and the calculated osmolality are shown on the abscissa and the difference between the measured osmolality and the calculated osmolality on the ordinate

Results

Patient characteristics

Active plasma constituents (as outlined in Laboratory assays) were measured in anonymized samples from 41 outpatients and 195 acutely ill inpatients (total 236 adult subjects) at a university hospital in Graz, Austria, between 1 July and 19 November 2010. The sex of 232 of the 236 subjects was known; 110 (47 %) were female. The age of 231 subjects was recorded (mean age 58 years, range 17–88 years, SD 16 years). The patient mix according to treating specialties is shown in Table 2.

Outpatients

The normal values for the calculation of osmolality in healthy subjects are (mmol/l): Na^+ 142, K 4.5, Cl^- 103, lactate$^-$ 1.5, HCO_3^- 24 (at pH 7.400/pCO_2 40 mmHg), glucose 5, urea 5^+ [2]. The measured values of the 41 outpatients in our study were (mmol/l): Na^+ 143 ± 1.3, K^+ 4.1 ± 0.3, Cl^- 101.4 ± 1.5, lactate$^-$ 1.7 ± 0.4, HCO_3^- 26.7 ± 2.0, glucose 5.1 ± 0.6, urea 4.5 ± 1.2 (which overall represents good agreement. The calculated osmolality using these values in the novel formula (formula 35) was 288.7 ± 2.9 mosmol/kg H_2O and the measured osmolality was 288.8 ± 3.4 mosmol/kg H_2O. The concordance was therefore excellent indicating accuracy of the assumed as well as the measured single values and the formula for calculation of the osmolality. Of note, 33 out of the 36 formulas showed an osmolal gap in >10 % of the outpatients. Only formulas 16, 18 and 35 showed no osmolal gap in >90 % of samples.

Measured osmolality

Measured osmolality was 291 ± 9 mosmol/kg H_2O (range 244–320 mosmol/kg H_2O). The characteristics of the variables from which the various types of osmolality were calculated are shown in Table 3.

Table 2 Specialities from which the study subjects were drawn

Group	Number	%
Outpatients	41	17
Anaesthesia	15	6
Surgery	25	11
Internal medicine	113	48
Neurosurgery	33	14
Unclassified	9	4
Total	236	

Table 3 Characteristics of the variables from which the various types of osmolality were calculated

	Mean	Standard deviation	Range
Na^+ (mmol/l)	141	4	125–152
K^+ (mmol/l)	3.54	0.65	2.00–5.00
Ionized Ca (mmol/l)	0.99	0.11	0.00–1.00
Cl^- (mmol/l)	101	4	77–110
Glucose (mmol/l)	5.8	2.1	2.0–15.0
Lactate$^-$ (mmol/l)	1.9	1.3	0.0–8.0
Urea (mmol/l)	6.7	4.5	1.0–29.0
pH	7.367	0.055	7.198–7.529
pCO_2 (mmHg)	46.6	7.5	31.0–77.0
$cHCO_3^-$ (mmol/l)	25.7	3.3	16.0–44.0
Base excess (mmol/l)	−0.2	3.2	−11.0–14.0
Colloid osmotic pressure (mmHg)	19.7	3.1	14.0–26.0
Osmolality (mosmol/kg H_2O)	291	9	244–320

Bias 1: mean difference between calculated and measured osmolality

Of the 35 formulas, 15 showed mean differences of <5 mosmol/kg H_2O. A further 14 formulas showed mean differences between 5 and 10 mosmol/kg H_2O, with the remaining 6 formulas showed mean differences above 10 mosmol/kg H_2O. The novel formula showed a negligible mean difference of 0.5 mosmol/kg H_2O (95 %CI 0.0–1.0 mosmol/kg H_2O) and the closest 95 % limits of agreement ranging from −6.5 to 7.5 mosmol/kg H_2O (Table 4).

Bias 2: correlation between the means of the two osmolalities and the differences between the two

Higher mean calculated and measured osmolality readings correlated with a higher difference between calculated and measured osmolality in all formulas with the exception of formula 2 (Table 4). The novel formula showed a regression coefficient of 0.16, positioning it within the best third of all formulas.

Bias 3: correlation between the means of the two osmolalities and the variance of the differences between the two

With a regression coefficient of 0.046 ($p = 0.01$), the novel formula showed higher variance with higher osmolality values (Table 4).

Table 4 Results of the statistical evaluation of the 36 formulas in the overall cohort

Formula	Calculated osmolality		Bias 1: mean difference between calculated and measured osmolality (95 % CI)	Bias 2		Bias 3	
	Mean ± SD	Range		Regression coefficient	*p* value	Regression coefficient	*p* value
1	266.9 ± 6.8	235.0–290.0	23.1 (12.8 to 33.5)	0.345	0.0001	0.01	0.687
2	306.2 ± 9.5	263.0–334.0	−15.1 (−30.5 to 0.2)	−0.017	0.782	−0.003	0.937
3	272.4 ± 7.1	238.0–297.0	17.7 (7.3 to 28.1)	0.292	0.0001	0.007	0.797
4	300.2 ± 7.8	261.0–325.0	−9.2 (−19.1 to 0.7)	0.187	0.0001	−0.006	0.806
5	281.2 ± 7.4	244.0–304.0	8.8 (−1.3 to 19.0)	0.256	0.0001	−0.005	0.836
6	282.5 ± 7.2	250.0–304.0	7.8 (−6.3 to 21.8)	0.31	0.0001	0.016	0.674
7	292.2 ± 7.6	256.0–318.0	−1.4 (−11.3 to 8.4)	0.202	0.0001	−0.011	0.688
8	289.5 ± 7.2	257.0–311.0	1.1 (−12.5 to 14.8)	0.301	0.0001	0.015	0.688
9	292.5 ± 7.2	260.0–314.0	−1.7 (−15.4 to 11.9)	0.304	0.0001	0.004	0.912
10	288.7 ± 7.3	255.0–310.0	1.9 (−11.1 to 14,9)	0.277	0.0001	0.018	0.633
11	296.6 ± 7.6	262.0–319.0	−5.7 (−19.5 to 8.2)	0.227	0.0001	−0.01	0.792
12	291.9 ± 7.5	256.0–318.0	−1.2 (−11.2 to 8.9)	0.217	0.0001	0.0000394	0.999
13	295.7 ± 7.7	257.0–320.0	−4.8 (−14.4 to 4.8)	0.197	0.0001	−0.007	0.754
14	277.4 ± 7.1	243.0–302.0	12.7 (2.3 to 23.0)	0.294	0.0001	0.008	0.754
15	291.3 ± 7.5	255.0–317.0	−0.6 (−10.6 to 9.4)	0.215	0.0001	0.001	0.968
16	286.0 ± 7.5	251.0–312.0	4.3 (−6.6 to 15.1)	0.226	0.0001	−0.003	0.919
17	292.9 ± 7.7	256.0–319.0	−2.2 (−11.8 to 7.4)	0.189	0.0001	0	0.99
18	285.7 ± 7.5	248.0–309.0	4.5 (−5.1 to 14.2)	0.224	0.0001	−0.005	0.834
19	271.4 ± 6.9	237.0–291.0	18.7 (7.2 to 30.2)	0.338	0.0001	0.001	0.967
20	282.4 ± 7.1	248.0–307.0	7.7 (−2.5 to 18.0)	0.283	0.0001	0.013	0.615
21a	281.4 ± 7.1	247.0–306.0	8.7 (−1.5 to 19.0)	0.284	0.0001	0.013	0.628
21b	284.9 ± 8.1	249.0–314.0	5.2 (−3.0 to 13.5)	0.148	0.0001	0.022	0.294
22	300.0 ± 7.8	261.0–324.0	−9.0 (−19.0 to 1.1)	0.189	0.0001	−0.001	0.962
23	293.9 ± 8.5	255.0–323.0	−3.1 (−10.8 to 4.7)	0.097	0.001	0.012	0.528
24	293.4 ± 8.4	254.0–321.0	−2.5 (−10.2 to 5.1)	0.107	0.0001	0.019	0.322
25	299.3 ± 7.5	263.0–325.0	−8.3 (−18.8 to 2.2)	0.235	0.0001	0.007	0.789
26	268.0 ± 7.2	234.0–293.0	22.0 (12.3 to 31.7)	0.28	0.0001	0.003	0.889
27	296.7 ± 5.9	271.0–316.0	−5.8 (−16.6 to 5.0)	0.471	0.0001	0.045	0.081
28	326.0 ± 8.4	288.0–356.0	−34.9 (−43.5 to −26.3)	0.106	0.001	0.014	0.525
29	291.1 ± 7.3	256.0–316.0	−0.4 (−10.1 to 9.2)	0.248	0.0001	0.009	0.734
30	290.7 ± 7.5	253.0–314.0	−0.1 (−9.4 to 9.3)	0.215	0.0001	−0.007	0.776
31	283.4 ± 8.4	244.0–311.0	6.7 (−1.6 to 15.0)	0.108	0.001	0.026	0.215
32	296.7 ± 8.6	258.0–327.0	−5.8 (−14.0 to 2.5)	0.082	0.009	0.01	0.608
33	298.3 ± 8.4	259.0–326.0	−7.3 (−15.2 to 0.6)	0.104	0.001	0.019	0.309
34	299.7 ± 8.6	261.0–331.0	−8.7 (−17.0 to −0.3)	0.083	0.009	0.012	0.571
35	290.0 ± 7.9	253.0–322.0	0.5 (−6.5 to 7.5)	0.161	0.0001	0.046	0.01

Discussion

We present a statistical evaluation of 36 published formulas for calculating plasma osmolality including Zander's novel formula. Previous evidence-based data in the field are scarce [8]. When judging the quality of the above formulas, the feature of the highest clinical relevance in our opinion was the mean difference between calculated and measured osmolality, here called bias 1. We consider a mean difference of <2 mosmol/kg H_2O as desirable, with a value above 5 mosmol/kg H_2O significantly compromising the usefulness of the formula, as an observed difference of above 5 mosmol/kg H_2O by definition would indicate the presence of an osmolal gap. Only 9 out of the 36 formulas showed a mean difference of <2 mosmol/kg H_2O and only four formulas including the novel formula showed mean differences of <1 mosmol/kg H_2O. When comparing the three formulas with the lowest mean differences (formulas 29, 30 and 35), the novel formula showed the narrowest 95 % levels of agreement: −6.5 to 7.5 compared to −10.1 to 9.2 and −9.4 to 9.3 for formulas 29 and 30, respectively. We speculate that the additional inclusion of chloride, lactate and actual bicarbonate in the novel formula led to a narrower level of agreement.

We also evaluated the performance of the formulas in 41 outpatients. The presence of a clinically significant osmolal gap is unlikely in this cohort, and therefore correct identification of the absence of an osmolal gap is of the highest clinical relevance. The novel formula showed 98 % of the outpatients to have no osmolal gap (i.e. an absolute difference between measured and calculated osmolality of <5 mosmol/kg H_2O). The novel formula showed the highest regression coefficient for bias 3, with higher variance in the differences between calculated and measured osmolality with higher osmolality values. Arguably, this point is of little clinical relevance.

Our study had several strengths: the inclusion of a large and diverse sample of patients, the identification of a large number of formulas published over the last decades, and evaluation of the formulas within a validated statistical framework including the presentation of three different biases. A limitation of our study could be that the patient mix was chosen on personal experience in an attempt to reflect the areas where measuring osmolality is of the highest relevance. Our patient cohort might not necessarily reflect the particular areas of interest of individual readers. A further limitation could be that we do not know whether the best formula overall would also be the best choice in certain states of hypo- or hyperosmolality. Overall we would like to suggest that the above limitations do not significantly impact on the quality of our data.

Conclusion

Our study shows that only 4 out of the 36 evaluated formulas showed mean differences between measured and calculated osmolality of <1 mosmol/kg H_2O. Zander's novel formula for calculating osmolality showed excellent concordance with measured osmolality, and facilitates a more precise diagnosis based on blood gas analysers. The new equation has the potential to replace separate measurements of osmolality in many cases.

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Conflicts of interest A.S.F. and H.J.S. declare no conflicts of interest; G.C.F. receives lecture fees from Roche Diagnostics; R.Z. has previously worked as a consultant for Roche Diagnostics; D.S.K. and I.Z. are current employees of Roche Diagnostics; H.R. is a former employee of Roche Diagnostics.

Appendix

The development of Zander's optimized equation for plasma is described in three steps. The following is the English translation of Zander's original publication, which can be accessed via the Physioklin website (http://www.physioklin.de/physiopoc/saeure-basen-sauerstoff-elektrolyt-status/optimale-berechnung-der-osmolalitaet.html):

1. Addition of all osmotically active constituents in terms of mosmol per liter of plasma results in the theoretical osmolarity, expressed in mmol/l. Amounts (mmol/l) of 142 Na, 4.5 K, 1.3 ionized Ca, 0.7 ionized Mg, 103 Cl, 24 HCO_3, 1.5 lactate, 1 HPO_4, 0.5 SO_4, 3.0 organic acids plus proteinate, 5 glucose and 5 urea were taken as normal values from the literature [2]. The resulting value amounts to 291.5 mosmol/l.
2. Corresponding to the fact that electrolytes, mainly sodium and chloride, are osmotically active only in part, i.e. only to 92.6 % (the so called osmotic coefficient 0.926; for glucose 1.013) [2], the resulting real osmolarity amounts to only 269.9 mosmol/l.
3. Taking into account the water content of plasma with 94 % the calculated real osmolality of 287.2 mosmol/kg H_2O is given a value, which has been lowered by 6 % as a result of the reduced distribution space of all osmotically active substances.

Now, comparison between the measured normal value of plasma osmolality (288 mosmol/kg H_2O) and the calculated value (287 mosmol/kg H_2O, rounded) leads to the surprising result that the measured real normal value of osmolality is by chance the same as the osmolarity of the plasma. This might be the reason for the confusion within the literature concerning these two values. On this basis, the optimized formula for calculation of osmolality is as follows (the concentrations of calcium and magnesium and those of phosphate, sulphate, organic acids and proteinate are summarized as constants for clinical reasons):

Osmolarity (mosmol/l) = [Na^+ (142) + K^+ (4.5) + const. Ca^{++}/Mg^{++} (2.0) + Cl^- (103) + HCO_3^- (24) + lactate$^-$ (1.5) + const. phosphate/sulphate/organic acids/proteinate$^-$ (4.5) + glucose (5.0) + urea (5.0)] = 291.5 mosmol/l × 0.926 (osmot. coefficient) = 269.9 mosmol/l.

Osmolality (mosmol/kg H_2O) = osmolarity: 0.94 (water content) = 287.1 mosmol/kg H_2O.

The calculation of plasma osmolality (mosmol/kg H_2O) is now given as:

Plasma osmolality = ($Na^+ + K^+ + Cl^- +$ lactate$^-$ + glucose + urea + HCO_3^- + 6.5) × 0.985.

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