Status of serum potassium in patients with type 2 diabetes mellitus with and without complications

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Abstract
Accumulating evidence that metabolism of several essential elements is altered in diabetes mellitus (DM) and might have specific roles in the pathogenesis and progress of this disease.1 Data underscore the adverse effects of glucose and insulin on potassium levels and the high incidence of cardiovascular and renal complications in patients with diabetes mellitus. Chronic hyperglycemia of diabetes mellitus is associated with long term damage and dysfunction of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. These findings have not been comprehensively evaluated in critical reviews.2 **Aim:** To estimate the serum potassium levels in type 2 diabetes mellitus with and without complications. **Setting and Design:** A hospital based cross sectional study in the rural setting of Haryana. **Material and Methods:** 250 subjects were selected, 50 were healthy controls and 200 were taking the treatment for T2DM, including patients with and without complications were recruited from Medicine OPD of MMIMSR, Mullana, Ambala (Haryana), and their potassium levels were measured and compared. **Statistical Analysis:** By SPSS version 12{SPSS v12 (Spss Inc; Chicago, IL)}. **Results and Conclusion:** Subtle changes in serum potassium levels in T2DM as they might have a bearing with disease complications.
Keywords: Complications, potassium, type 2 diabetes mellitus

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INTRODUCTION

Hypomagnesemia is common in type 2 DM (T2DM)[1] and with complications.[2] Hypokalemia is a common event in hypomagnesemic patients, occurring in 40 to 60% of cases.[3] Potassium secretion from the cell into the lumen in the cell of the thick ascending limb and cortical collecting tubule is mediated by ATP inhibitable luminal potassium channels.[4] Hypomagnesemia is associated with a reduction in cell magnesium concentration, which may then lead to a decline in ATP activity, and, due to removal of ATP inhibition, an increase in the number of open potassium channels. Decreasing cytosolic magnesium has been shown to directly increase the activity of potassium channels of ascending limb cells.[5] Given the very high cell potassium concentration, these changes would promote potassium secretion from the cell into the lumen and enhanced urinary losses.[6] A prospective study in Japanese men not using antihypertensive suggested that mild to moderately low serum potassium levels, within the normal range and without frank hypokalemia, could be predictive of T2DM. Another prospective study showed strong correlation between hypokalemia and hypomagnesemia. Coexisting hypomagnesemia and hypokalemic patients were 45%.[7] Therefore, the present study was planned to explore the status of serum potassium in patients with T2DM, with or without some of the disease complications.

MATERIALS AND METHODS

A hospital-based cross sectional study and was conducted in the Department of Biochemistry, M.M.I.M.S.R,

Mullana, Ambala in which healthy individuals and diabetic patients attending the Medicine Department of M.M.I.M.S.R, Mullana, Ambala, were studied. Out of the 250 subjects (age 30 years and above of either sex) selected, 50 were healthy controls (Group I) and 200 were taking the treatment for T2DM (Group II), including patients without complication (Group IIA, 100 individuals) and those with complications (Group IIB, 100 individuals). DM was defined as fasting plasma glucose $\geq$ 126 mg/dl (7.0mmol/l) and 2-hours postprandial glucose $\geq$ 200 mg/dl (11.1mmol/l).[8] Complications refer to microvascular complications including diabetic retinopathy, nephropathy and neuropathy as diagnosed by Department of **Medicine**

1. Diabetic Retinopathy (Non-proliferative), was assessed by fundus examination, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microaneurysms and hemorrhages. However, Diabetic Retinopathy (Proliferative) was characterized by vitreous hemorrhage, fibrosis and retinal detachment.
2. Diabetic Nephropathy, was assessed by microalbuminuria defined as urinary albumin excretion of 30-300 mg/24 hrs.[9]
3. Diabetic Neuropathy, was assessed by diminished tendon reflexes and sensory impairment.[8]

Patients suffering from diabetic ketoacidosis, hyperthyroidism, hyperpituitarism, pancreatitis, carcinoma of pancreas, and Cushing's disease were excluded. Patient taking any medicine which would alter the blood glucose levels like phenothiazines, caffeine, nicotine, levodopa, morphine, steroids, oral contraceptives, α-interferon etc, were also excluded from the study group. 5ml of venous blood was aseptically collected from antecubital vein. The whole blood was divided in two equal parts. One part was put in vial with anticoagulant, mixed properly and centrifuged to separate plasma for estimation of glucose. Another part of blood was put in vial with no anticoagulant and allowed to stand for some time so that serum was separated for estimation of potassium levels. The diabetic patient was advised to collect his/her urine sample collected for the full 24 hours in a clean container and then come to the laboratory for the estimation of albumin. Plasma glucose was estimated by Glucose Oxidase-Peroxidase (GOD-POD) method.[10] Serum potassium was estimated by Ion Selective Electrode.[11] 24 hours urine sample was estimated by pyrogallol red-molybdate method for albumin.[9] The normal range of serum potassium is 3.5-5.5 mEq/l.[12] The data obtained were analyzed as per standard statistical methods.

Ion Selective Electrode[10] Principle

An ideal Ion Selective Electrode consists of a thin membrane across which only the intended ion can be transported. The transport of ions from a high concentration to a low one through a selective binding with some sites within the membrane creates a potential difference. The membrane potential is dependent on the activities of the potassium ions on the either side of the membrane and was described by Nernst:

$$E_m = \frac{RT}{nF} \ln \frac{a_0}{a_1}$$ --------------------equation 1

Where E_m is the membrane potential, a is the activity of the potassium ions, R is the universal gas constant, T is the temperature in degrees Kelvin, F is the Faraday's constant and n is the charge of the measured ion:

+1 for potassium ions

When the glass tubing is filled with a salt solution of constant composition, called the internal filling solution, (IFS) the electric potential of the membrane depends only on the solution outside the membrane as follows:

$$E_m = E_0 + \frac{RT}{nF} \ln a_0$$ ------------------ equation 2

Where E_0 is a constant that includes a term for a_0, the activity of the ion in the IFS. We can convert from the natural log (ln) in equation 2 to a base 10 log and device an equivalent equation:

$$E_m = E_0 + 2.303 \frac{RT}{nF} \log a_0$$ --------------- equation 3

in order to measure the potential on the ion selective membrane; a complete electrical circuit is needed. There are two electrodes, reference electrode and ion selective electrode. The potential of the reference electrode is maintained constant; that of the Ion Selective Electrode varies, depending on the activity of the ion if interest in test solution. A voltmeter is used to measure the potential difference between the ion selective elective electrode and the reference electrode. The potential difference of the entire electrode measuring circuit, E_{cell}, is equal to the algebraic sum of the potential from the ion selective electrode, E_m, the reference electrode, E_r, and the junctional potential, E_j

$$E_{cell} = E_m - E_r - E_j$$ ----------------- equation 4

The junctional potential developed at the liquid/liquid junction between the reference electrode and the test solution. Using high concentration of salts that are equitransferent minimizes the magnitude of the liquid junction potential (that is, have similar ionic metabolites in solution).

By setting

$$S = 2.303 \frac{RT}{nF}$$

and substituting equation 3 for E_m, equation 3 can be rewritten

$$E_{cell} = E_m + S \log a_0 - E_r - E_j$$ ------------ equation 5

S is called the electrode slope. Under ideal conditions at 37^0C, it is theoretically equal to 30.8 mV per decade change in activity for a divalent ion, and 61.5 mV for a univalent ion. It is the slope of the line obtained by graphing potential, E, vs the log of the concentration (or activity). Such a line is described by Nernst equation.

$$S = \frac{E_{StdB} - E_{StdA}}{log\frac{B}{A}}$$ -------------------- equation 6

Where B is the activity of standard B and A is the activity of standard A.

When unknown activity of the ion of interest is measured in a test solution, the potential of the test solution, E_x is compared with that of a known. Most of the terms cancel out as follows:

$E_{x} = E_0 + S \log a_x - E_r - E_j$ ------------------ equation 7

$E_{std} = E_0 + S \log a_{std} - E_r - E$ ---------------- equation 8

$\Delta E = E_x - E_{Std} = S \log \frac{a_x}{a_{Std}}$ ----------------- equation 9

Thus, the difference in potential between the 2 solutions, E, is dependent only on the ratio of the activity of the ion of interest in the test solution, a_x, and the activity of the ion of interest in the standard solution.

Calculation of K^+ Concentration

The activity of an ion is a measure of its "effective" concentration in solution. It is equal to the product of C, its concentration in solution, and f, its ionic activity coefficient. a = (f) (c). The activity coefficient relates concentration to activity, and is a function of ionic strength. Thus, equation 9 can be rewritten in terms of concentration:

$$\Delta E = E_x - E_{Std} = S \log \frac{(fC)_0}{(fC)_i} - E_r - E_j$$ ---------- equation 10

The ionic strength of whole blood, plasma and serum tends to remain relatively constant over the physiological range. As a result, the activity coefficient of potassium can be assumed to be constant. The internal standards are formulated to reflect the same ionic strength as that of serum. Therefore, a given ion's activity coefficient can be

6.

assumed to be equal in the standard and sample. Now equation 10 can be rewritten as

$E_{cell} = E' + S \log F(C_0, C_1)$ ------------------- equation 11

Where,

$$E' = E_0 + S \log \frac{f_0}{f_i} - E_r - E_j$$ ----------------- equation 12

Thus, when E_{cell}, the potential of the test solution, is measured against that of standard solution in which the concentration of the ion of interest is known, the potential difference between the 2 solutions is dependent only on the difference between the concentrations of the ion of interest in the test and standard solutions:

Letting $E_{cell} = E$:

$E_{x\ minus} = E' + S \log (C_x/C_i)$ --------- equation 13

$E_{std} = E' + S \log (C_{Std}/C_i)$ ------------ equation 14

$E = E_x - E_{std} = S \log(C_x/C_{std})$ ------- equation 15

By holding C_{std} in equation 15 constant, E is dependent on only one variable, C_x, the concentration of the ion of interest in the sample. This equation 15 can be rearranged to isolate this variable:

$C_x = (C_{std}) 10^{(\Delta E/s)}$ ------------- equation 16

The microcomputer uses the last equation 16 to calculate the concentration of potassium in the sample.

Advantages of Ion Selective Electrode

1. Linear response
2. Non-destructive: no consumption of analyte.
3. Non-contaminating.
4. Short response time: in sec. or min. useful in industrial applications.
5. Unaffected by colour or turbidity.

Limitations of Ion Selective Electrode

1. Precision is rarely better than 1%.
2. Electrodes can be fouled by proteins or other organic solutes.
3. Interference by other ions.
4. Electrodes are fragile and have limited shelf life.
5. Electrodes respond to the activity of uncomplexed ion. So ligands must be absent or masked.

RESULTS AND DISCUSSION

Table 1: Comparison of study groups according to fasting plasma glucose levels

Sr. No	Range of fasting plasma glucose (mg/dl)	Group I		Group IIA		Group IIB	
		No.	%	No.	%	No.	%
1	<110	50	100	2	2	1	1
2	110-135	0	0	33	33	2	2
3	136-180	0	0	56	56	19	19
4	>180	0	0	9	9	78	78

p<0.001

All the subjects in Group I had fasting blood glucose levels <110 mg/dl. Majority of subjects in Group IIA had fasting blood glucose levels between 136-180 mg/dl whereas majority of subjects in Group IIB had fasting blood glucose levels above 180 mg/dl. On comparing the data statistically, a significant difference was observed among the three groups (p<0.001, Table 1).

Table 2: Distribution of subjects according to serum potassium levels

Sr. No	Serum potassium levels (mEq/l)	Group I		Group IIA		Group IIB	
		No.	%	No.	%	No.	%
1	<3.5	1	2	6	6	8	8
2	3.5-5.0	43	86	87	87	75	75
3	>5.0	6	12	7	7	17	17
	Mean ±SD (Range)	4.61±0.44 (2.3-5.3)		4.35±0.54 (2.3-5.5)		4.43±0.67 (2.4-6.2)	

p=0.127 (NS) F=3.202; p=0.042

Majority of subjects in all the three groups had serum potassium levels between 3.5-5.0 mEq/L (Table 2). Categorically, the differences among groups were not significant statistically (χ^2=7.167; p=0.127). However, parametrically, a significant difference in mean serum potassium levels among groups was observed with mean value of Group I subjects being maximum (4.61±0.44 mEq/L) and that of Group IIA being minimum (4.35±0.54 mEq/L) (F=3.202; p=0.042).

Table 3: Association of serum potassium levels with different types of diabetic complications (n=100)

Sr. No	Complication	No. of cases	Serum potassium levels (mEq/l)	
			Mean	SD
1	Retinopathy only	21	4.12	0.55
2	Neuropathy only	32	4.30	0.63
3	Nephropathy only	30	4.71	0.63
4	Multiple complications	17	4.56	0.79

F=4.220; p=0.008

Mean serum potassium levels were found to be maximum in patients with diabetic nephropathy and minimum in patients with diabetic retinopathy (Table 3). A significant difference in mean serum potassium levels of patients with different complications of diabetes was observed (F=4.220; p=0.008).

CONCLUSION

Subtle changes in serum potassium merit attention in T2DM patients as they might have a bearing with disease complications.

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