Inverse Distribution of Serum Sodium and Potassium in Uncontrolled Inpatients with Diabetes Mellitus

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Abstract. It has been reported that there is an inverse relationship between serum sodium (Na) and potassium (K) levels in patients with diabetic coma. The present study was undertaken to determine whether such an inverse relation depends upon plasma glucose levels in diabetic patients for their glycemic control. We examined two hundred and fifty-two patients with diabetes mellitus admitted to our hospital during the one-year period to control their plasma glucose levels, except for those having nephropathy or liver dysfunction. Serum Na and K, plasma glucose, and serum and urinary C-peptide levels were determined. There was a negative correlation between serum Na levels and fasting plasma glucose (FPG), and, conversely, a positive correlation between serum K levels and FPG. The changes were more evident in the patients with insulin-dependent diabetes mellitus than those with non-insulin-dependent diabetes mellitus. There was an inverse relation between serum Na and K levels and it was profoundly dependent upon plasma glucose levels in all the diabetic patients before tight control of their glycemic levels. The disorder may be based on the movement of electrolytes between intra- and extracellular spaces, dependent on the impaired insulin action as well as hyperosmolality.

Key words: Serum Na, Serum K, Blood glucose, Insulin, Diabetes mellitus

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HYPONATREMIA was described in patients with diabetic coma, and serum sodium (Na) levels have been reported to decrease at the rate of 1.6 mEq/l per 100 mg/dl increase in plasma glucose [1–5]. In our previous study, we analyzed 26 patients with diabetic coma, who had noticeable hyperglycemia associated with serious dehydration [6]. There were opposite changes in serum Na and potassium (K) levels, namely hyponatremia with hyperkalemia, and hypernatremia with hypokalemia [6]. The alterations in serum Na and

K levels were closely linked with one another, suggesting that hyperosmolality was not the sole cause of the change [6]. Such a volume-depleted state increases plasma arginine vasopressin, plasma renin activity and plasma aldosterone concentration in diabetic coma [7, 8]. In this context, such changes may be observed in diabetic patients whose plasma glucose levels are not so high as those in the comatose state. McNair *et al.* [9] reported similar findings in insulin-treated diabetic out-patients.

The present study was undertaken to determine whether the distribution of serum Na and K levels is dependent upon plasma glucose levels in diabetic in-patients with uncontrolled glycemic levels, including those with diabetic coma, during the one-year period. Also, what factors, in addition to hyperosmolality, are involved in the mechanism for the changes in serum Na and K were evaluated.

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Subjects and Methods

Two hundred and fifty-two patients with diabetes mellitus were examined between March, 1996 and February, 1997, who were admitted to the Endocrine and Metabolic Ward of Jichi Medical School Hospital in order to control their hyperglycemia. Those patients with diabetic nephropathy and liver dysfunction were excluded from the present study. The protocol was approved by the ethical committee of Jichi Medical School Hospital for human study. No patient had proteinuria examined qualitatively using N-Multistex SGL (Miles-Sankyo, Tokyo). Seventy-three patients with diabetic neuropathy were included. One hundred and seven patients had diabetic retinopathy; 55 patients had simple retinopathy, 41 had preproliferative retinopathy and 11 had proliferative retinopathy. They were 120 males and 132 females whose ages ranged from 12 to 86 years (53.5 ± 17.5 years, Mean $\pm$ SD). The duration of diabetes mellitus was 7.2 ± 3.4 years. Non-insulin-dependent diabetes mellitus (NIDDM) was defined by fasting serum C-peptide more than 1.0 ng/ml and urinary excretion of C-peptide more than 30 μ g/day in the steady state. They consisted of 220 patients with NIDDM and 32 patients with insulin-dependent diabetes mellitus (IDDM) (Table 1). Fourteen out of 252 diabetic patients had been diagnosed as having diabetic coma on admission, including diabetic ketoacidosis ($n=11$) and non-ketotic hyperosmolar coma ($n=3$). On admission, 51 patients had been treated with diet therapy, 91 patients with sulfonylureas and/or α -glucosidase inhibitors, and 110 patients with insulin therapy. Fasting plasma glucose (FPG) was 190.7 ± 5.5 mg/dl (mean $\pm$ SEM) in the patients except for those with diabetic coma, and hemoglobin A_{1c} (HbA_{1c}) was $9.4 \pm 0.2\%$. Fasting serum C-peptide and 24-hour urinary excretion of C-peptide were 2.4 ± 0.1

ng/ml and 86.6 ± 4.9 μ g/day in the patients with NIDDM, respectively. Similarly, in the patients with IDDM, fasting serum C-peptide was 0.4 ± 0.1 ng/ml and 24-h urinary excretion of C-peptide 12.1 ± 2.5 μ g/day. We could not evaluate the intake of NaCl before admission in each case. One hundred and thirty-four of 252 patients had hypertension and they had been treated with Ca²⁺-blockers, inhibitors of angiotensin converting enzyme, α -blockers and/or chlorothiazides. The number of patients treated by α -blockers or chlorothiazides was smaller than the number of those treated with the former two drugs.

We studied the distribution of serum Na and K levels on the admission in 252 patients with diabetes mellitus. We analyzed the relationship among serum Na levels, serum K levels and FPG. As an exception, plasma glucose levels on admission were employed instead of FPG in the patients with diabetic coma, because they were immediately treated with a continuous infusion of insulin and fluid. The patients were subgrouped into four groups according to the levels of FPG; i.e., Group 1, patients whose FPG was 60–200 mg/dl; Group 2, FPG 201–300 mg/dl; Group 3, FPG 301–500 mg/dl; and Group 4, FPG (or plasma glucose on admission for comatose patients) more than 500 mg/dl. Also, we evaluated the distribution of serum Na and K levels in all the patients on discharge, when FPG was well controlled. Fasting serum C-peptide and 24-h urinary excretion of C-peptide were determined in a week after the hospitalization.

We also analyzed hematocrit on admission and discharge, and the percent change in circulating blood volume was calculated by taking the data on discharge as zero, determined by the changes in hematocrit (Ht): $(Ht_2 - Ht_1)/Ht_2 \times 100$ (%) [10].

All the data are shown as means $\pm$ SEM. Simple linear regression analysis was performed to calculate correlations. One-way factorial analysis

Table 1. Profile of 252 patients with diabetes mellitus

	N	Age (years)	HbA _{1c} %	Fasting serum C-peptide (ng/ml)	Urinary excretion of C-peptide (μ g/day)	Diabetic coma* (N)
NIDDM	220	55.6 ± 1.1	9.2 ± 0.2	2.4 ± 0.1	86.6 ± 4.9	3
IDDM	32	39.1 ± 3.2	11.1 ± 0.7	0.4 ± 0.1	12.1 ± 2.5	11

*Numbers of diabetic ketoacidosis or non-ketotic hyperosmolar coma on admission. Values are the means $\pm$ SEM.

ANOVA accompanied with Fisher's multiple comparison test was used to compare the difference. The statistical package of StatView for Macintosh, version 4.1, was employed for the present analysis. A *P* value less than 0.05 was considered significant.

Results

Figure 1A shows the relationship between serum Na levels and FPG in all the 252 patients with diabetes mellitus on admission. Serum Na levels ranged from 120 to 164 mEq/l. FPG less than 200 mg/dl was obtained from 149 out of 252 patients (Group 1) and serum Na levels in Group 1 were within the normal range (136 to 146 mEq/l). Serum Na levels less than 135 mEq/l were obtained in 31 patients whose FPG levels were higher than 219 mg/dl. As shown in Fig. 1A, there was an inverse correlation between serum Na levels and FPG [S_{Na} (mEq/l) = $-0.02 \times \text{FPG}$ (mg/dl) + 142.8; $r=0.585$, $P<0.0001$].

Fig. 1B shows the relationship between FPG and serum K levels in all the patients with diabetes mellitus on admission. Serum K levels ranged from 3.2 to 7.9 mEq/l. However, the serum K levels were distributed between 3.2 and 5.1 mEq/l in 149 patients whose FPG was less than 200 mg/dl. There was a positive correlation between FPG and serum K levels [S_K (mEq/l) = $3.84 + 0.002 \times \text{FPG}$ (mg/dl); $r=0.878$, $P<0.0001$]. In addition, we conducted separate analysis of the relationships for the patients with NIDDM and IDDM. The regression line was twice as great in the patients with IDDM as in those with NIDDM (regression constant; 0.002 *vs.* 0.001).

We analyzed the relationship between serum Na and K levels on admission in all the patients (Fig. 2). As shown in Fig. 2A, an inverse correlation was obtained between serum Na and K levels; S_{Na} (mEq/l) = $156.23 - 3.98 \times S_K$ (mEq/l), $r=0.415$, $P<0.0001$. We further evaluated their relation according to the FPG on admission. As noted in the method, we divided the patients into 4 subgroups according to the levels of FPG. The lower Na and the higher K levels in serum were observed with the higher FPG on admission (Fig. 2B). The values in the 4 groups are shown in Table 2. A hypernatremic and hypokalemic state was found in only two patients with non-ketotic

Fig. 1. The relationships of serum Na and K levels to fasting plasma glucose (FPG) on admission in 252 patients with diabetes mellitus. (A) Serum Na levels *vs.* FPG. (B) Serum K levels *vs.* FPG. Closed circles (●) show the patients with NIDDM, and open circles (○) show the patients with IDDM. As an exception, plasma glucose levels on admission were used for analysis in the patients with diabetic coma.

hyperosmolar coma. On discharge, plasma glucose was well controlled, and serum Na and K levels in all the four groups were in the normal ranges (data not shown).

Lastly, a decrease in circulating blood volume was determined by the changes in hematocrit during the hospitalization. The greater reduction in circulating blood volume was found with the higher levels of FPG on admission (Fig. 3). There was an inverse correlation between FPG and percent changes in circulating blood volume [percent changes in circulating blood volume (%) = $-1.74 - 0.02 \times \text{FPG}$ (mg/dl); $r=0.397$, $P<0.0001$].

Fig. 2. Serum Na and K levels on admission in the patients with diabetes mellitus. They were divided into 4 groups following fasting plasma glucose (FPG) levels. Closed circles (●) show the patients whose FPG was 60–200 mg/dl. Closed triangles (▲) show those whose FPG was 201–300 mg/dl. Closed squares (■) show those whose FPG was 301–500 mg/dl. Open squares (□) show those whose FPG was more than 500 mg/dl. As an exception, plasma glucose on admission was employed in the patients with diabetic coma. (A) The distribution. (B) The data show mean $\pm$ SEM, with their distribution in each group.

Table 2. Serum Na and K levels on admission in the patients with diabetes mellitus

Fasting plasma glucose (FPG) (mg/dl)	N	Serum Na (mEq/l)	Serum K (mEq/l)
60–200	149	141.3 $\pm$ 0.2	4.12 $\pm$ 0.03
201–300	63	138.7 $\pm$ 0.4	4.23 $\pm$ 0.05
301–500	25	134.2 $\pm$ 0.9	4.40 $\pm$ 0.09
500<	15	131.9 $\pm$ 2.7	5.13 $\pm$ 0.27

For exception, plasma glucose levels on admission were used for analysis of the patients with diabetic coma. Values are the means $\pm$ SEM.

Fig. 3. The distribution of percent decrease in circulating blood volume dependent on fasting plasma glucose (FPG) in the patients with diabetes mellitus. Closed circles (●) show the patients with NIDDM, and open circles (○) show the patients with IDDM. As an exception, plasma glucose levels on admission were used for analysis in the patients with diabetic coma.

Discussion

We evaluated the distribution of serum Na and K levels in 252 patients, including both NIDDM and IDDM, who had been admitted to our hospital during the one-year period. The patients with diabetic nephropathy were excluded from the present study, because they might have latent disorders of nephrons. The distribution of serum Na and K levels is shown in Fig. 2, and they were divided into 4 groups according to the level of fasting plasma glucose. The greater level of FPG produced the lower level of serum Na and the

higher level of serum K. Hyponatremia was manifest when the plasma glucose level elevated to approximately 220 mg/dl, and hyperkalemia was obvious when the plasma glucose level elevated to more than 500 mg/dl. This is in concert with the study in insulin-treated diabetic out-patients [9]. In the present study, the findings were similarly obtained in the patients treated with sulfonylureas and/or α -glucosidase inhibitors and those with insulin therapy. Hyponatremia was not infrequently found in the uncontrolled in-patients with diabetes mellitus, as approximately 12% of the in-patients had hyponatremia less than 135 mEq/l during the one-year period. Such an alteration was more evident in the patients with IDDM, whose insulin secretion was absolutely impaired. The present study shows that distribution of the serum Na and K levels is dependent on plasma glucose levels in the diabetic patients including those with diabetic coma, and suggests that the alteration in serum Na and K levels is closely related to one another. After plasma glucose levels were well controlled, serum Na and K levels reached the normal ranges in all the four groups of patients. In addition, exceptional distribution, namely hypernatremia and hypokalemia, were observed in two patients with non-ketotic hyperosmolar coma, as described previously in our report [6].

What mechanisms are involved in the opposite alteration in serum Na and K levels? There are several factors possibly participating in the mechanisms. Hyperglycemia produces osmotic diuresis, resulting in the decrease in circulating blood volume. The higher level of plasma glucose results in the greater reduction in circulating blood volume, as there was a significant negative correlation between plasma glucose and percent changes in circulating blood volume, estimated by the changes in hematocrits. These changes may have increased the concentrations of both serum Na and K. Changes in the distribution of the electrolytes between intra- and extracellular spaces may well be the case, because hyperosmolality

causes a relative increase in extracellular fluid, derived from the intracellular spaces. This osmotic effect may have a diluting effect on the concentration of electrolytes. Also, hyperosmolality would promote cellular dehydration, thus providing an increase in K efflux from the cells. The renin-aldosterone system was activated in such a hypovolemic state [6, 11], and this may have antagonized the observed changes, although hyporeninemic hypoaldosteronism, which is sometimes observed in patients with diabetic neuropathy, may have attenuated this effect [12, 13]. Urinary loss of K, however, was not evaluated in the present study.

The altered distribution is not merely based on hyperosmolality. The important factor is insulin [14, 15], as absolute and/or relative deficiency of insulin secretion is present in diabetic patients. There was no direct relationship between C-peptide levels and the changes in serum electrolytes, but the increase in serum K levels was greater in the patients with IDDM than those with NIDDM. This may be due to the mixed groups of the patients with NIDDM and IDDM. Besides, one-third of the NIDDM patients were treated with insulin. Serum and urinary C-peptide levels were low in the patients with IDDM, but varied in the NIDDM patients. Insulin activates the activity of Na^+ , K^+ -ATPase [16–18]. The activity of Na^+ , K^+ -ATPase could be attenuated in the diabetic patients whose insulin secretion was blunted and/or insulin resistance was present. Taken together, the altered distribution of serum Na and K is based on the flux of the electrolytes between intra- and extracellular spaces, and its pathogenesis may depend on the insufficient effect of insulin on Na^+ , K^+ -ATPase on plasma membrane, in addition to the effect of hyperosmolality.

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