OSMOLAL GAP IN HEMODIALYSED UREMIC PATIENTS

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INTRODUCTION

The term ‘osmolality’ is used to denote the total number of particles in a solution. In the body, the fluids are in osmotic equilibrium. Therefore, in normal humans, the osmolality of cytoplasmic and extracellular fluids are equal. Changes in intracellular or extracellular solute concentrations generate a transmembrane osmotic gradient. Any such gradient results in the immediate flow of water into or out of the cells until osmotic equilibrium is restored. The measured serum osmolality by osmometer expresses the total number of particles in a solution and it reflects the osmotic strength of a solution (1,2). However, serum osmolality can be calculated by summing the concentrations of the major dissolved constituents of serum (sodium, urea, glucose). The difference between measured and calculated osmolality is termed osmolal gap, which shows the accumulation in serum of unidentified osmoles in some clinical conditions (1,3).

In this study, the measured and calculated serum osmolality were determined and osmolal gap was estimated pre- and post- HD in uremic patients and the difference from normal subjects is evaluated.

PATIENTS AND METHODS

In this study 24 hemodialysed uremic patients and 22 healthy subjects were included. Patients were on regular hemodialysis 3 times weekly (4 hours per session) for more than 12 months, their hematocrit levels ranged from 34% to 39% (median 35%) (Hb: 11.5) and age from 38 – 80 years (median 61 years).

None of the patients exhibited serious dysfunction in any other organ system diabetics, patients with systemic diseases, septic and with malignancy were excluded. The hemodialysis procedure included dialysate bath with bicarbonate, Na+ 140-142, K+ 1,5 (mEq/L) blood flow ranged from 280- 320 ml/min and weight loss 2-4,5 Kg/HD session. The stable medication treatment included erythropoietin, phosphate binders and vitamins.

In patients blood samples were collected pre- and post- HD in the first weekly HD-session from arterial line in the morning. Also, blood samples were collected of 22 healthy people in the morning. In these blood samples, serum measured osmolality Na+, urea and glucose were determined and calculated osmolality (2Na + UN/2,8 + Glucose/18) and osmolal gap (measured – calculated osmolality) were estimated (1,3).

Data were expressed as the mean +/- SD. Student’s t-test was used to compare the data. Differences between patients and controls of measured and calculated osmolality and osmolal gap. were considered different to be significant when p<0,05. Following analysis of variance, testing was performed to test differences between groups (SPSS version 10, SPSS, Inc, Chicago, IL, USA).
RESULTS

The mean value (± SD) of determined parameter of patients pre- and post- HD and of controls are described in table I. The changes of measured and calculated osmolality and of osmolal gap in hemodialysed patients and the difference of these parameters between patients and controls are illustrated in figures 1, 2 and 3. Figure 1 shows that the measured osmolality of hemodialysed uremic patients pre-HD (313,33 ± 2,88 mOsm/KgH2O) and post-HD (302,08 ± 2,43) is significantly higher (p<0,001) than in controls (293,72 ± 2,37), also, the value post-HD is significantly decreased (p<0,001) in comparison to that pre-HD. Figure 2 shows that the calculated osmolality of patients pre-HD (302,33 ± 4,03) and post-HD (294,7 ± 2,96) is significantly higher (p<0,001 and p<0,05 respectively) in comparison to controls (290,54 ± 3,11) also, the value post-HD is significantly decreased in comparison to that pre-HD. Figure 3, shows that the osmolal gap of patients pre-HD (11 ± 2,08) and post-HD (7,29 ± 1,94) is significantly higher (p<0,001) in comparison to that of controls (3,18 ± 1,46) also the value post-HD is significantly decreased in comparison to that pre-HD (p<0,001).

These results shows that the measured and calculated osmolality and the osmolal gap are increased in uremic hemodialysed patients inspite the significant decrease by HD, they remain significantly higher post-HD in comparison to the values of controls.

DISCUSSION

The term “osmolality” is used to indicate the concentrations of solute particles per volume of the solution. Serum osmolality is a reflection of the number of particles in serum irrespective of the particle size, shape and weight. Under normal conditions the osmolality between intracellular and extracellular fluid is stable and equal. Changes in intracellular or extracellular solute concentrations generate a transmembrane osmotic gradient. Because cell membranes are freely permeable to water any such gradient results in the immediate flow of water into or out of the cell until osmotic equilibrium is restored. This transmembrane water flow may cause cell swelling and shrinkage. To these volume disturbances, cells respond by activating mechanisms that regulate their volume. Cell volume can be corrected by the gain or loss osmotically active solutes, primarily inorganic ions such as Na+, K+ Cl- or small organic molecules called organic osmolytes which are polyols, amino acids and methylamines and may act as cytoprotectant factors. The organic osmolytes are “compatible” solutes without deleterious effects to the cells. They have unique biophysical and biochemical properties that allow cells to accumulate high concentrations of them or to withstand large shifts in their concentration without side-effects on cellular morphology and function. In contrast, solutes, such as electrolytes or urea can damage cells or disturb metabolic functions, when they are present at high concentrations or when large shifts in their concentrations occur.

In acute osmolar disorder the cells regulate their volume by electrolytes while in prolonged osmolar disorders the most excess electrolytes are replaced by organic solutes (idiogenic osmoles) (1,2,3).
Measurement of serum osmolality is a simple and widely available test, but its particular usefulness in clinical practice is often misunderstood. The serum osmolality measurement may have two particular uses. One is to determine whether serum water deviates widely from normal levels. The other is to screen for the presence of foreign low molecular weight substances in blood. However, in both conditions, the interpretation of serum osmolality requires the measured and calculated osmolality. The calculated osmolality can be easily determined from three major osmotic constituents of normal serum (sodium, urea, glucose) by a simple formula. There are some situations in which direct measure of serum osmolality coupled with its calculation has specific diagnostic, therapeutic and prognostic implications, because the osmolar gap, the difference between measured and calculated osmolality allows clinicians to estimate the concentration of some unmeasured osmoles in a patient’s blood. The serum measured osmolality is about 290mOsm per kilogram of water and in normal subjects the measured osmolality may exceed the calculated less than 10mOsm/Kg H2O (osmolal gap). An increase of osmolal gap may present in some circumstances, if there is not analytical error. A negative osmolal gap indicates an error in the collection of the blood in the measurement or in the calculation (1,3,5,6). A variety of disease, states or conditions, such as diabetes mellitus, dehydration, renal failure, circulatory shock are associated with elevation of serum osmolality. The increase of osmolal gap in patients with multiple organ system failure can be attributed to elevation of serum amino acid concentrations, The ischemia results in generarion of amino-acids and other unknown intracellular catabolic products, also may increase cellular membrane permeability and the leakage of solutes into the circulation (2,4,7).

In our findings, the uremic patients under regular HD present significantly high measured osmolality and osmolal gap pre-HD in comparison to that of post-HD and that of controls. In spite the decrease post-HD they remain higher than in controls. The causes of an increased serum osmolal gap may be exogenous, endogenous or artifactual. The increased osmolal gap of uremic hemodialysed patients probably resulted from an accumulation of unmeasured solute in the blood. The osmolal gap value higher than 10mOsm/Kg/H2O pre-HD is considered a critical value (6,8,9).

In uremic patients many molecules which are either excreted or metabolized by the kidney are accumulated in blood. These uremic retention molecules (URMs) may contribute to the uremic syndrome. The URMs according to their origination are distinguished to the endogenous metabolism, microbial metabolism and to the exogenous intake. The phenols, indoles and amines, which are the key bacterial URMs have been studied in uremic patients. The URMs, apart from toxic effects, may contribute to the high measured osmolality and osmolal gap in uremic hemodialysed patients. During HD, disorders of osmolality may result in hemodynamic instability with hypotension and the neurological complications. A decline in serum osmolality, relative to intracellular, that results from the removal of urea and other solutes, leads to the movement of water to the intracellular space, to the impairing peripheral vasoconstriction and to the autonomic dysfunction with the consequence the hemodynamic instability and hypotension (8,10,11).

For the neurological deterioration after fast hemodialysis (disequilibrium syndrome), which is also an osmotic disorder, two explanations are proposed the “reverse urea hypothesis” and the “idiogenic osmole hypothesis”. The first suggests that urea removes more slowly from the brain than the plasma by HD, resulting in osmotic gradient and cerebral edema. The second suggests that an osmotic gradient
between brain and plasma is produced by newly formed brain osmoles, in fast HD. The ‘‘reverse urea hypothesis’’ remains more acceptable (2,12).

In conclusion, measuring the serum osmolality and osmolal gap in hemodialysed uremic patients is a useful indirect method for the detection the accumulation of unidentified osmoles in the serum. In our results the osmolal gap pre-HD is higher than 10mOsm/Kg, which is considered a critical value and it is decreased by HD. The importance of determination of serum osmolality and osmolal gap, in uremic hemodialysed patients, is the prevention of hypotensive events and neurological disorders during HD-session.

**Table I.** Mean value ± SD of measured parameters in the blood pre- and post- HD in 24 uremic patients and in 22 controls.

<table>
<thead>
<tr>
<th>SERUM MEASURED PARAMETERS</th>
<th>CONTROLS n =22</th>
<th>UREMIC PATIENTS n = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured Osmolality (mOsm/Kg/H₂O)</td>
<td>293,36 ± 2,37</td>
<td>313,33 ± 2,88</td>
</tr>
<tr>
<td>Calculated Osmolality (mOsm/Kg/H₂O)</td>
<td>290,54 ± 3,11</td>
<td>302,33 ± 4,03</td>
</tr>
<tr>
<td>Osmolal Gap (mOsm/Kg/H₂O)</td>
<td>3,18 ± 1,46</td>
<td>11,00 ± 2,08</td>
</tr>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>139,27 ± 1,16</td>
<td>135,58 ± 1,52</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>97,41 ± 7,00</td>
<td>93,54 ± 8,31</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>39,95 ± 5,26</td>
<td>159,33 ± 26,03</td>
</tr>
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</table>
Figure 1. Serum measured osmolality of hemodialysed uremic patients is significantly higher pre- and post-HD than in controls (p<0.001), also, the value post-HD is significantly decreased in comparison to that pre-HD (p<0.001).
Figure 2. Serum calculated osmolality of hemodialysed uremic patients is significantly higher pre-HD (p<0.001) and post-HD (p<0.05) than in controls, also, the value post-HD is significantly decreased in comparison to that pre-HD (p<0.001).
**Figure 3.** Serum osmolal gap of hemodialysed patients is significantly higher (0.001) pre- and post-HD than in controls (p<0.001), also, the value post-HD is significantly lower in comparison to that pre-HD (p<0.001).
REFERENCES


