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Prevalence of Hyperkalemia in Type 2 Diabetics Treated with Inhibitors of the Renin-Angiotensin-Aldosterone System: A Multicenter Study

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Abstract: Background and Aim: Hyperkalemia is a common risk among patients treated with renin-angiotensin-aldosterone system (RAAS) inhibitors, especially diabetics. The aim of this study was to measure the prevalence of hyperkalemia among patients with type-2 diabetics treated with ARBs and/or ACEIs, and compare them with controls. **Subjects and methods:** This study was carried out in four primary health care centers in Bahrain using a comparative ex-post-facto cross-sectional design with a control group. It included 305 type-2 diabetes patients in these settings. They were categorized into four groups: A) controls not on RAAS medications; B) ARB alone; C) ACE Inhibitors alone; D) combination of both. Data were collected from medical records. The study protocol was approved by the research committee in the Ministry of Health in the Kingdom of Bahrain. **Results:** The prevalence of hyperkalemia among those on ACE inhibitor and/or ARB medications was 16.51% (95% CI: 11.84 – 22.12%), while severe hyperkalemia was 1.38% (95% CI: 0.28 – 3.97%). The patients in the group taking both ARB and ACE inhibitor medications had significantly higher level of serum potassium but better control of their Fasting Blood Sugar (FBS) compared to the other 3 groups. In multivariate analysis, the medication group was not a statistically significant predictor of hyperkalemia. **Conclusion:** A combined ACEi/ARB therapy may pose a higher risk of increased serum potassium compared with mono-treatment or control. Hence, caution should be exercised especially in those with advanced kidney disease, heart failure, on renal replacement therapy, on potassium sparing diuretics.

Keywords: Diabetes, Hyperkalemia, Renin-Angiotensin-Aldosterone, Potassium

1. Introduction

Hyperkalemia, a potentially life-threatening condition, is a relatively common risk among patients treated with renin-angiotensin-aldosterone system (RAAS) inhibitors, particularly in those suffering from diabetes, heart failure, or advances chronic kidney disease (CKD).[1]However, these medications such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may be used safely in diabetic patients if they have impaired renal functions, and they are effective in improving their renal outcomes.[2] According to Winkelmayer et al. (2005),[3] the use of ACEIs and ARBs depends on patient's age, with an inverse relation so that the use declines with advanced age.

Among patients with type 2 diabetes, in addition to the positive effect on control of hypertension, the use of RAAS blocking agents demonstrated effective reduction of the progress of micro-albuminuria to macro-albuminuria, with significant reduction in the hazard ratio for diabetic nephropathy.[4,5]However, the risk of hyperkalemia among the patients on this therapy should be considered, since diabetes is an independent predictor of hyperkalemia.[6,7] Hence, their baseline serum potassium levels and estimated glomerular filtration rate (eGFR) should be documented[8] in addition to care for co-treatment with medications or dietary regimen that may affect their potassium levels.[9]

Nevertheless, the ACEIs and ARBs are increasingly used in a variety of situations such as heart failure, renal failure, arterial hypertension, and diabetic nephropathy. In patients with diabetes, both ACE inhibitors and ARBs are considered first line therapies in the treatment of hypertension.

Additionally, they have important reno-protective actions independent of their blood pressure-lowering action, which is of particular benefit in these patients. The blockade of the RAAS with these agents appears to play an important role not only in protecting from renal disease, but it may also help to reduce morbidity and mortality related to vascular diseases. Hence, the use of ACEIs and ARBs is still recommended given their positive impact on renal function preservation even with hyperkalemia. With cautious management, no significant increases in the incidence of hyperkalemia do occur.[10]Studies showed that hyperkalemia is more common with ARBs than ACEIs. ARB use, when compared to ACEI, was associated with a 42% increase in the odds of hyperkalemia. Moreover, diabetes, serum glucose, total carbon dioxide content, creatinine, and estimated glomerular filtration rate (GFR) are significantly associated with hyperkalemia.[11,15]

However, the question of the use of monotherapy (with one of these two agents) or combined therapy (both ACEI and ARB) still has no confirmed answer. This is particularly important given the wide disparity in the definitions of hyperkalemia in various studies.[16]Hence, the aim of this study was to measure the prevalence of hyperkalemia among patients with type-2 diabetics treated with ARBs and/or ACEIs, and compare them with controls.

2. Subjects and Methods

This multi-center study was carried out in four primary health care centers in Bahrain, namely Aali, Hamad Town, Ahmed Ali Kanoo and East Riffaa,[17]using a comparative ex-post-facto cross-sectional design with a control group. The participants consisted of all the patients diagnosed as having type-2 diabetes and attending the study settings for management of diabetes throughout a 3-month period.The sample size was calculated to estimate a prevalence rate of hyperkalemia of 5% or higher with 2.5% absolute precision at 95% level of confidence. Using the sample size equation for a single proportion (Epi-Info 6.04) the required sample size was 305 patients after compensation for a non-response rate of approximately 5%.

The patients were categorized into four groups for comparison. These were: A) controls not on RAAS medications; B) ARB alone; C) ACE Inhibitors alone; D) combination of both. Patients with End Stage Renal disease (ESRD), liver cirrhosis, on K-sparing diuretics, chronic laxative user, diabetic ketoacidosis, and rhabdmyolysis were excluded. Type-2 diabetes was defined according to the American Diabetes Association. [18] Hyperkalemia was defined as blood potassium level 5.0 mEq/L or higher more than once during the study period, and a level of 5.0 mEq/L or higher for severe hyperkalemia.[19]

Data were collected using a specially designed abstraction form to document required data from patients' medical records. The main study exposure variable was the use of ACEIs, ARBs, or both along with their types, doses, duration of use, etc. The main outcome variable was hyperkalemia defined as more than once blood potassium level of 5.0mEq/L or above during the study period. The background variables and potential confounders were some demographic data such as age, gender, nationality, as well as the diabetes disease data such as age at onset, duration, diabetes medications used, etc. The data collected also included blood pressure level: one reading at the time of recruitment in the study, and laboratory measurements such as HbA1c, fasting blood glucose, and serum potassium.

The study protocol was approved by the research committee in the Ministry of Health in the Kingdom of Bahrain. Official permissions to use the data from medical records were secured from pertinent authorities. The data abstracted from the medical records were anonymous, and strict confidentiality was ensured. The researchers declare no conflict of interest.

Data entry and statistical analysis were done using SPSS 18.0 statistical software package. Data were presented using descriptive statistics in the form of frequencies and percentages for qualitative variables, and means and standard deviations and medians for quantitative variables. Quantitative continuous data were compared using the non-parametric Mann-Whitney or Kruskal-Wallis tests when normal distribution of the data could not be shown. Qualitative categorical variables were compared using chi-square test. To identify the independent predictors of the risk of hyperkalemia, multiple logistic regression analysis was used. Statistical significance was considered at p-value <0.05.

3. Results

Three hundred and five patients were interviewed in the study period. As illustrated in Table 1, the gender distribution is almost equal in all groups, except for the group on both ACE inhibitor and ARB medications, which had more preponderance of women (70.6%), but with no statistically significant difference. Meanwhile, the control group patients had significantly younger age compared to the other three groups. More than half of the patients in the ARB and ARB/ACE groups had their diabetes for 15 years or more, but the differences among groups were not statistically significant. The patients in the control group had also significantly lower prevalence of hypertension compared to the other three groups.

Concerning patients' laboratory results, Table 2 demonstrates that the patients in the group taking both ARB and ACE inhibitor medications had significantly better control of their Fasting Blood Sugar (FBS) compared to the other three groups. However, no statistically significant differences could be shown among the four groups regarding their glycated hemoglobin (HbA1c). Meanwhile, the level of serum potassium was significantly higher among the patients on both medications compared with the other groups.

Table 3 indicates that the prevalence of hyperkalemia among those on ACE inhibitor and/or ARB medications was 16.51% (95% CI: 11.84 – 22.12%). Among the three groups, the highest prevalence was among patients on both medications, whereas the lowest was among those on ACE.

Although the prevalence in the control group was lower than in all three groups on ACE/ARB medications, the difference was not statistically significant. Meanwhile, the prevalence of severe hyperkalemia was 1.38% (95% CI: 0.28 – 3.97%).

Table 1. *Socio-demographic and health characteristics of patients in the four study groups.*

	Group							
	Control(n=87)		ARB(n=88)		ACE(n=113)		Both(n=17)	
	No.	%	No.	%	No.	%	No.	%
Gender:								
Male	38	43.7	46	52.3	48	42.5	5	29.4
Female	49	56.3	42	47.7	65	57.5	12	70.6
Age:								
Range	46.0-75.0		29.0-85.0		22.0-94.0		36.0-71.0	
Mean± SD	53.9±11.1		59.5±8.8		59.3±9.6		58.8±8.7	
Median	56.0*		60.0		60.0		60.0	
Nationality								
Non-Bahraini	2	2.3	4	4.5	4	3.5	0	0.0
Bahraini	85	97.7	84	95.5	109	96.5	17	100.0
Duration of DM(years):								
<5	13	14.9	8	9.1	17	15.0	2	11.8
5-	49	56.3	34	38.6	52	46.0	5	29.4
15+	25	28.7	46	52.3	44	38.9	10	58.8
Systolic BP(130+):	25	28.7*#@	63	71.6*	69	61.1#	15	88.2@
Diastolic BP(80+):	33	37.9*	57	64.8*	55	48.7	9	52.9
Hypertension:	44	50.6*#@	76	86.4*	79	69.9#	15	88.2@

(*-*,#-#,@-@)Statistically significant at p<0.05

As regards the predictors of hyperkalemia and severe hyperkalemia, Table 4 demonstrates that the medication group was not a statistically significant predictor. The only possible predictor is hypertension, although not statistically significant, p=0.077 and p=0.091 respectively. Moreover, the models have weak fits as shown by their low pseudo-R square values.

Table 2. *Laboratory results of patients in the four study groups.*

	Group							
	Control(n=87)		ARB(n=88)		ACE(n=113)		Both(n=17)	
	No.	%	No.	%	No.	%	No.	%
FBS:								
<7	19	21.8	10	11.4	22	19.5	7	41.2
7+	68	78.2*	78	88.6#	91	80.5@	10	58.8*#@
Range	5.0-20.0		3.0-30.0		4.0-26.0		5.0-17.0	
Mean± SD	9.1±3.3		9.8±4.3		10.5±5.0		8.5±3.9	
Median	8.00		9.00		9.00		7.00	
A1c:								
<7	23	26.4	16	18.2	34	30.1	6	35.3
7+	64	73.6	72	81.8	79	69.9	11	64.7
Range	5.0-13.0		5.0-13.0		5.0-13.0		5.0-14.0	
Mean± SD	8.3±1.9		9.0±2.0		8.8±2.2		8.1±2.5	
Median	8.00		8.50		9.00		9.00	
Serum Potassium:								
Range	4.0-6.0		4.0-7.0		3.0-6.0		4.0-6.0	
Mean± SD	4.7±0.5*		4.6±0.6#		4.7±0.6@		5.0±0.4*#@	
Median	5.00		5.00		5.00		5.00	

(*-*,#-#,@-@)Statistically significant at p<0.05

Table 3. *Prevalence of hyperkalemia among patients in the four study groups.*

Groups	Hyperkalemia		95%confidenceinterval(Clopper-Pearson Exact)	
	No.	%	Upper	Lower
Hyperkalemia(>5mEq/L):				
Control(n=87)	12	13.79	7.34	22.85
ARB(n=88)	16	18.18	10.76	27.84
ACE(n=113)	16	14.16	8.32	21.97
Both(n=17)	4	23.53	6.81	49.9
Total without control(n=218)	36	16.51	11.84	22.12
Severe hyperkalemia(>6mEq/L):				
Total without control(n=218)	3	1.38	0.28	3.97

Table 4. *Best fitting multiple logistic regression model for the occurrence of hyperkalemia.*

	Wald	Df	P	OR	95.0%CIforOR	
					Upper	Lower
Hyperkalemia(>5mEq/L)						
Constant	20.026	1	<0.001	.011		
Hypertension	3.132	1	.077	6.332	.820	48.888
Nagelkerke R Square:0.052						
Hosmer and Lemeshow Test: p=0.970						
Omnibus Tests of Model Coefficients: p=0.02						
Severe hyperkalemia (>6mEq/L)						
Constant	20.026	1	<0.001	.011		
Hypertension	2.855	1	.091	5.850	.754	45.402
NagelkerkeRSquare:0.048						
Hosmer and Lemeshow Test: p=0.975						
Omnibus Tests of Model Coefficients: p=0.032						

4. Discussion

In our study, high prevalence of hyperkalemia was demonstrated particularly among the patients taking both ACE inhibitor and ARB. The rates are considerably higher than reported by Weir and Rolfe (2010),[20]where rates less or equal to 2% were reported in RAASIs monotherapy and 5% in combined therapy. The higher rates in the present study might be attributed to the presence of concomitant predisposing factors in our patients since all of them had diabetes, which is known to increase the risk of hyperkalemia.[7]It could also be due to variations in the cutoff point of hyperkalemia, which varies between 5 and 6 mEq/L,[9,21]or even the use of vague terms such as "Clinically important increases in serum potassium."[22]This led de Denus et al (2006)[21]to recommend caution in making comparisons with published figures of hyperkalemia.

Nonetheless, in congruence with our findings regarding the very low prevalence of severe hyperkalemia (>=6.0 mEq/L), Bakris et al (2013)[23]in their double-blind study on hypertensive patients with type 2 diabetes and stage 1 or 2 chronic kidney disease (CKD) randomized to receive combined aliskiren/valsartan or monotherapy. The results revealed that none of the patients in either group had confirmed serum potassium values ≥6.0 mEq/L.

The current study has also demonstrated significantly higher level of serum potassium among the patients on combined RAASIs therapy. The finding is in agreement with Susantitaphong et al (2013)[24]whose systematic review revealed that the incidence of hyperkalemia increased by 3.4% when ARB and ACE inhibitor are used in combination. Moreover, the combined therapy was associated with more adverse renal outcomes, particularly hyperkalemia, higher serum creatinine, and more need for dialysis.[25-28]

Also in line with our study findings concerning the higher levels of serum potassium with combined ACEi/ARB therapy, two recent studies revealed higher rates of hyperkalemia with this approach to therapy. Thus, Parving et al. (2012)[29]in the Aliskiren Trial on patietns with Type 2 Diabetes, and Fried et al. (2013)[28]in the Veterans Affairs Nephropathy in Diabetes study, reported more than twofold higher rates of severe hyperkalemia (potassium≥6.0 mEq/L) with combined therapy compared with monotherapy. The findings led to premature stopping of both trials for safety issues. Thus, a recent meta-analysis of clinical trials recommended monotherapy over combined therapy.[30]

According to the present study results, the patients on combined ACEi and ARB had significantly lower levels of the fasting blood sugar, which may indicate better control of their diabetes. However, the levels of glycosylated hemoglobin did not show statistically significant differences among the treatment groups and the control group. This may point to lack of any adverse effects of these medications on patients' metabolic indicators. In agreement with this, Appel et al (2003)[31]in their post-hoc analysis of the RENAAL study reported no adverse effects of Losartan on patients' lipid profile or glycemic control. However, as in the present study, it was associated with some increase in serum potassium level, but this did not lead to higher rate of discontinuation for this reason compared with the control (placebo) group.

Meanwhile, no significant differences could be demonstrated between the ACEi and ARB groups, as well as between these two groups and the control group patients regarding the prevalence of hyperkalemia. This further shows that the higher risk of hyperkalemia may come combined therapy rather than monotherapy. In line with this, and Preston et al (2009)[32]who compared the effect of ACEIs and ARBs on serum potassium concentration found that diabetic patients treated with candesartan and Lisinopril demonstrated no difference in their serum potassium levels or in their fractional excretion of potassium.

As regards the current study results of multivariate analysis, hypertension turned to be the only independent predictor of the occurrence of hyperkalemia or severe hyperkalemia. Although no statistical significance was reached, still there were trends with p-values 0.077 and 0.091 respectively. Moreover, the model fit is low as indicated by the pseudo-R-square values. This points to the possibility of presence of other risk factors not included in the analysis such as the renal functions. In this respect, Bakris et al (2003)[33]found that the baseline systolic blood pressure is

an independent predictor of renal outcomes in patients with non-insulin-dependent diabetes mellitus (NIDDM) treated with Losartan.

Our study concludes that a combined ACEi/ARB therapy may pose a higher risk of increased serum potassium compared with mono-treatment with either one or none of them. Most patients can and should benefit from the beneficial effects of these agents, but caution should be exercised especially in those with advanced kidney disease, heart failure, on renal replacement therapy, on potassium sparing diuretics. However, the findings should be interpreted with caution taking into consideration the study limitations such as its retrospective design precluding any temporal relations concerning the time frame of development of hyperkalemia after the start of ACEIs or ARBs, and the lack of data concerning patients' renal functions, which could affect patients' responses to these medications.

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