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The measurement of serum osmolality and its application to clinical practice and laboratory: literature review

A medida da osmolalidade sérica e sua aplicação na prática clínica e laboratorial: revisão da literatura

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ABSTRACT

Introduction: Serum osmolality is an essential laboratory parameter to understand several clinical disorders such as electrolyte disturbances, exogenous intoxication and hydration status. **Objective:** This study aims to update knowledge about the osmolality examination through research papers published to date. **Materials and methods:** The survey was conducted on PubMed database. It highlights main concepts, both historical and physiological aspects, and the clinical applications of the serum osmolality test. In addition, an extensive survey of formulas for the serum osmolality calculation was conducted. **Discussion:** The measurement of serum osmolality is relevant in changes in intracellular and extracellular balance, as a trusted and valuable indicator of solute concentration in the blood. The mathematical equations for serum osmolality calculation acquire relevance in health services where serum is not available, and situations in which calculation of the osmolal gap is necessary, but the variability of the formulas is a significant bias. **Conclusion:** The measurement of serum osmolality is useful in cases of dehydration, sodium and potassium disorders, glucose alteration, exogenous poisoning, adrenal insufficiency, neurological injury, physical exercise and others.

Key words: osmolar concentration; osmosis; osmometry; plasma osmolality; serum osmolality; osmolal gap.

INTRODUCTION

The human body has a unique functional architecture, is regulated by a sophisticated system for the maintenance of balance in intra- and extracellular compartments. Numerous chemical reactions and different modalities of transport occur simultaneously between these compartments. However, the whole homeostatic process is prone to imbalances induced by different diseases. The measurement of serum osmolality is an important evaluation and decision-making laboratory tool in cases of hydroelectrolytic imbalance.

OBJECTIVE

This work aims to update knowledge about the osmolality test by means of a survey on scientific articles published to date. The paper also deals with the role of osmolal gap calculation.

MATERIALS AND METHODS

The survey was conducted on PubMed database, using a combined filter with the terms "serum osmolality review article"

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and "plasmatic osmolality review article", aiming at the search of papers in the English language. The search resulted in 364 articles, 272 with full-text access, which were classified according to the discussed theme (**Table 1**).

TABLE 1 – Inventory of the 272 articles found at the PubMed database, using the combined filter with the terms "serum osmolality article review" and "plasmatic osmolality review article"

Theme	No. of articles
Sodium disorders (hypernatremia and hyponatremia)	39
Diabetes mellitus and insipidus	25
Therapeutic drugs in hyperosmolar or hyposmolar states	19
Acute kidney injury, chronic kidney disease	17
Physiological aspects of osmolality	15
Acute and chronic neurological injury (traumatic and non-traumatic)	14
Exogenous intoxication (alcohol and other drugs)	13
Use of contrast medium	13
Albumin	11
Endocrine diseases†	11
Syndrome of inappropriate antidiuretic hormone secretion	10
Hypervolemic syndromes (ascites and heart failure)	9
Ocular osmolality	8
Dialysis	8
Water intoxication (primary polydipsia)	5
Osmolal gap calculation	4
Dehydration	4
Potassium, calcium or magnesium deficiency	4
Osmotic demyelination syndrome (pontine myelinolysis)	4
Sports medicine	4
Veterinary medicine	4
Physiological aspects in children	3
Sepsis	2
Hyperviscosity in oncological diseases	2
Mannitol	2
Copeptin	2
Hypovolemic shock	2
Diarrhea	2
Urine osmolality	2
Acid-base imbalance	2
Polyuria	1
Fluids during pregnancy	1
Cerebral salt-wasting syndrome	1
Gastrointestinal surgeries	1
Cardiac arrest	1
Acute respiratory failure	1
Spherocytosis	1
Sarcoidosis	1
Chron's disease	1
Enteral nutrition	1
Plasmapheresis	1
Extracorporeal circulation	1

†: disorders related to thyroid hormones, lipoproteins, growth hormone, parathormone, aldosterone, glucocorticoids, and vitamin D.

The survey was also complemented with articles located from other terms: "historical aspects of osmolality", "serum osmolality calculation" and "serum osmolal gap".

Sixty-five formulas for the calculation of serum osmolality were found, most of them based on the levels of sodium, urea, and glucose (**Table 2**).

DISCUSSION

Definitions

Osmolality is the measure of the number of osmoles of solute per kilogram of water. Usually, osmolal concentration is expressed in milli-osmoles per kilogram of water (mOsm/KgH_2O). The osmolality of a solution does not depend on the nature of the particle, but on the number of the dispersed particles[1, 12].

Osmosis is the movement of a solvent through a semipermeable membrane. The pressure required to avoid solvent movement between two solutions of different concentrations, separated by a semipermeable membrane, is called osmotic pressure. The higher the solution concentration, the higher its osmotic pressure[1, 12].

Osmometry is the technique employed to measure osmolality of solutions of a biological sample, by means of a device called osmometer, which uses the colligative properties to take the measurements. Colligative properties of a solution depend on the number of solute particles dispersed at a certain quantity of solvent, regardless of the chemical nature of the solute[1, 12].

The colligative properties of interest to osmometry are:

• tonometry – study of the effect of lowering of maximum vapor pressure of a solvent when one adds a non-volatile solute to it;

• ebullioscopy– study of the effect of boiling point elevation of a liquid caused by dissolution of a non-volatile solid;

• membrane osmometry – study of the measure of osmotic pressure of a solution;

• cryoscopy – study of the depression of freezing temperature or fusion point of a liquid, resulting from the addition of a non-volatile solute.

Tonicity or effective osmolality describes the effect of plasma on cell volume. Solutes such as urea and ethanol freely cross cell membranes, and thus do not participate in effective osmolality[18,19].

Mathematical equations for the calculation of serum osmolality are useful when specific measurement is not available

TABLE 2 – Formulas for the calculation of serum osmolality found in the PubMed search

No.	Formulas	References
1	Osm = 2*Na + BUN/2.8 + glucose/18	1-8
2	Osm = 1.86*Na + BUN/2.8 + glucose/18 + 9	1, 2, 5, 7, 9
3	Osm = 1.85*Na + BUN/2.18 + glucose/17,5 + ethanol/4.22	2
4	Osm = 1.86*Na + BUN/2.8 + glucose/18	2, 5-7
5	Osm = 1.86*Na + BUN/2.8 + glucose/18 + 5	2, 5, 7
6	Osm = 2*(Na + K) + BUN/2.8 + glucose/18	2, 5, 7
7	Osm = 2*Na + BUN/3 + glucose/20	2, 5, 7
8	Osm = 2.1*Na	2, 5, 7, 10
9	Osm = 2.63*Na – 65.4	2, 5, 7, 10
10	Osm = 1.75*Na + BUN/2.8 + glucose/18 + 10.1	2, 7
11	Osm = 1.85*Na + 1.84*K + BUN/2.8 + glucose/18 + calcium + 1.17*magnesium + 1.14	2, 7
12	Osm = 2*Na + BUN/2.8	2, 7
13	Osm = 2*Na + glucose/18	2, 7
14	Osm = 2*Na	2, 7, 10
15	Osm = 2*Na + 7	2, 7, 10
16	Osm = 1.5*Na + BUN/2.8 + glucose/18 + 45	5
17	Osm = 1.8*(total of cations) + BUN/6 + glucose/18	5
18	Osm = 1.85*Na + 1.84*K + BUN/2.8 + glucose/18 + 1.15*calcium + 1.17*magnesium + 1.15	5
19	Osm = 1.86*(Na + K) + BUN/2.8 + glucose/18 + 10	5
20	Osm = 1.89*Na + 1.38*K + BUN/2.7 + glucose/16.7 + 7.45	5
21	Osm = 2*Na + BUN/3 + glucose/20 + 8	5
22	Osm = (1.86*Na + BUN/2.8 + glucose/18)/0.93	5, 6
23	Osm = 2*Na + BUN/2.8 + glucose/18 + ethanol/4.6	5, 8
24	Osm = 2*Na + 10	5, 10
25	Osm = 1.82*Na + BUN/2.9 + glucose/23.9 + 24	6
26	Osm = 2*Na + BUN/2.8 + glucose/18 + ethanol/3.7	8
27	Osm = 1.09*1.86*Na + BUN + glucose	10
28	Osm = 1.36*Na + 0.45*BUN + 1.6*glucose + 91.75	10
29	Osm = 1.75*Na + BUN/2 + glucose + 10.1	10
30	Osm = 1.8*(Na + K + calcium) + 0.47*BUN/2 + glucose	10
31	Osm = 1.85*Na + BUN/2 + glucose + 8.55	10
32	Osm = 1.85*Na + 1.84*K + BUN/2 + glucose + 1.15*calcium + 1.17*magnesium	10
33	Osm = 1.86*Na + BUN/2 + glucose	10
34	Osm = 1.86*Na + BUN/2 + glucose + 5	10
35	Osm = 1.86*Na + BUN/2 + glucose + 9	10
36	Osm = (1.86*Na + BUN/2 + glucose)/0.93	10
37	Osm = (1.86*Na + 1.28*BUN/2 + 1.03*glucose)*0.985	10
38	Osm = 1.86*(Na + K) + BUN + glucose	10
39	Osm = 1.897*Na + BUN/2 + glucose + 13.5	10
40	Osm = 1.9*(Na + K) + BUN/2 + glucose	10
41	Osm = 1.9*(Na + K) + BUN/2 + glucose + 5	10
42	Osm = 2*Na + BUN/2	10
43	Osm = 2*Na + glucose	10
44	Osm = 2*Na + BUN/2 + glucose	10
45	Osm = 2*Na + 0.93*BUN/2 + glucose	10
46	Osm = 2*Na + 0.93*BUN/2 + 0.9*glucose	10
47	Osm = 2*Na + 0.93*BUN/2 + 0.9*glucose + 8	10
48	Osm = (2*Na + BUN + glucose + 35.2)*0.985	10
49	Osm = [2*(Na + K) + BUN/2 + glucose]*0.985	10
50	Osm = 2*(Na + K) + BUN/2 + glucose	10
51	Osm = 2*(Na + K) + 0.93*BUN/2 + glucose	10
52	Osm = (Na + K + chlorine + lactate + glucose + bicarbonate + BUN + 6.5)*0.985	10

53	Osm = 2*Na + BUN + 1.15*glucose	10, 11
54	Osm = 1.86*(Na + K) + BUN + 1.15glucose + 14	10, 11, 12
55	Osm = 1.86*Na + BUN + glucose + 9	9, 10
56	Osm = 1.86*(Na + K) + BUN + glucose + 10	9, 10
57	Osm = 1.89*Na + 1.38*K + 1.03*BUN + 1.08*glucose + 7.47	9, 10
58	Osm = 2*Na + BUN + glucose	13
59	Osm = 1.86*(Na + K) + BUN + 1.15*glucose + 1.2* ethanol + 14	11
60	Osm = 2*Na + BUN + 1.15 × glucose + 1.2*ethanol	11
61	Osm = 2*Na + BUN + glucose + ethanol	14
62	Osm = 2*Na + BUN + glucose + 1,25*ethanol	14
63	Osm = 2*Na + BUN/2.8 + 1.15*glucose/18	15
64	Osm = 2*Na + BUN/2.8 + 1.15*glucose/18 + 1.2*ethanol/4.6	16, 17
65	Osm = 1.86*(Na + K) + BUN + glucose + 9	9

*Serum osmolality: mOsm/kgH_2O; Na (sodium): mEq/l; K (potassium): mEq/l; BUN (blood urea nitrogen): mg/dl; glucose: mg/dl; ethanol: mg/dl; serum urea (mg/dl): BUN (mg/dl)*2.14.*

and also when calculation of osmolal gap is necessary. This is the difference between measured osmolality and calculated osmolality[4, 13, 20, 21, 22].

Serum osmolal gap = measured serum osmolality - calculated serum osmolality

A divergence is observed among the different authors regarding the normality range of serum osmolal gap. However, a great number of works adopt the range 1-10 mOsm/kgH_2O[4, 13,19-23].

Number 1 equation expressed in Table 2, according to the literature, is the most commonly used formula for the calculation of serum osmolality, having the range between 275 and 295 mOsm/KgH_2O as reference values[1, 10, 19, 21, 22].

Historical aspects

In 1828, the French researcher René Joachim Henri de Dutrochet (1776-1847) created the first osmometer. The device was made of a container with concentrated solution, sealed in one of the sides with a semipermeable membrane, submerged in a second container with pure solvent. He observed movement of fluids through the semipermeable membrane, by forces that he termed endosmosis or rapid phase of transfer of the solvent, and exosmosis or slower phase on the opposite direction, corresponding to the diffusion of solutes[24].

Charles Blagden (1748-1820) documented the result of the phenomenon of depression of the freezing point in response to solute concentration (Blagden law), which is the most frequently used principle in equipment to measure osmolality[25].

In 1854, the Scottish chemist Thomas Graham (1805-1869) described exosmosis as the passage by diffusion of substances dissolved in the solution, due to its concentration and molecular mass, coining the term dialysis for this phenomenon[26].

In 1865, Moritz Traube (1806-1892) postulates the concept of semipermeable membrane on the movement of fluids, which was improved by the German Wilhelm Friedrich Philipp Pfeffer (1845-1935)[26, 27].

The Dutch botanist Hugo de Vries (1848-1935) described the isotonic coefficient, observing that the osmotic pressure effect followed a regularity similar to that of the freezing point of solutions. By studying the researches of Pfeffer, De Vries worked as a link, influencing the advances of other Dutchmen: Hartog Jakob Hamburger and Jacobus Henricus Van't Hoff[26, 28].

In 1883, Hartog Jakob Hamburger (1859-1924), Dutch chemist and physiologist, lecturer in pathology at the Utrecht Veterinary School, documents water movement to erythrocytes due to the difference of osmotic pressure, leading to hemolysis. The theory of isotonicity of blood and 0.9% saline *in vitro* is attributed to Hamburger[28].

In 1886, the Dutch Jacobus Henricus Van't Hoff (1852-1911), founder of the discipline physical chemistry, developed the law principles that rule the phenomena of pressure, volume and temperature in gas diffusion. His studies were in agreement with the researches by Wilhelm Ostwald (1853-1932), who unified the colligative properties[20, 29].

Van't Hoff equation:

$\pi = R * \Sigma C * T$

π: osmotic pressure

R: universal gas proportionality constant

ΣC: sum of solute concentrations

T: absolute temperature

François M. Raoult (1830-1901) and Svante August Arrhenius (1859-1927), by means of the freezing point depression osmometer, demonstrated that the formula could be applied to both organic matter and electrolytes[26]. In 1892, Heinrich Dreser (1860-1925) took the first measure of osmolality by cryoscopy, *in vivo*, in a patient with diabetes insipidus[26, 29].

Sándor Korányi (1866-1944) measured serum and urine osmolality by cryoscopy to evaluate renal function[26, 30].

In 1897, the French Emile Charles Achard and Joseph Castaigne administered methylene blue subcutaneously and assessed permeability and the percentage of dye that showed up in the urine within a 24-h period[26, 30].

All these discoveries and knowledge aided in the comprehension of osmotic physiology and permitted the development of equipment based on colligative properties, promoting the measurement of osmolality in diverse biological materials.

Physiological aspects

Water is the most abundant component in the human being and accounts for approximately 60% of the body weight of a healthy adult, being distributed in two compartments: intra- and extracellular. Fluid movement between these intravascular and interstitial spaces occurs through capillary walls and is actively determined by solute concentration. Concentration of solute or fluid particles is known as osmolality[1, 31, 32].

Thirst and secretion of the antidiuretic hormone [(ADH) or arginine vasopressin] are the major stimuli to maintenance of hydroelectrolytic balance, controlled by a mechanism of feedback regulated by the hypothalamus, the neurohypophysis and the kidneys[33].

ADH is produced by hypothalamic supraoptic and paraventricular nuclei from a precursor named preprovasopressin, in response to small variations of serum osmolality, being stored in the neurohypophysis. Preprovasopressin is subject to a cascade of enzymatic reactions, originating bioactive peptides: ADH, neurophysin II, and copeptin[34, 35].

The released ADH acts on the V1 receptors, found in smooth muscle fibers, exerting vasopressor activity, and V2 renal receptors, exerting their antidiuretic effect through activation of water channels[36].

Aquaporins (AQPs) are transmembrane channel proteins that permit selective transport of water and other solutes.

- AQP1 plays an important role in the countercurrent mechanism, concentrating the luminal fluid, and is also expressed in erythrocytes;
- AQP2 is related to polyuric disorders associated with dilutional hyponatremia;
- AQP3 conducts glycerol and water;
- AQP4 is the most abundant channel in the brain[31, 33, 37].

Sodium is the main ion determining serum osmolality. The increased sodium concentration stimulates thirst and ADH secretion. Circulating ADH interacts in the kidneys with epithelial sodium channels beta and gamma subunits, encoded by genes *SCNN1B* and *SCNN1C*, respectively, expressed in the connecting tubule and collector duct. Epithelial sodium channels subunit alpha are influenced by aldosterone[31, 33, 38].

Aldosterone is a hormone related to renin-angiotensin-aldosterone system (RAAS), synthesized by the enzymatic cascade beginning with the conversion of cholesterol into pregnenolone. The increased circulating concentrations of aldosterone result in the reabsorption of sodium and excretion of potassium, directly influencing serum osmolality[31, 33, 38].

Clinical applications

Disorders of hydration status may present of several forms, corresponding to an overall variation of the amount of water or abnormal distribution between the extra- and intracellular compartments. The loss of hypotonic liquids eliminated at the expense of extracellular liquids cause the increase of serum osmolality, being a parameter to evaluate dehydration[38].

In the disorders related to potassium handling, for example in cases of renal tubular acidosis, the diagnostic approach is the calculation of transtubular potassium gradient (TTKG), in which knowledge of serum and urine osmolality values is necessary[39, 40].

$$TTKG = \frac{[\text{urine potassium (mEq/l)}] \times [\text{serum osmolality (mOsm/kg } H_2O)]}{[\text{serum potassium (mEq/l)}] \times [\text{urine osmolality (mOsm/kg } H_2O)]}$$

Hypernatremia is associated with an elevated mortality rate, generally due to the deficit of fluid intake, such as in severe hydric

restriction, excessive sodium intake, or iatrogenic administration of hyperosmolar solution[32, 41].

Hypernatremia also occurs in renal losses of water or hypotonic fluids, in which there is inadequate ADH secretion (pituitary diabetes insipidus), due to the lack of sensitivity to ADH in the nephron (nephrogenic diabetes insipidus), by the use of ADH-antagonist drugs, in the presence of osmotic diuresis (important hyperglycemias, hypercalcemias) or by extrarenal losses of water or hypotonic fluids (as in the cases of prolonged vomiting, pulmonary hyperventilation, and prolonged diarrhea). Measuring serum osmolality contributes to the elucidation of etiology in these circumstances, as it translates the increase of sodium in extracellular fluids[32, 41].

The decreased plasma sodium concentration or the increased amount of water causes hyponatremia by dilution. In the guidelines proposed by the investigation of hyponatremias, serum osmolality is the main parameter in the differentiation of possible etiologies. In hyponatremia, serum osmolality may be increased, normal, or decreased[22, 42].

Hyponatremia with increased serum osmolality is mainly caused by hyperglycemia, hypertonic mannitol, sucrose, maltose, and low-molecular-weight dextran. In patients with diabetes, the increased concentration of plasma glucose moves water from the intracellular space to the extracellular space, diluting the extracellular sodium concentration. In general, for each increase of 100 mg/dl in glycemia above 100 mg/dl, sodium must be corrected with an increase of 1.6 mEq/l[22, 42].

Pseudohyponatremias co-occur with normal serum osmolality. This can happen in cases of multiple myeloma with hyperproteinemia, severe hyperlipoproteinemia and in the measurements by means of flame photometry. Nowadays, in most services, sodium is measured using the principle of ion selective electrode (ISE), in which the electrode is immersed in a biological sample, with the activity of sodium measured depending on the difference of electric potential[18, 43, 44].

Hyponatremias caused by depletion with decreased osmolality occur because of prolonged and excessive low-sodium diets, digestive losses (excessive vomiting, prolonged diarrhea, and digestive fistulas) or renal losses (treatment with thiazide diuretics, and adrenal insufficiency)[42, 45].

Hyponatremia with decreased serum osmolality can also occur in situations of excessive fluid intake or water retention higher than electrolyte retention, as observed in the presence of heart failure of low cardiac output, hepatic cirrhosis, hypothyroidism, and severe renal failure[42, 45].

In the syndrome of inappropriate antidiuretic hormone secretion (SIADH), increased ADH causes fluid retention and hypervolemia, increasing natriuresis and decreasing serum osmolality[35, 42, 45].

Psychogenic polydipsia is manifested as the search and excessive water intake, and co-occurs with diminished serum osmolality[42, 45].

In the high anion gap metabolic acidosis, serum osmolality and principally calculation of osmolal gap are valuable tools in the presence of intoxication by alcohol and other drugs[2, 3, 8, 46].

Measurement of methanol and ethylene glycol is not available in most hospitals. Measurement of serum osmolality, along with increased osmolal gap calculation, can contribute to clinical suspicion, as a screening method in these patients[2, 8, 46].

Adrenal insufficiency is a condition characterized by the decreased production or reduction of glucocorticoid action, with or without mineralocorticoid deficiency. In secondary and tertiary adrenal insufficiency, serum osmolality is generally reduced[47].

In patients with neurological lesions to whom osmotherapy with mannitol or hypertonic saline is indicated, measuring serum osmolality can be used as a laboratory parameter in the follow-up of these patients[48].

In physical exercise, measuring serum osmolality is the main laboratory parameter to evaluate athletes' hydration status[49, 50].

CONCLUSION

Measuring serum osmolality is greatly useful in the management of hydroelectrolytic disorders associated with sodium, appearing in several guidelines[51]. It helps in the diagnosis of hyperglycemias, adrenal insufficiency, therapies with hypertonic solutions in neurological lesions, and in physical exercise. In exogenous intoxications, the osmolal gap has high sensitivity, principally in the detection of alcohol intoxication. The pieces of equipment currently available in the market are based on principles of colligative properties of solutions: osmotic-pressure elevation, vapor-pressure lowering, and freezing-point depression. When there is no possibility of measuring serum osmolality in the laboratory, formulas can be applied that have good correlation with the clinical picture and the effective measure. This study tries to demystify the measurement of serum osmolality, a procedure widely available in clinical laboratories, but so little understood regarding its uses and limitations.

RESUMO

Introdução: *A osmolalidade sérica constitui um parâmetro laboratorial importante para compreensão de diversas desordens clínicas, como os distúrbios eletrolíticos, as intoxicações exógenas e o* status *de hidratação.* ***Objetivo:*** *Este trabalho visa atualizar os conhecimentos acerca do exame de osmolalidade por meio da pesquisa de artigos científicos publicados até a presente data.* ***Materiais e métodos:*** *A pesquisa foi realizada no banco de dados do PubMed. Este artigo de atualização aborda os principais conceitos, aspectos históricos, aspectos fisiológicos e aplicações clínicas do exame de osmolalidade sérica. Foi também realizado um levantamento das diferentes fórmulas propostas para o cálculo da osmolalidade sérica.* ***Discussão:*** *A medida da osmolalidade sérica é pertinente nas alterações do equilíbrio intra e extracelular, sendo um bom indicador para avaliar as concentrações de solutos no sangue. As fórmulas matemáticas para o cálculo da osmolalidade sérica são úteis quando a medida laboratorial não está disponível, bem como nas situações em que o cálculo do* gap *osmolal se faz necessário, mas a variabilidade das fórmulas é um viés significativo.* ***Conclusão:*** *A medida da osmolalidade sérica é útil na avaliação de diversas condições clínicas, como na desidratação, nos distúrbios dos íons sódio e potássio, nas disglicemias, nas intoxicações exógenas, na insuficiência adrenal, nas lesões neurológicas, nos exercícios físicos, entre outras.*

Unitermos: *concentração osmolar; osmose; osmometria; osmolalidade plasmática; osmolalidade sérica;* gap *osmolal.*

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