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Original Article

The Evaluation of Kidney Function in Elderly Individuals Under Renin Angiotensin Aldosterone System Inhibitor Therapy

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ABSTRACT

Background: We aim to investigate the impact of hydration status (12-hour fasting or 12-hour water-free fasting) on the estimated glomerular filtration rate (eGFR) and serum potassium in renin-angiotensin-aldosterone (RAAS) blocker users during biochemical assessments.

Material and Methods: A total of 90 individuals were enrolled in this longitudinal study. 57 of those were advised to be hydrated for at least 1 L before the next hospital visit. 33 of 90 individuals remained in the non-hydrated group and their blood samples were evaluated following 12-hour fasting. Hypertensive patients were divided according to the antihypertensive medicine group (RAAS blockers, RAAS blockers + diuretics, and others). eGFR, serum potassium, calcium, magnesium, albumin, and glucose levels were compared between hydrated and non-hydrated individuals.

Results: The mean age was 48.21±16.59 in hydrated and 47.42±17.12 in non-hydrated groups (p=0.831). Hypertension prevalence was 59.6% in the hydrated group and 54.5% in non hydrated group. In the RAAS blocker users, following hydration, eGFR elevated up to 8-11 ml/dk ($p<0.05$). In the hydrated individuals with age ≥65 years and receiving RAAS blockers, the increment in eGFR was most prominent (p=0.002). Hydration increased eGFR in individuals with RAAS blockers-free and nonhypertensive, however, those increments were not statistically significant ($p>0.05$). Similarly, serum potassium levels decreased following hydration in RAAS blocker users ($p<0.05$). Hyperkalemia (serum potassium ≥ 5 mEq/L) risk decreased from 9.2 fold to 6.16 fold following hydration ($p<0.05$).

Conclusion: Twelve-hour fasting is associated with lower eGFR and higher serum potassium levels. An assessment of eGFR and serum potassium following hydration (12-hour water-free fasting) is beneficial for accurately assessing. This impact is more prominent in RAAS blocker users, especially in individuals ≥65 years.

Keywords: RAAS blockers, GFR, elderly, hydration, fasting, biochemical assessment

INTRODUCTION

A fasting of 10-12 hours is believed to be necessary before biochemical screening since it is thought that postprandial lipid components and electrolytes can be quite different from fasting values according to the ingested foods. However, recent data have suggested fasting is not routinely required for a serum lipid profile, electrolyte, and protein level assessment (1-3).

Ensure a fasting interval lasting 12 hours in children and elderly carries some handicap during clinical implementations. While maintaining in children a long fasting interval is very difficult, in elderly individuals, kidney functions can be affected, especially in individuals under the therapy of renin-angiotensin-aldosterone system inhibitor, during a 12-hour of hunger and thirst (4). An unexpectedly low level of estimated glomerular filtration rate (eGFR) can be observed following 12-hour fasting in the elderly and this is a concern for optimizing renin-angiotensin-aldosterone system (RAAS) blocker-

involving therapies when higher dosages are necessary.

In this study, we aimed to investigate the impact of hydration status on a biochemical evaluation for eGFR assessment, and its association with RAAS blocker use, in family medicine polyclinics.

MATERIAL AND METHODS

Study Design and Participants

This longitudinal study was conducted at Gunyuzu Sehit Melih Ozcan State Hospital, Department of Family Medicine between 2018-2019 years. The patients who admitted to outpatient polyclinics due to various complaints were enrolled in the study. On the first visit, the individuals who had no sign of illness (active/chronic infection, acute or severe heart failure, acute kidney injury, cirrhosis, malnutrition, diarrhea) underwent a biochemical analysis including eGFR, following 12-hour fasting. Also, a recent or current nonsteroidal anti inflammatory medicine using was considered for exclusion.

The patients were asked to be hydrated with at least 1 L of water before performing a biochemistry analysis on the next visit (generally within 3 months). The selected patients commonly were on maintenance therapies for hypertension, anemia, thyroid disorders, and preserved heart failure. They were admitting to our polyclinics periodically to reestablish their prescriptions. The clinical features of the participants were noted. Anti-hypertensive medicine users were also noted and divided into subgroups for further analysis (RAAS blockers, RAAS blockers + diuretics, and others). If patients were receiving both RAAS blockers + calcium channel blockers (CCB) and/or alpha-beta blockers, they were included in the RAAS groups. Patients were not instructed specifically for further salt or potassium restrictions during this period. Additionally, participants were divided into two groups according to age; 18-65 years and ≥65 years.

Inclusion and exclusion criteria: Patients who applied to the family medicine outpatient clinic and were required to come for the next control within 3 months were included in the study.

Laboratory measurements

We studied the biochemical tests in an in-center laboratory. The samples were studied within 30 minutes following the drawing of blood samples. Serum creatinine, sodium, potassium, magnesium, calcium, albumin, and glucose levels were noted. Serum potassium level above 5 mEq/L was accepted as hyperkalemia. The estimated glomerular filtration rate was calculated by Chronic Kidney Disease Epidemiology Collaboration 2009 (CKD-EPI 2009) equation by utilizing an online website (www.mdrd.com). eGFRs were compared as paired (first registry; eGFR1 and following control; eGFR2).

The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices. Since the study was retrospective a consent form is not available

STATISTICAL ANALYSIS

Data were analyzed using SPSS (Statistical Package for the Social Sciences) version 23.0. Kolmogorov-Smirnov and skewness and kurtosis tests were used to find the data distribution features. Descriptive data were expressed as mean + standard deviation (SD) and median (minimum-maximum). The paired-Samples T-test was used for the comparison of consecutive longitudinal (before-after) values. Independent-Samples T-test was used for the comparison of the groups. A linear correlation test was used to evaluate the association between parameters. Pearson and Fisher's exact tests were used in the 2*2 Chi-Square analysis of categorical variables. $P < 0.05$ was considered significant at the 95% confidence interval.

RESULTS

A total of 90 individuals (50 males and 40 females) were evaluated. The mean age was 47.92±16.65 in this cohort. 52 individuals were under antihypertensive therapy. In the hydrated group, 59.6% of the participants (n=31) were receiving RAAS blockers. 17 of those 31 individuals were also receiving diuretics. 57 individuals were referred to be hydrated for the next visit. The clinical and laboratory findings of the participants were given in **Table 1**. Age significantly correlated with eGFR regarding all participants ($p<0.0001$ and $r^2=0.233$). Hypertension prevalence was 57.8 in this cohort; 59.6% in the hydrated group and 54.5% in non hydrated group.

Potassium and eGFR values of hydrated and non-hydrated participants were compared on the basis of antihypertensive medicine use (**Table 2**). The most significant p-value was obtained among RAAS blockers + diuretic users in the paired test both in ages of 18-65 years and ≥65 years. In fact, all groups expressed an improvement in eGFR and potassium levels, however, while some groups reached a statistically significant level the others revealed an improvement that was not statistically significant (Table 2).

Prehydration hyperkalemia risk was higher in RAAS blocker users (p=0.012, OR: 9.20, 95% CI; 1.45 – 58.35), and the risk decreased following hydration (p=0.052, OR:6.16, 95% CI;0.792-48.03). All individuals with post-hydration hyperkalemia were ≥65 years old.

DISCUSSION

The estimated glomerular filtration rate can decrease over years. Additionally, hypertension and RAAS blockers (especially angiotensin-converting enzyme

Table 1. The comparison of the hydrated and non-hydrated patients in regard to clinical and laboratory features

	Hydrated, n=57	Non-Hydrated, n=33	P value
Age, years	48.21±16.59	47.42±17.12	0.831
Gender, male/female, n	32/25	18/15	0.528
Age groups, n • 18-65 years • ≥65 years	 43 14	 27 6	0.602
Anti-hypertensive use • RAAS blockers • RAAS blockers + diuretics • Others (beta and/or alpha-blocker and/or CCB) • None-HT	 8 13 13 23	 6 4 8 15	0.650
BMI, kg/m^2	26.35±5.12	26.65±3.79	0.766
eGFR1, ml/min/1.73 kg/m^2	79.82±16.39	76.78±15.64	0.392
eGFR2, ml/min/1.73 kg/m^2	85.59±16.65	78.93±14.67	0.060
Potassium1, mEq/L	4.41±0.31	4.37±0.50	0.728
Potassium2, mEq/L	4.11±0.31	4.36±0.41	**<0.001**
Sodium1, mEq/L	137.31±2.73	137.00±2.82	0.604
Sodium2, mEq/L	137.64±2.81	137.51±2.99	0.832
Calcium1, mg/dl	9.10±0.66	9.13±0.67	0.789
Calcium2, mg/dl	9.22±0.67	8.96±0.54	0.062
Magnesium1, mg/dl	2.13±0.34	2.19±0.38	0.485
Magnesium2, mg/dl	2.26±0.31	2.26±0.25	0.925
Albumin1, gr/dl	4.25±0.41	4.19±0.36	0.496
Albumin2, gr/dl	4.15±0.39	4.31±0.40	0.062
Glucose1, mg/dl	88.49±10.64	86.45±8.88	0.350
Glucose2, mg/dl	86.49±10.46	89.78±9.61	0.121

RAAS; renin-angiotensin-aldosterone system, BMI; body mass index, CCB; calcium channel blockers, HT; hypertension, eGFR; estimated glomerular filtration rate (GFR1 first polyclinics registry and GFR2 is the following

[ACE] inhibitors and angiotensin receptor 1 [AT1] blockers) contribute to the development of a lower eGFR in the elderly. The eGFR evaluation following 12-hour fasting in elderly individuals (especially those who are under therapy involving RAAS blockers) carries some negative perceptions (due to lower eGFR) in regard to RAAS therapy optimization. In this study, we have demonstrated that hydrated individuals (hydrated during 12-hour fasting), compared to individuals with 12-hour fasting (water restricted), have significantly higher levels of eGFR and low serum levels of potassium. So, we suggest that the evaluation of kidney functions in elderly individuals be performed in a hydrated status, especially in individuals who are under RAAS blocker therapy.

RAAS is one of the main pharmacological targets for managing hypertension, diabetic nephropathy, and heart failure. RAAS serves as blood volume and arteriolar tone check-point, on a long-term basis. Studies reported that both ACE inhibitors and AT1 receptor antagonists can induce hyperkalemia due to the inhibition of aldosterone secretion and an abrupt acute reversible decline in GFR up to 20-30% at the onset of the therapy (5,6). Due to the decrease in total and extracellular body water by aging, a small amount of water decrement even may carry a critical hazard in maintaining kidney functions (7,8). Additionally, it has been reported that dehydration prevalence is up to 20-30% among older adults (9). Unfortunately, dehydration in the elderly is underdiagnosed due to bland clinical signs and symptoms. Given all these, before screening kidney functions, instructing older individuals to 12-hour fasting will result in lower eGFR, especially when under a RAAS blocker-involving therapy. This study indicates the importance of hydration status in the elderly and hydration can reverse eGFR up to 6-7 ml/min/1.73 m^2 in 18-65 years individuals under RAAS blockers therapy. In similar conditions, the recovery of eGFR rises up to 8-11 ml/min/1.73 m^2 in individuals > 65 years old. The impact of hydration was independent of being

Table 2. The comparison of hydrated and non-hydrated individuals on an age-based view and eGFR and K+ changes following hydrated status.

	Hydrated, n=57	
	18-65 years (p value)	≥65 years (p value)
RAAS blockers • eGFR1 vs eGFR2 • K1 vs K2	n=5 78.00±17.72 vs 84.80±21.34 (0.042) 4.70±0.39 vs 4.12±0.19 (0.020)	n=3 53.33±10.06 vs 61.66±12.05 (0.002) 4.90±0.36 vs 4.25±0.51 (0.023)
RAAS blockers + diuretics • eGFR1 vs eGFR2 • K1 vs K2	n=8 89.87±11.81vs 96.25±12.91 (0.014) 4.51±0.18 vs 4.37±0.24 (0.041)	n=5 64.60±20.40 vs 75.00±19.03 (0.002) 5.02±0.27 vs 4.20±0.30 (0.003)
Other antihypertensives • eGFR1 vs eGFR2 • K1 vs K2	n=10 89.00±9.58 vs 90.9±11.34 (0.876) 4.01±0.31 vs 4.02±0.22 (0.292)	n=3 65.66±20.25 vs 70.66±22.18 (0.090) 4.73±0.82 vs 4.30±0.30 (0.385)
No-HT • eGFR1 vs eGFR2 • K1 vs K2	N=20 82.75±13.11 vs 83.55±14.01 (0.121) 4.24±0.39 vs 4.16±0.39 (0.121)	n=3 72.00±8.54 vs 79.00±7.81 (0.094) 4.30±0.17 vs 4.13±0.28 (0.253)
	Non-Hydrated, n=33	
	18-65 years (p value)	≥65 years (p value)
RAAS blockers • eGFR1 vs eGFR2 • K1 vs K2	n=5 72.20±13.02 vs 75.20±14.34 (0.109) 4.38±0.68 vs 4.32±0.63 (0.208)	n=1 72.00 vs 79.00 NA 4.80 vs 4.90 NA
RAAS blockers + diuretics • eGFR1 vs eGFR2 • K1 vs K2	n=2 75.00±9.89 vs 80.50±10.70 (0.614) 4.85±0.77 vs 4.40±0.14 (0.553)	n=2 59.50±3.53 vs 60.50±3.53 (0.823) 4.35±0.21 vs 4.25±0.49 (0.705)
Other antihypertensives • eGFR1 vs eGFR2 • K1 vs K2	n=6 61.33±16.80 vs 62.00±16.94 (0.501) 4.65±0.41 vs 4.65±0.36 (1.000)	n=2 93.50±10.60 vs 94.50±7.77 (0.705) 4.35±0.21 vs 4.35±0.07 (1.000)
No-HT • eGFR1 vs eGFR2 • K1 vs K2	n=14 86.85±9.29 vs 86.42±9.52 (0.742) 4.10±0.34 vs 4.20±0.32 (0.072)	n=1 61.00 vs 66.00 NA 5.30 vs 4.90 NA

eGFR; estimated glomerular filtration rate, K+; potassium, NA; not applicable

hypertensive since non-hypertensive individuals with ≥65 years exhibited also an elevation of up to 7 ml/min/1.73 m^2 in eGFR. However, the recovery in eGFR reached statistically a significant level only in RAAS blockers users. Additionally, potassium levels decrease as well as eGFR following hydration in RAAS blockers users. The improvement was more prominent among individuals > 65 years. Those findings are suggestive of the data indicating prolonged thirst can activate RAAS (thus may contribute to hyperkalemia) (10,11).

Hyperkalemia is a limiting factor in the use of drugs that block RAAS. Hyperkalemia incidence is 7% at the first visit following starting to receive the drug, prevalence reaches 11% in individuals with chronic kidney disease and approximately 45% of hyperkalemia cases are in therapy with ACE inhibitör or AT1 receptor blocker (12). The elderly tend to have hyperkalemia as a result of underlying abnormalities in potassium homeostasis. These include undiagnosed renal dysfunction, tubulointerstitial disease in the kidney, disturbed aldosterone production, and abnormal salt and water balance (13). In community-acquired hyperkalemia among individuals ≥65 years, ACE inhibitors and AT1 receptor blockers increase the risk of hyperkalemia development up to 2.5 times, and if a renal injury is accompanying the risk increases 30-fold (14). Moreover, dehydration and a decrease in urinary concentrating ability contribute to hyperkalemia development in the elderly (4,15). In this study, hyperkalemia prevalence was 11.2% (10.5% in hydrated and 15.2% in non hydrated individuals and p=0.523). In the next hospital visit, hyperkalemia prevalence decreased to 0% among hydrated individuals and remained at 12.1% among non hydrated individuals (p=0.016). The most significant decrease in serum potassium levels following hydration was observed among RAAS blockers users. On the other hand, in a recent study, Wetmore et al. reported that hyperkalemia risk was increased in patients with heart failure, diabetes, CKD, or other comorbid conditions.

The rate of RAAS inhibitor interruption was greater for individuals with heart failure or diabetes mellitus than for those without, while the risk of both interruption and cessation was greater for individuals with advanced stages of CKD than for those without (16). So, the evaluation of those individuals with comorbidities is essential in regard to therapy optimization

The clinical findings of this study have two main implications. First, evaluation of eGFR in RAAS blockers users after 12 hours of fasting without water restriction will provide a higher estimate of GFR and avoid unnecessary dose reduction of RAAS blockers. Second, and most importantly, this approach may increase your suitability for using more aggressive RAAS blockers, especially in people who have the potential to need an aldosterone **a**ntagonist such as spironolactone.

The study's main limitations are the small sample size, the lack of data on hypertension duration and smoking, and single laboratory measurements. The hydration status of participants depended on their statements, so the amount of ingested water may be substantially different from instructed. Moreover, the fasting longevity may be different between patients since the waiting duration and the booking time in polyclinics may affect the duration of blood drawn. A few patients were under spironolactone and/or diuretic therapies, however, the sample size was small and further analysis could not be performed

DECLARATIONS

Ethical approval: This study was carried out in accordance with the Declaration of Helsinki. The study was approved by the Medicana International Hospital Scientific Research Ethics Committee (Date:15.03.2023, Approval number: BŞH-2023/06).

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