Role of hyperglycemia in the pathogenesis of Na⁺/K⁺ disturbance

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ABSTRACT

Background: Electrolytes play an important role in maintaining acid-base balance, blood-clotting, control body fluid, muscle contraction, nerve conduction. The diabetic patients develop frequently a constellation of electrolyte imbalance. Imbalance in electrolyte concentration may affect the course of diabetes and its management. It has been reported that there is an inverse relationship between serum sodium (Na⁺) and potassium (K⁺) levels in diabetic patients. The aim of present study was to determine whether such relation is seen in context of Nepal and whether this inverse relation depends upon serum glucose levels in diabetic patients for their glycemic control.

Methods: This is a retrospective study performed on records of 135 diabetic patients who were treated at out-patient clinic of Kist Medical College and Teaching Hospital from 15 June 2015-15 July 2015. Fasting blood glucose (FPG) level was analyzed with semiautomatic analyzer- humalyzer 3000 by GOD-POD method and Na⁺ and K⁺ levels were analyzed with ion selective electrode- nova electrolyte. The relationship among serum Na⁺ level, serum K⁺ levels and Fasting plasma glucose levels were determined by SPSS version 20.

Results: Serum Na⁺ level was insignificantly negatively correlated (r=-0.091, p=0.296) with FPG level while a positive correlation of serum K⁺ level (r=0.235, p=0.006) was seen with FPG level and an inverse relation between serum Na⁺ and K⁺ was found. Age showed insignificant negative correlation with serum Na⁺ (r=-0.203, p=0.018), insignificant positive correlation with K⁺ (r=0.067, p=0.443) and insignificant negative correlation with FPG (r=-0.045, p=0.608).

Conclusions: Hyperglycemia disrupts the balance of serum Na⁺ and K⁺ in uncontrolled diabetes mellitus.

Keywords: Hyperglycemia, Serum Na⁺, Serum K⁺, FPG, DM

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease characterized by disorders in carbohydrate, fat and protein metabolism, a consequence of insulin resistance or impaired β-cell function, resulting in insulin deficiency or absence. Failure of some tissues, especially muscle and adipose tissue, to take up glucose due to insulin resistance (Type 2 diabetes mellitus) or absence of insulin (Type 1 diabetes mellitus) because GLUT-4 remains sequestered within cells, contributes greatly to hyperglycemia.⁴ High glucose levels may cause retinopathy, nephropathy, neuropathy and also an increased risk for cardiovascular disease. The complications of diabetes are metabolic imbalance, blood vessel degeneration, electrolyte imbalance have become a leading cause of impairment of human health.⁵,⁶

Electrolytes play an important role in maintaining acid-base balance, membrane potential, blood clotting, muscle contraction, nerve conduction and control body fluid.⁷

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Major electrolytes present in intracellular fluid (ICF) are potassium (K\(^+\)), magnesium (Mg\(^{2+}\)), phosphate (PO\(_4^{3-}\)) and sulphate (SO\(_4^{2-}\)) whereas major electrolytes found in extracellular fluid (ECF) are sodium (Na\(^+\)), chloride (Cl\(^-\)) and bicarbonate (HCO\(_3^-\)). Na\(^+\) is mainly associated with acid-base regulation of body fluids, maintenance of osmotic equilibrium as well as uniform distribution and conservation of body fluids. K\(^+\) is mainly responsible for the neuromuscular excitability, acid-base balance, cardiac action and acts as cofactor for the enzyme pyruvate kinase. The disturbed electrolyte may affect the course of diabetes and its management.  

Alterations in Na\(^+\)/K\(^+\) homeostasis may be the result of physiologic disorders associated with compromised renal function, vomiting and dehydration. Additionally, insulin activates Na\(^+\)/K\(^+\)-ATPase activity. Therefore, low serum insulin level compromises Na\(^+\)/K\(^+\)-ATPase activity with concomitant poor Na\(^+\) and K\(^+\) metabolism, transport across biomembranes as well as hindered monosaccharide uptake by intestinal epithelia. In diabetes mellitus, hyperglycemia imposes glucose-induced osmotic diuresis with resultant loss of body fluids and electrolytes. Study by De Fronzo et al has suggested that insulin and glucose have significant effects on renal tubular electrolyte transport and have shown that hyperinsulinemia is associated with antinatriuresis. Alteration of renin-angiotensin-aldosteron system (RAAS) imposes considerable alteration in electrolyte metabolism in diabetes patients by altering expression and activity of different ion-channels in renal tissue.  

The relation between blood glucose and electrolytes is complex and is related to a no. of other factors like age and associated conditions. Several works have been done to establish association between electrolytes levels and diabetes. It has been reported that there is an inverse relationship between serum sodium (Na\(^+\)) and potassium (K\(^+\)) levels in diabetic patients. The aim of this study was to determine whether such relation is seen in context of Nepal and whether this inverse relation depends upon serum glucose levels in diabetic patients for their better glycemic control.  

**METHODS**

This is a retrospective study performed on records of 135 diabetic patients who were treated at out-patient clinic of Kist Medical College and Teaching Hospital from 15 June 2015-15 July 2015. Patients of type 1 diabetes mellitus (insulin dependent diabetes mellitus), type 2 diabetes mellitus (non-insulin dependent diabetes mellitus) and gestational diabetes mellitus with diabetes onset ≤10 years were included in this study. Patients with diabetic nephropathy, myocardial disorder, liver disfunction were excluded from this study.  

Fasting blood glucose (FPG) level was analysed with semiautomatic analyser- humalyzer 3000 by GOD-POD method and Na\(^+\) and K\(^+\) levels were analysed with ion selective electrode- Nova electrolyte.  

The patients were classified into four groups on the basis of level of fasting plasma glucose i.e. group A- patients with FPG level 60-126 mg/dl, group B- patients with FPG level 127-200mg/dl, group C- patients with FPG level 201-250mg/dl and group D- patients with FPG level >250mg/dl. The relationship among serum Na\(^+\) level, serum K\(^+\) levels and Fasting plasma glucose levels were determined by linear regression and ANOVA with software SPSS version 20. A 95% confidence interval was used. P -values less than 0.05 were considered as statistically significant.  

**RESULTS**

Out of 135 diabetes mellitus patients 70 were females (mean age 51) and 65 were Males (mean age 51) and age ranged from 14 to 85 years. The duration of onset of diabetes mellitus was 6.3±3.4 years. They consisted of 7 Type 1 DM, 123 Type 2 DM and 5 Gestational DM patients. Min. level of FPG was 62.3, max level 324 mg/dl with mean 143.3±47.  

Table 1 shows the changes in Na\(^+\) and K\(^+\) levels with fasting plasma glucose. Serum Na\(^+\) was decreased with increasing fasting plasma glucose. Conversely, serum K\(^+\) level was found increasing with increased fasting plasma glucose.  

**Table 1: Correlations of serum Na+ and K+ with FPG.**

<table>
<thead>
<tr>
<th>FPG (mg/dl)</th>
<th>N</th>
<th>Serum Na+ (mEq/l)</th>
<th>Serum K+ (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-126</td>
<td>53</td>
<td>140.2±4.2</td>
<td>4.47±0.7</td>
</tr>
<tr>
<td>127-200</td>
<td>69</td>
<td>139.6±6.8</td>
<td>4.57±0.79</td>
</tr>
<tr>
<td>201-250</td>
<td>8</td>
<td>138.0±8.3</td>
<td>4.82±1.1</td>
</tr>
<tr>
<td>&gt;250</td>
<td>5</td>
<td>137.5±7.8</td>
<td>5.38±0.54</td>
</tr>
</tbody>
</table>

![Figure 1: Correlation of serum Na+ with fasting plasma glucose.](image-url)
Figure 1 shows the correlations between serum Na⁺ level and FPG of all the 135 patients. Serum Na⁺ level ranged from 116 to 152.8 mEq/l and the mean was 139.6±6.0. There was an insignificant negative correlation between serum Na⁺ level and FPG [r=-0.091, p=0.296].

![Correlation of serum Na+ with fasting plasma glucose.](image1)

**Figure 2: Correlation of serum K+ with fasting plasma glucose.**

Figure 2 shows the correlations between serum K⁺ level with FPG. Serum K⁺ ranged from 2.6 to 6.1 mEq/l and the mean was 4.58±0.78. There was a significant positive correlation between serum K⁺ level and FPG [r=0.235, p=0.006].

Table 2 shows the correlations of FPG, serum Na⁺ and K⁺ with age. FPG and Na⁺ decreases with age while serum K⁺ increases with age.

**Table 2: Correlations of Serum Na⁺, K⁺ & FPG with age.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Serum Na⁺</th>
<th>Serum K⁺</th>
<th>FPG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r=-0.203, p=0.018</td>
<td>r=0.067, p=0.443</td>
<td>r=-0.045, p=0.608</td>
</tr>
</tbody>
</table>

![Correlation of serum Na+ with gender and plasma glucose.](image2)

**Figure 3: Correlation of serum Na+ with gender and plasma glucose.**

Table 3 shows the mean level of serum Na⁺ and K⁺ in Male and female. Gender did not show considerable variation on serum Na⁺ and K⁺ levels.

**Table 3: Relation of Na+ and K+ distribution with gender.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Serum Na⁺(mEq/l)</th>
<th>Serum K⁺(mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>139.8±5.6</td>
<td>4.55±0.84</td>
</tr>
<tr>
<td>Male</td>
<td>139.58±6.4</td>
<td>4.61±0.72</td>
</tr>
</tbody>
</table>

![Relation of K+ with gender and plasma glucose.](image3)

**Figure 4: Relation of K+ with gender and plasma glucose.**

**DISCUSSION**

The patients were divided into four groups according to the level of fasting plasma glucose. The greater level of FPG showed the lower level of serum Na⁺ and conversely, higher level of serum K⁺. It suggests that distribution of serum Na⁺ and K⁺ is dependent on plasma glucose level. Hyponatraemia was observed in several studies of diabetic patients and our study is in agreement with Jameil NA and Saito, et al.⁷,⁸ There are several factors possibly involved in alteration of these electrolytes distribution. Hyperglycemia causes osmotic diuresis, resulting hypovolemia. The higher the level of plasma glucose results in the greater depletion in circulating blood volume.⁸ Serum Na⁺ is reabsorbed in proximal convoluted tubule of nephron and excessive urination due to hyperglycemia is known to be the mechanical cause of depleted Na⁺ concentration.⁷

Hyperosmolality ensuing hyperglycemia causes a relative increase in extracellular fluid derived from interstitial spaces. These osmotic effects have a diluting effect on the concentration of serum electrolytes which may have caused hyponatraemia. In addition, hyperosmolality promotes cellular dehydration, thus providing an increase in K⁺ efflux from cells into serum. This may be hypothesized as a reason behind inverse relations of serum Na⁺ and K⁺ with FPG.
Insulin may be purposed as an important factor behind altered distribution of serum Na⁺ and K⁺. Absolute or relative deficiency of insulin secretion or insulin resistance is found in DM patients. Insulin is required for the activity of Na⁺/K⁺-ATPase. This transporter is responsible for maintaining the transmembrane gradients of Na⁺ and K⁺. The activity of this transport protein could be attenuated in diabetic patients suffering from insufficient insulin secretion or insulin resistance. Attenuated activity of Na⁺/K⁺-ATPase may be a reason for inverse relation of serum Na⁺ and K⁺ levels during hyperglycemic conditions. Rationale behind this is a significant decrease in this protein activity has been reported in uncontrolled type 1 diabetic patients and intensive insulin therapy restores erythrocyte Na⁺/K⁺-ATPase activity in these patients. Disturbance of membrane lipid organization can explain the decrease in Na⁺/K⁺-ATPase activity. A volume depleted state tends to increase plasma arginine vasopressin, plasma renin activity and plasma aldosterone concentration. But hyporeninemic hypoaldosteronism is seen in diabetic patients. Hypo-secretion of aldosterone results in decreased activity of Epithelial Na⁺ channel (ENaC) - a Na⁺-selective channel found at the apical membrane of salt-reabsorbing tight epithelia of distal nephron. Decreased activity of ENaC interferes with Na⁺ reabsorption and thus hyponatraemia results. Due to suppressed aldosterone, expression and activity of Renal Outer Medullary K⁺ (ROMK) channel - apical K⁺ channel responsible for K⁺ secretion in glomerular filtrate – is also reduced. Low plasma aldosterone reduces the ROMK by increased internalization and degradation of the channel and thus hyponatraemia results. Water reabsorption in the collecting duct through aquaporin mainly AQP2 in the apical and combination of AQP3 and AQP4 in the basolateral membranes respectively is the key event for maintenance of body water balance. The binding of vasopressin to its receptor (V₂R) on basolateral membrane induces an increase in intracellular cAMP level which leads to activation of protein kinase A (PKA) and to phosphorylation of AQP2 channels. The phosphorylation of AQP2 channels stimulates its redistribution from the storage vesicles to the apical membrane rendering this membrane permeable to water reabsorption. It has been suggested that the altered vasopressin regulation in diabetes mellitus, the increased insulin-induced potentiation of vasopressin-induced AQP2 water channel’s expression and the absorption of water from the GI tract due to slower stomach emptying may play a role in the association between diabetes mellitus and decreased serum Na⁺ levels.

Some studies found opposite changes in serum Na⁺ and K⁺ levels viz. hypernatraemia with hypokalaemia. In our study also 6 patients were found with this exceptional distribution i.e. high serum Na⁺ and low serum K⁺. Mc Donnell, et al, Kavelars, et al, and Hosen B reported high serum Na⁺ level in hyperosmolar diabetes mellitus. Nitzan and Zalmanovski showed hypernatraemia in glucose intolerant rats. The development is associated with both - impairment of insulin-mediated glucose metabolism and glucagon-dependant glucose release. Thus hypernatraemia and hyperosmolarity should be considered as contributing factors to the occurrence of hyperglycemia in critically ill patients.

The causes of hypokalaemia in diabetes patients are: (1) redistribution of K⁺ from extracellular to intracellular fluid compartments due to insulin administration, (2) gestational loss due to malabsorption syndrome (diabetes induced motility disorders, bacterial overgrowth, chronic diarrhea) and (3) renal loss of K⁺ (due to osmotic diuresis and/or coexistent hypomagnesemia). The majority of patients with diabetes ketoacidosis (DKA) and HHS are markedly K⁺ depleted. A no. of factors responsible for K⁺ loss in these patients are vomiting, increased renal losses due to osmotic diuresis and ketoacid anion excretion and the loss of K⁺ from the cells due to glycosgenolysis and proteolysis.

CONCLUSION

This study showed hyponatraemia and hyperkalaemia with increased hyperglycemia i.e. there is inverse relation between serum Na⁺ and K⁺ levels and it is dependent plasma glucose level. Taking in consideration of the multifactorial origin of hyponatraemia and hyperkalaemia, a cause-specific treatment is required to avoid any risk. However our study has a small sample size which reflects low power to detect minor to modest associations. Thus multi-center study with large sample size is necessary.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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