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A CLINICAL INVESTIGATION ON THE THERAPEUTIC OUTCOMES OF DIURETICS IN DIABETIC PATIENTS WITH COMORBIDITIES

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ABSTRACT: This prospective observational study measures the prevalence of electrolyte disturbances in diabetes mellitus patients with co-morbidities who were under diuretic therapy. Further the levels of serum electrolytes and fasting blood glucose the patients were correlated with each other. Of all the 120 patients, 33.33% (40) were having diabetes with chronic kidney disease, 56.67% (68) were having diabetes with cardiovascular disease, 10% (12) were having diabetes with both comorbidities. Among them, 2.5% (3) were having hyperkalaemia, 14.17% (17) were having hypokalaemia, 10.83% (13) were having hyponatraemia, 5% (6) were having hypercalcaemia, 10% (12) were having hypocalcaemia, 2.5% (3) were having hyperchloraemia, 13.33% (16) were having hypochloraemia and 5.84% (7) were having hypomagnesaemia. 35.83% (43) were having no electrolyte disturbances. In diabetes mellitus patients with chronic kidney disease under furosemide, a negative correlation was observed between serum potassium and fasting blood glucose. A negative correlation was observed between serum potassium and fasting blood glucose. In diabetes mellitus patients with cardiovascular disease, on furosemide, a negative correlation was observed between serum potassium and fasting blood glucose. In patients on torasemide, a negative correlation was observed between serum potassium and fasting blood glucose. In patients on hydrochlorothiazide, a negative correlation was observed between serum potassium and fasting blood glucose. In patients on furosemide and spironolactone, a negative correlation was observed between serum sodium and fasting blood glucose. There was a varying spectrum in the relationship between the serum electrolytes and fasting blood glucose in various classes of diabetes mellitus patients.

INTRODUCTION: Diuretics are currently recommended as the first line therapy for the treatment of hypertension by the Seventh Report of the Joint National Commission.

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In addition, diuretics are equally effective in controlling cardiovascular events as ACE inhibitors or calcium channel blockers [1, 2, 3]. They effectively reduce both cardiovascular and cerebrovascular morbidity and mortality.

Diuretics are the therapeutic agents which are used to increase the rate of urine flow and sodium excretion in order to adjust the volume and composition of body fluids or to eliminate excess of fluids from tissues. They are used in clinical therapy for the treatment of various diseases and

syndromes including hypertension, heart failure, liver cirrhosis [4, 5], renal failure, kidney and lung diseases, and in the reduction of adverse effects of salt and water retention. Among the diuretics, torasamide (2.5-5 mg daily) is preferred more because of its longer effect even though dry mouth is its considerable side-effect. Intrahepatic cholestasis is a chief side effect caused by furosemide. Thiazides act by reducing the Ca2+ excretion, while skin rash is an important side-effect of hydrochlorothiazide. For treating hirsutism, acne, and seborrhoea in females, aldosterone antagonists are important preferences, even-though thrombocytopenia being a challenging side effect, while GI bleeding is a painful side-effect of amiloride hydrochloride. For cystic fibrosis dry mannitol powder is given by inhalation [6, 7].

Acting osmotically, it dilutes the viscid bronchial fluid, thereby promoting the mucociliary clearance. With spironolactone at daily doses of ≤50 mg, the incidence of gynaecomastia [8, 9, 10] was 6.9% and at daily doses of ≥ 150 mg, the incidence was 52.2%. Diuretics have an inevitable place in the treatment of nephrogenic diabetes insipidus [11, 12, 13]. Probenecid competes with furosemide and thiazides for tubular secretion and counters their diuretic effect as smaller amounts of these diuretics reach the tubular fluid. Mannitol and urea are contraindicated in intracranial haemorrhage [14, 15, 16] because their infusion can cause an acute increase in intravascular volume that may promote bleeding. Ethacrynic acid appears to induce ototoxicity more often than other loop diuretics do and should be used only in patients who cannot tolerate other loop diuretics. Recent studies on diuretics emphasis the implications of non-loop diuretics in ICU settings while the usage of loop diuretics are the frontliners. But some researches say that combinations of various classes of diuretics play effective role in treating cardiac emergencies like ACF [17, 18, 19, 20].

This study was conducted to assess the outcomes associated with the use of diuretics in diabetic patients with co-morbidities. The prevalence of electrolyte disturbances in DM patients with co-morbidities who were under diuretic therapy was measured in this study. Further the levels of serum electrolytes and fasting blood glucose the patients were correlated with each other.

MATERIALS AND METHODS: The study was prospective observational, conducted in the department of general medicine at Vivekanandha Medical Care Hospital (VMCH), Elayampalayam, Tiruchengode, during the time period of November 2017 to October 2018. The study was approved (Ref. No: VMCH/IEC/FEB/2018/01) by the Institutional Ethics Committee of Vivekanandha Medical Care Hospital.

Inclusion Criteria:

- DM patients on diuretic therapy
- DM patients with cardiac events and renal disease as co- morbidities
- Patients on OHA or insulin or both
- Age > 30 years
- Gender – both male and female
- Both in-patients and out-patients

Exclusion Criteria:

- Patients with liver disease
- Immobile & comatose patients
- Patients presenting with frequent hypoglycaemia
- Gestational diabetic patients
- Pregnancy and lactation

Study Method: Totally 240 diabetic patients those who were on diuretic therapy for their co-morbid conditions were screened and 130 patients were selected for the study. Data were collected by interviewing patients/caretakers and from the medical records department.

Among the diabetic patients, those who were having cardiac events and renal disease as co-morbid conditions were segregated. Patients were recruited as per the inclusion and exclusion criteria. The patient pro forma was prepared to collect information about patient's demographic details along with the laboratory investigation. Data was collected by reviewing the prescription of the out-patients and treatment charts of the in-patients

prospectively. The objective of this study was to measure the prevalence of electrolyte disturbances in DM patients with comorbidities who are under diuretic therapy and to correlate the levels of serum electrolytes and fasting blood glucose for the same patients. A specially designed data entry form was used in this study. It consisted of the following details name, age, sex, IP No, reason for admission, past medical history, past medication history, family history, social history, laboratory investigations, diagnosis and therapeutic chart.

Statistical analysis was done using SPSS v. 23 (Statistical package for the social sciences). Results were expressed as r, where r is the correlation coefficient. Pearson's correlation coefficient was used to analyze the statistical correlation between serum electrolytes and fasting blood sugar $p < 0.05$ was considered statistically significant.

RESULTS:

Age Distribution among the Study Population: Among the 120 cases, 15.83% (19) were in the age group of 30-50 years, 60% (72) were in the age group of 50-70 and 24.17% (29) were in the age group of 70-90 years. There were 69.17% (83) males and 30.83% (37) females. Among them, 43.33% (52 patients) were in normal body weight, 9.17% (11 patients) were underweight, 40% (48 patients) were overweight and 7.50% (9 patients) were obese. 36.67% (44) were smokers and 63.33% (76) were non-smokers. Among the patients, 26.65% (32) were alcoholic and 73.34% (88) were non- alcoholic. Of all the 120 patients, 33.33% (40) were having diabetes with CKD, 56.67% (68) were having diabetes with CVD, 10% (12) were having diabetes with both CKD and CVD. Among them, 2.5%(3) were having hyperkalaemia, 14.17% (17) were having hypokalaemia, 10.83%(13) were having hyponatraemia, 5%(6) were having hypercalcaemia, 10% (12) were having hypo-calcaemia, 2.5%(3) were having hyperchloraemia, 13.33% (16) were having hypochloraemia and 5.84% (7) were having hypomagnesaemia. 35.83% (43) were having no electrolyte disturbances.

TABLE 1: CORRELATION BETWEEN SERUM ELECTROLYTES AND FASTING BLOOD SUGAR

S. no.	Comorbidities	Diuretics Prescribed	Serum K+	Serum Na+	Serum Ca2+	Serum Cl-
1	DM+CKD	Furosemide	-0.522*	-0.255**	0.898**	0.218
		Torasemide	-0.48	-0.325	0.244	0.281
2	DM+CVD	Furosemide	-0.598**	-0.315*	0.953	0.562**
		Furosemide+Spironolactone	-0.291	-0.713	0.588	0.754
		Torasemide	-0.413*	-0.141	0.758	0.511
		Torasemide+Spironolactone	-0.456	-0.124	0.32	0.282
		Spironolactone	-0.226	-0.043	0.222	0.361
		Hydrochlorothiaz-ide	-0.881**	-0.580**	0.168**	0.198
3	DM+CKD +CVD	Furosemide	-0.657*	-0.578*	0.848	0.216
		Furosemide+Spironolactone	-0.664	-0.593*	0.199	0.793
		Torasemide	-0.869	-0.904	0.876	0.753

DISCUSSION: This study specifically tried to find out the prevalence of serum electrolyte disorders and to investigate the association between the serum electrolyte and fasting blood glucose levels by Pearson's correlation coefficient. The study comprised of 120 patients out of which, most of the patients were in the age group of 50-70 years. This coincides with the study conducted by, where age group above 50 years are prone to diabetes than the other age groups. In this study, males were 69.17% (83) and females were 30.83% (37). Male patients (69.17%) were dominant over the female patients (30.83%). Among 120 patients, 43.33% (52 patients) were in normal body weight, 9.17% (11 patients) were underweight, 40% (48 patients) were overweight and 7.50% (9 patients) were obese. This shows that majority of patients were in normal weight range. In this study, 36.67% (44) were smokers, 63.33% (76) were non-smokers, 26.67% (32) were alcoholic and 73.34% (88) were non-alcoholic. Regarding the social history, smokers and non-alcoholics were more exposed to drug related outcomes than smokers and alcoholics. In this study co-morbidities like CKD, CVD and both exist as co-morbities in DM patients. According to this study, 33.33% (40) were having diabetes with CKD, 56.67% (68) were having diabetes with CVD, 10% (12) were having diabetes with both CKD and CVD. This reveals that patients having CVD as co morbidity are dominant.

This study coincides with the study conducted by Addis *et al* which resulted that cardiovascular disease was the most common co-morbidity found in diabetic patients [21].

Among the study population of the current study, furosemide is the most prescribed diuretic. From which 17.5% DM patients with CKD, 17.5% DM patients with CVD, and 4.17% DM patients with both were prescribed with furosemide.

Prevalence of Electrolyte Disturbances among Study Population: In this study, 2.5% (3) were having hyperkalaemia, 14.17% (17) were having hypokalaemia, 10.83% (13) were having hypo-natraemia, 5% (6) were having hypercalcaemia, 10% (12) were having hypocalcaemia, 2.5% (3) were having hyperchloraemia, 13.33% (16) were having hypochloraemia and 5.84% (7) were having hypomagnesaemia. This shows that patients were highly affected by hypokalaemia.

Prevalence of Electrolyte Disturbances Based on Gender: In this study, males were more prone to electrolyte disturbances than female except in the case of hyponatraemia, where 5% (6) of the patients were male and 6% (7) were female. A results of a study conducted by Zeeshan *et a*l is similar to this study stating that hyponatraemia most commonly occurs with elderly women patients [22].

Prevalence of Electrolyte Disturbances Based on Diuretics used: Electrolyte disturbances were most commonly seen in patients on loop diuretics and thiazides therapy. Patients taking spironolactone, furosemide and spironolactone were prone to hyperkalaemia.

Correlation between serum potassium and FBS: In this study, the correlation between serum potassium and FBS in DM patients with CKD on furosemide was found to be (r = -0.522*), where r is the Pearson's correlation coefficient **Table 1.** There was a negative correlation between serum sodium and FBS and the correlation is significant at the 0.05 level ($p < 0.05$). The correlation between serum potassium and FBS in DM patients with CVD on furosemide was found to be 0.598** ($p < 0.01$). The correlation between serum potassium and FBS in DM patients with CKD on torasemide was found to be (r = -0.413*). There was a negative correlation between serum sodium and FBS and the correlation is significant at the 0.05 level ($p < 0.05$). The correlation between serum potassium and FBS in DM patients with CVD on hydrochlorothiazide was found to be (r = -0.881**). There was a negative correlation between serum sodium and FBS and the correlation is significant at the 0.01 level ($p < 0.01$). As the correlation coefficient is closer to the value of -1, the linear correlation was stronger and also the negative correlation shows that the serum potassium decreases with the increase in fasting blood sugar and vice versa. reported that the Pearson's correlation coefficient for the relationship between glucose and potassium was -0.54. This study reveals that thiazide induced hypokalaemia is associated with increased blood glucose. The correlation between serum potassium and FBS in DM patients with CKD and CVD on furosemide was found to be (r = 0.657*).

There was a negative correlation between serum sodium and FBS and the correlation is significant at the 0.05 level ($p < 0.05$). This coincides with the study conducted by Qaisar *et al*, which resulted that hypokalaemia is a common finding in patients treated with loop or high dose thiazide diuretics [23].

Correlation between serum sodium and FBS: In this study, the correlation between serum sodium and FBS in DM patients with CKD on furosemide was found to be (r = -0.255**). There was a negative correlation between serum sodium and FBS, where the correlation is significant at the 0.01 level ($p < 0.01$). The correlation between serum sodium and FBS in DM patients with CVD on furosemide was found to be (r = -0.315*, $p < 0.05$).

The correlation between serum sodium and FBS on hydrochlorothiazide was found to be (r = -0.580**, $p < 0.01$). The correlation between serum sodium and FBS in DM patients with CKD and CVD on furosemide was found to be (r = -0.578*, $p < 0.05$). The correlation between serum sodium and Fasting blood glucose in DM patients with CKD and CVD on furosemide and spironolactone was found to be (r = -0.593*, $p < 0.05$). The negative correlation shows that the serum sodium decreases with the increase in fasting blood sugar and vice versa. A study conducted by Nandennagari *et al* show that

there is a strong association between hyponatraemia and diuretics. They state that thiazides are more likely to cause hyponatraemia than loop diuretics [24].

Correlation between serum calcium and FBS: In this study, the correlation between serum calcium and FBS in DM patients with CKD on furosemide was found to be (r = 0.898**). There was a positive correlation between serum sodium and FBS, where the correlation is significant at the 0.01 level ($p < 0.01$). As the correlation coefficient is closer to the value of -1, the linear correlation was stronger. The positive correlation shows that the serum calcium decreases with the decrease in fasting blood sugar and vice versa. The correlation between serum calcium and FBS in DM patients and CVD on hydrochlorothiazide was found to be (r = 0.168**, $p < 0.01$). A study by Gulajkar *et al* reported that the altered serum calcium levels were significantly correlated with the glucose level [25].

Correlation between serum chloride and FBS: In this study, the correlation between serum chloride and FBS in DM patients with CVD on furosemide was found to be (r = 0.562**). There was a positive correlation between serum sodium and FBS, where the correlation is significant at the 0.01 level ($p < 0.01$)

CONCLUSION: Hypokalaemia is the most common electrolyte disturbance found among the study population than others, in which prevalence of hyponatraemia is more common in female than in male patients. Diuretic related electrolyte disturbances were found to be high in patients on thiazides and loop diuretic therapy. However, every diuretic shows electrolyte disturbances according to its mechanism of action. In diabetes mellitus patients with CKD who were on furosemide, serum potassium and serum sodium exhibited a negative correlation with fasting blood glucose. In patients with CVD comorbidity who were on furosemide, serum potassium and serum sodium shared a negative correlation with fasting blood glucose. In patients on torasemide, a negative correlation was observed between serum potassium and fasting blood glucose. In patients on hydrochlorothiazide, a negative correlation was observed between serum potassium and fasting blood glucose, while serum sodium also had a negative correlation with fasting blood glucose. In DM patients with CVD and CKD comorbidities who were on furosemide, a negative correlation was observed between serum potassium and fasting blood glucose, where as a negative correlation was observed between serum sodium and fasting blood glucose. In patients on furosemide and spironolactone, a negative correlation was observed between serum sodium and fasting blood glucose.

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CONFLICTS OF INTEREST: Nil

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