HYPERKALEMIA – FREQUENCY IN A GROUP OF HYPERTENSIVE DIABETICS

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ABSTRACT

Objective: To evaluate the Frequency of hyperkalemia in a cohort of hypertensive diabetic patients.

Study design: A prospective analytical cohort study.

Place and duration of study: The study was carried out in department of medicine (nephrology) Military Hospital (MH) and Armed Forces Institute of Urology (AFIU) Rawalpindi from Jun 2007-Jun 2009.

Patients and methods: A total of 110 hypertensive, middle aged diabetic patients attending medical OPD in MH and AFIU Rawalpindi were followed over two years from Jun 2007 - Jun 2009 for development of hyperkalemia and monitored for changes in eGFR, Serum Urea, creatinine and blood glucose random besides changes in blood pressure and ECG findings. SPSS version 13 was employed for statistical analysis.

Results: During the course of study 9 patients were lost to follow up. There were 7 deaths among study subjects before the end of study after about ten to twelve months. Out of the 94 patients followed up mean Serum Urea at the end of study was 13.50 mmol/l against a serum creatinine level of 2.26 mmol/l and an estimated GFR of 21.08 ml/min. The Frequency of raised serum Potassium of 5.1-6.0 mmol/l was 46.80% and 26.59% of the patients had serum Potassium of 6.1-7.2 mmol/l at the end of study. This was against an initial level of 4.5-5.0 mmol/l in 100% of the study subjects. Paired sample t-test revealed significant changes in each variable studied but a borderline positive correlation of 0.619 was observed only between serum potassium and change in eGFR at the end of study. The mean blood glucose random dropped from 16.14 mmol/l to 10.41 mmol/l.At the end of study mean systolic BP was 122 mm Hg and diastolic BP 80.2 mm Hg. The ECG revealed tall T waves in 64.9% of cases while at the start of study all subjects had their electrocardiograms within normal limits. There was a trend of increase in frequency of tall T waves with the rise in serum potassium levels.

Conclusion: Raised serum potassium is a significant potential complication among long standing diabetics with covert nephropathy treated with ACE inhibitors, ARBs, potassium sparing diuretics or a combination of these drugs. Co morbidities and development of this complication must therefore be considered by physicians when dealing with such patients.

Keywords: Hypertensive diabetics, ACE inhibitors, ARBs, hyperkalemia.

INTRODUCTION

Hyperkalemia is defined as a 'serum potassium level greater than 5.5 mEq/L'[1]. Ranges are 5.5-6.0 mEq/L (Mild), 6.1-7.0 mEq/L (Moderate), 7.0 mEq/L and greater (Severe).

Hyperkalemia is a potentially life-threatening complication resulting from the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers(ARBs) in diabetics with covert nephropathy; data to guide the intensity of monitoring for or responding to hyperkalemia in outpatients are limited[2]. Angiotensin converting enzyme (ACE) inhibitors are now one of the most frequently used classes of antihypertensive drugs. Although ACE inhibitor therapy usually improves renal blood flow (RBF) and sodium excretion rates in CHF and reduces the rate of progressive renal injury in chronic renal disease, its use can also be associated with a syndrome of "functional renal insufficiency" and/or hyperkalemia. This form of acute renal failure (ARF) most commonly develops shortly after initiation of ACE inhibitor therapy but can be observed after months or years of therapy, even in the absence of prior ill effects. ARF is most likely to occur

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when renal perfusion pressure cannot be sustained because of substantial decreases in mean arterial pressure (MAP) or when glomerular filtration rate (GFR) is highly angiotensin II (Ang II) dependent. Conditions that predict an adverse hemodynamic effect of ACE inhibitors in patients with CHF are preexisting hypotension and low cardiac filling pressures[3]. Hyperkalemia is relatively common in ACE inhibitor–treated patients with CHF or uremia. Fortunately, increases in plasma potassium are generally fairly modest (1 mEq/L), and severe hyperkalemia with ACE inhibitors is uncommon[4]. Mechanistically, by lowering plasma aldosterone levels and thereby reducing urinary potassium excretion, ACE inhibitor therapy may lead to hyperkalemia[5]. Thus, disruption of internal homeostasis may occur in patients with diabetes and hyperglycemia, in individuals receiving ß-blockers, or in individuals receiving potassium supplements, heparin, or potassium-sparing diuretics.

The aim of the study was to determine the Frequency of hyperkalemia among a cohort of hypertensive diabetics over a period of two years.

PATIENTS AND METHODS

This was an observational prospective cohort study,during the period June 2007 to June 2009 in the department of nephrology Military Hospital (MH) and Armed Forces Institute of Urology (AFIU) Rawalpindi. For our study, a cohort of 110 hypertensive diabetic patients managed in outdoor on ACE inhibitors and ARBs was selected. Study cohort were defined as those patients aged 50 -60 years of age who were known diabetics for 10 years or more ,had no known history of ischemic heart disease, cardiac conduction defects,congestive cardiac failure or renal function defect. They were all residents of Rawalpindi and were dependent upon military hospitals for medical treatment in OPD as well as emergency or indoor management. This condition was included to circumvent attrition due to loss to follow up. Registration records included complete present and past history and drugs taken in outdoor. ECG, Blood pressure recording, blood glucose (R) and blood chemistry including Serum urea, creatinine, Potassium and ultrasonographic report on renal size and echotexture. Hyperkalemia was defined as Serum potassium level of 5.1 m.mol/l and above.

The cohort was followed up for next two years in routine OPD till June 2009. Outcome variables i.e changes in clinical or blood chemical profile after two years were recorded at the end of study for analysis.

Statistical Analysis

The data collected was analysed on SPSS version 13. paired sample T-test was applied to estimate significant changes at 5% level of confidence and 95% confidence interval for various factors checked and their correlation factors. Before and after frequencies of various variables and their association with changes in serum potassium were noted.

RESULTS

At the end of two years period of the study, out of the total 110 patients registered for follow up at the beginning ,data of 94 patients was complete as there were 9 patients who were lost to follow up for unidentified reasons . While 4 patients were brought as cases of suspected cardiac arrest but their data was not complete and confirmed so they were excluded from the study. Rest 3 of the patients died of other causes so they were also not included. Out of the 94 patients followed up mean Serum Urea at the end of study was 13.50 mmol/l (STD: 3.051) against a serum creatinine level of 2.26 mmol/l (STD: 1.115) and an estimated GFR of 21.08 ml/min (STD: 3.684). The Frequency of raised serum Potassium of 5.1-6.0 mmol/l was 46.80% and 26.59% of the patients had serum Potassium of 6.1-7.2 mmol/l at the end of study. This was against an initial level of 4.5-5.0 mmol/l in 100% of the study subjects. The detailed comparison of Biochemical profile comprising these elements is shown in table 1. Paired sample t-test was employed to determine the significance of biochemical changes in each during the study as shown in table 2. Paired samples t- test was also applied to determine the correlation in Serum potassium levels with other renal function

profile at the start and end of study. The only positive correlation of 0.619 was observed between serum potassium at the end of study and change in eGFR. The 'r' value of each pair is shown in figure 1. The other important clinical observations were of changes in systolic and diastolic blood pressure, renal ultrasonographic findings and ECG. Details of these data are shown in table 3. There was a fall in mean systolic and diastolic BP over the period of study alongwith blood glucose ® levels. The most frequent ECG change noted was tall T waves among 64% of the subjects which showed a gradual increase with rising serum potassium levels against a starting level of within normal limits ECG and Serum potassium level of 4.5-5.0 mmol/l among 100% of the subjects. The changes in Serum potassium and ECG among the study subjects are compared in figure 2.

DISCUSSION

In the present study, the mean S potassium at the start of study was 4.7 mmol/l while at the end of study., the mean S. Potassium was 5.8 mmol/l.while 46.8% of patients had values between 5.1-6.0 mmol/l and 26.5% had hyperkalemia in the range of 6.1-7.2 mmol/l . Reardon LC et al in their study 3reported that of 1818 patients using ACE inhibitors, 194 (11%) developed hyperkalemia. After 1 year of follow-up, 15 (10%) of 146 case patients remaining on a regimen of an ACE inhibitor developed severe hyperkalemia (potassium level > 6.0 mmol/L). Mild hyperkalemia is common in medical outpatients using ACE inhibitors, especially in those with renal insufficiency or congestive heart failure. Hunt SA and Baker et al reported that in recent years, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers

Table-1: Biochemical profile of patients before and after the study

		Start	End of Study
		Mean - n (%)	Mean - n (%)
	eGFR ml/min	28.50 (std dev:1.305)	21.08 (std dev:3.684)
	25-30	94 (100%)	10 (10.7)
	15-24		84 (89.3)
2.	S.Urea mmol/l	7.89 (std dev:0.475)	13.50 (std dev:3.051)
	7-8	49(52.12)	
	8-9	45(47.87)	37(39.36)
	9-10		21(22.34)
	>10		36(38.29)
3	S .Creatinine mmol/l	1.03 (std dev:0.129)	2.26 (std dev:1.115)
	<1.0	31(32.97)	
	1.0-1.2	63(67.02)	12(12.76)
	1.3-2.0		56(59.57)
	>2.0		26(27.65)
4	S. Potassium m.mol/l	4.7 (std dev:0.129)	5.8 (std dev:0.797)
	4.5-5.0	94(100)	25(26.59)
	5.1-6.0		44(46.80)
	6.1-7.2		25(26.59)
5	Bl.glucose®mmol/l	16.14 (std dev:2.251)	10.41 (std dev:0.986)
	6-9		30(31.91)
	10-14	34(36.17)	64(68.08)
	15-19	60(63.82)	

Table 2: paired sample t- test of significance for follow up profile

	Mean	Std Dev	95% CI of Difference		t-value	Significance
			Lower	Upper		
Egfr	7.42	3.23	6.76	8.08	22.27	0.00
S. Urea	-5.60	3.16	-6.25	-4.96	-17.17	0.00
S. Creatinine	-1.23	1.14	-1.47	-1.00	10.45	0.00
S. Potassium	-1.10	0.76	-1.26	-0.94	-13.99	0.00

Table-3: Clinical Profile of Patients during Study

		Start of study	End of study
		Mean n (%)	Mean n (%)
1	Systolic BP mmHg	144 (std dev:11.7)	122 (std dev:15.8)
	100-119.9		
	120-139.9	37(39.4)	10(10.4)
	140-160.0	57(60.7)	84(89.4)
2	Diastolic BP mmHg	93.72 (std dev:4.8)	80.21 (std dev:3.01)
	70-79.9		75(79.8)
	80-89.9	59(62.8)	19(20.2)
	90-100	35(37.2)	
3	ECG		
	Within Normal limits	94(100)	13(13.8)
	Tall T waves		61(64.9)
	Broad QRS complex		16(17.0)
	Heart block		4(4.3)
4	Renal USG		
	Normal study	94(100)	83(88.3)
	Parenchymal or size changes		11(11.7)

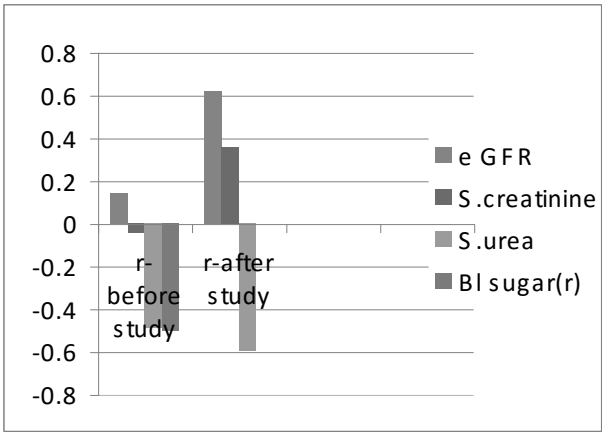

Fig 1: Paired Sample correlation of S.Potassium and biochemical profile follow up

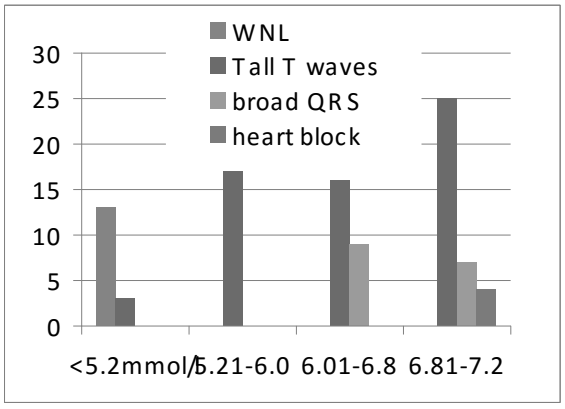

Fig 2: Comparison of Serum Potassium changes with ECG changes

(ARBs), spironolactone and beta-adrenergic antagonists have been used to treat heart failure as first-line therapy[6]. However, these medications can cause hyperkalaemia as a side-effect. Although the exact prevalence of hyperkalemia in community-based medical practice is unknown, potassium elevation is a common, potentially life-threatening problem most often occuring in patients with chronic renal failure or other illnesses that reduce renal potassium excretion . In these patients, acute hyperkalemia often is precipitated by stressors such as illness, dehydration, or initiation of medicines that alter potassium homeostasis with hyporeninemic hypoaldosteronism as a possible underlying mechanism in diabetics[7].

The mean Serum creatinine level raised from 1.03 mmol/l at the start to 2.26 mmol/l at the end of study with 59.9% subjects having levels between 1.3- 2.0 mmol/l. A rise in serum creatinine may occur after initiation of therapy in patients with CHF. Serum creatinine often stabilizes and may decline thereafter[8]. The mean serum Urea level at the end of study was 13.50 mmol/l,with no less than 38.29% of subjects in the range of 15-20 mmol/l. Estimated GFR dropped from mean of 28.50% (with 100% subjects in the range of 25-30 ml/min) to 21.08% with 89.3% subjects in the 15-24 ml/min range. The renal size and echo texture as noted on ultrasonography revealed some changes in only 11% of subjects.

The mean blood glucose (R) dropped from 16.14 mmol/l to 10.41 mmol/l and the mean systolic and diastolic blood pressures also showed a downward trend. A number of studies have been performed to assess the systemic and regional hemodynamic effects of ACE inhibitors in the setting of CHF[9,10]. Acutely, a uniform reduction in MAP is observed after ACE inhibitor administration owing to a reduction in systemic vascular resistance. Total renal vascular resistance decreases, and an increase in RBF is observed in most patients. Nevertheless, the GFR usually remains unchanged or falls slightly[11, 12]. This discrepancy between RBF and GFR is due to the relatively greater effect of the ACE inhibitor in dilating postglomerular efferent than afferent arterioles, with a resultant reduction in glomerular capillary hydrostatic pressure and GFR[12].

ECG forms an important and easily accessible investigation known to reflect changes in serum potassium by subsequent changes in its various components. The commonest ECG change was appearance of tall T waves in 64.9% of cases while at the start of study all subjects had their electrocardiograms within normal limits. There was a trend of increase in frequency of tall T waves with the rise in serum potassium levels.

In experimental settings, hyperkalemia has been associated with a defined series of electrocardiogram (ECG) abnormalities, including shortening of QT interval, peaking of T waves, QRS prolongation, shortening of PR interval, reduction in amplitude of the P wave, loss of sinoatrial conduction with onset of a wide-complex "sine-wave" ventricular rhythm, and ultimately asystole[13]. Most severe cardiac manifestations have been shown to occur with serum potassium concentrations >9 mEq/L [14]. On the basis of these experimental observations, commonly used clinical references recommend ECG assessment as an integral part of the evaluation of patients with hyperkalemia[15].

In one published series of 127 patients with serum potassium concentrations ranging between 6 and 9.3 mEq/L, no serious arrhythmias were documented[16]. Only 46% of ECG were noted to have changes suggestive of hyperkalemia, including QRS widening, conduction defects, and peaking of T waves[17]. There are multiple case reports of patients with renal failure who presented without significant ECG changes despite markedly elevated potassium levels[18, 19]. Other, less typical ECG presentations of hyperkalemia include ST elevations mimicking acute myocardial infarction and rate-dependent bundle branch blocks[20].

CONCLUSION

In clinical practice the concomitant use of ACE - I and spironolactone has to be accompanied with a closer monitoring of potassium concentrations, careful evaluation of pre-disposing factors for hyperkalemia (e.g. renal failure, diabetes) to avoid iatrogenic hyperkalemia with its associated morbidity.

REFERENCES

1. Koch M J. Disorders of potassium balance: Washington Mannual Nephrology Subspeciality Consult 2004; 22: 179-191.
2. Schoowerth et al .Renal considerations in ACE inhibitor therapy : A statement for healthcare professionals from the council on the kidney in cardiovascular disease and the council for high blood pressure research of the American heart Association. *Circulation*2001; 104: 198-199.
3. Reardon LC, MacPherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors: how much should we worry?. *Arch Intern Med.* 1998; 158: 26–32.
4. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med.* 2000; 160: 685–693. (17)
5. Textor SC, Bravo EL, Fouad FM, et al. Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. *Am J Med.* 1982; 73: 719–725.
6. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cariology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* (2001) 38:2101–13.
7. Szerlip HM.Metabolic acidosis,primer on kidney diseases; Fourth Edition 2005;8: 74-89.
8. Kubo S, Nishioka A, Nishimura H, et al. Effects of captopril on arterial and venous pressure, renal function, and humoral factors in severe chronic congestive heart failure. *Clin Pharmacol Ther.* 1984; 36: 456–463.
9. Packer M, Medina N, Yushak M, et al. Hemodynamic patterns of response during long-term captopril therapy for severe chronic heart failure. *Circulation.* 1983; 68: 803–812.
10. Davidson NC, Coutie WJ, Webb DJ, et al. Hormonal and renal differences between low dose and high dose angiotensin converting enzyme inhibitor treatment in patients with chronic heart failure. *Heart.* 1996; 75: 576–581
11. van der Ent M, Remme WJ, de Leeuw PW, et al. Renal hemodynamic effects in patients with moderate to severe heart failure during chronic treatment with trandolapril. *Cardiovasc Drugs Ther.* 1998; 12: 395–403
12. Sica DA, Gehr TWB. Angiotensin-converting enzyme inhibitors.In: *Oparil S, Weber M, eds. Hypertension. 1st ed. Philadelphia, Pa: WB Saunders;* 1999: 599–608.

13. Ettinger PO, Regan TJ, Oldewurtel HA: Hyperkalemia, cardiac conduction, and the electrocardiogram: A review. *Am Heart J* 88: 360–371, 1974.

14. Rose B: Clinical manifestations and treatment of hyperkalemia, Up-To-Date, 2007. *http://www.utdol.com*.

15. Acker CG, Johnson JP, Palevsky PM, Greenberg A: Hyperkalemia in hospitalized patients: Causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. *Arch Intern Med* 158: 917–924, 1998.

16. Martinez-Vea A, Bardaji A, Garcia C, Oliver JA: Severe hyperkalemia with minimal electrocardiographic manifestations: A report of seven cases. *J Electrocardiol* 32: 45–49, 1999.

17. Aslam S, Friedman EA, Ifudu O: Electrocardiography is unreliable in detecting potentially lethal hyperkalaemia in haemodialysis patients. *Nephrol Dial Transplant* 17: 1639–1642, 2002.

18. Pastor JA, Castellanos A, Moleiro F, Myerburg RJ: Patterns of acute inferior wall myocardial infarction caused by hyperkalemia. *J Electrocardiol* 34: 53–58, 2001.

19. Vereckei A: Inferior wall pseudoinfarction pattern due to hyperkalemia. *Pacing Clin Electrophysiol* 26: 2181–2184, 2003.

20. Cook LK: An acute myocardial infarction? *Am J Crit Care* 14: 313–315, 2005.

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