Iranian Heart Journal; 2019; 20 (1)

Original Article

Effects of Spironolactone on Cardiovascular Complications in Hemodialysis Patients of Taleghani Hospital During the Period of 2016-2017: A Randomized Double-Blind Controlled Clinical Trial

Seyed Ahmad Reza Ziaee[1], MD; Mersedeh Karvandi[2], MD; Negar Sadat Ziaee[1], MD; Zohre Gholizadeh Ghozloujeh[3], MD; Mohammad Amin Shahrbaf[4], MD; Azamolsadat Roshan[5*], MD

ABSTRACT

Background: There is recent evidence that aldosterone plays a role in the pathogenesis of cardiovascular diseases in dialysis patients, which leads to the opportunity to block its actions for the benefit of these patients. In non-dialytic chronic kidney diseases, spironolactone was safe and effective in reducing left ventricular hypertrophy. However, its routine use has been precluded in hemodialysis patients due to the risk of hyperkalemia. The aim of the present study was to verify the safety and efficacy of spironolactone in the regression of left ventricular hypertrophy and ejection fraction in hemodialysis patients undergoing pharmacotherapeutic monitoring.

Methods: We performed a controlled, randomized, double-blind study evaluating 48 hemodialysis patients divided into 2 groups. The first group received spironolactone at a dose of 25 mg after hemodialysis over a few weeks, and the second group was the control. The patients were followed up for 9 months.

Results: Both groups were composed of 24 patients each. The study groups did not differ in their baseline characteristics. The group receiving spironolactone had a significant improvement in the left ventricular mass index and ejection fraction in comparison with the control group ($P<0.05$).

Conclusions: Spironolactone treatment in hemodialysis patients was safe and effective in regressing left ventricular hypertrophy and improving the ejection fraction as major risk factors for cardiovascular events in these patients. ***(Iranian Heart Journal 2019; 20(1):45-52)***

KEYWORDS: Chronic kidney disease, Echocardiography, Left ventricular hypertrophy, Spironolactone, Ejection fraction

[1] Department of Internal Medicine, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran.
[2] Department of Cardiology, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran.
[3] Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran.
[4] Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran.
[5] Department of Nephrology, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran.

***Corresponding Author:** Azamolsadat Roshan, MD; Department of Nephrology, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran.
Email: shivaroshana@yahoo.com **Tel:** 02122432560

Received: July 24, 2018 **Accepted:** October 16, 2018

Chronic kidney diseases (CKDs) are characterized by progressive and irreversible renal dysfunction. [1] The clinical manifestation of kidney failure is the uremic syndrome, which usually occurs with a glomerular filtration rate of less than 10 mL/min. The use of therapeutic methods such as hemodialysis, peritoneal dialysis, and kidney transplantation in the early stage of kidney failure is the usual way to cope with the occurrence of the uremic syndrome. [2,3]

Cardiovascular diseases (CVDs) are the main causes of mortality in patients with kidney failure. Patients on dialysis have a 10% to 20% higher mortality rate than do normal individuals. CVDs are almost epidemic in patients on dialysis and manifest themselves in 3 forms of coronary artery disease (CAD), hypertension, and left ventricular dysfunction (LVD). The increasing use of percutaneous and surgical treatments for heart disease has been unable to change this prognosis, and there is still a lack of effective medical interventions to improve outcomes in dialysis patients. [4-6] In patients with kidney failure, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers cause a decrease in proteinuria by 20% to 30%. [7,8] Spironolactone, an aldosterone antagonist, reduces proteinuria and subsequently improves heart failure symptoms in patients with kidney failure. [9-12]

In addition, some of the factors associated with hemodialysis, such as pathophysiologic stress, may enhance the incidence of CVDs due to repeatedly increased intravascular fluid volumes and corresponding effects on the myocardium. The most important cardiac complications in hemodialysis patients are LV structural and functional impairments, atherosclerosis, ischemic heart disease, pericardial diseases, valvular dysfunction, and congestive heart failure. [13] The structural and functional disorders of the LV are commonly found in patients with CKDs. Hypertension is the main cause of LV hypertrophy, followed by other contributing factors such as anemia, increased volume loads, malnutrition, secondary hyperparathyroidism, ischemic heart disease, arteriovenous fistulae, and myocardial calcification. [14]

Spironolactone is a steroid derivative and acts as an aldosterone pharmacological antagonist in afferent arterioles. This drug is combined with the intracellular receptor of aldosterone and inhibits it, thereby reducing the expression of the gene controlling the synthesis of the epithelial sodium channel (ENaC) and Na/K-ATPase. [15] Those drugs acting through the renin-angiotensin system appear to have beneficial effects on patients with CKDs suffering from brain and cardiovascular diseases.

According to previous studies, aldosterone is strongly associated with the risk of CVDs, including sudden death. Thus, the use of aldosterone inhibitors, such as spironolactone, can attenuate these complications. [4,13] One of the worrisome side effects of spironolactone as an aldosterone inhibitor is life-threatening hyperkalemia in patients. However, various studies have shown that this effect is negligible in patients undergoing dialysis and is used as an uncomplicated drug in these patients. [5,6]

Hence, the present study was conducted to evaluate and compare the effects of spironolactone as an aldosterone antagonist on improving the echocardiographic indices, including the ejection fraction (EF) and left ventricular hypertrophy (LVH) in patients with kidney failure undergoing permanent hemodialysis in Taleghani Hospital, Tehran, Iran.

METHODS

This randomized double-blind controlled clinical trial was conducted to evaluate the efficacy and safety of spironolactone in reducing the LV mass in hemodialysis patients.

After obtaining an approval from the Ethics Committee of Shahid Beheshti University of

Medical Sciences, all the eligible patients gave their written informed consent before the study. The inclusion criteria were comprised of age over 18 years, a history of at least 3 months of hemodialysis, at least 3 sessions of dialysis per week, a serum potassium level of lower than 5.5 mEq/lit, a systolic blood pressure of greater than 100 mm Hg at the beginning of the study, and a left ventricular mass (LVM) index of greater than 51 g/m^2 indexed for height, with a stable antihypertensive treatment in the preceding 6 months. The exclusion criteria consisted of a high risk of hyperkalemia (pre-dialysis serum potassium level of above 6 mEq/lit), kidney transplantation during the study, a dialysis dose of Kt/V less than 1.2, a history or evidence of angina or myocardial infarction, heart failure, peripheral vascular disease, previous hyperkalemia, valvular heart disease, atrial fibrillation, a hemoglobin level of less than 9.5 g/dL, and receiving treatment with spironolactone.

The patients were randomly assigned to control and intervention groups. In the allocation of the patients to the 2 groups, those who referred on even days were assigned to the control group, and those who referred on odd days were assigned to the case group (receiving spironolactone). In total, 48 patients were selected from the patients who met the inclusion criteria and they were finally divided into 2 groups of 24 patients each.

After a complete history taking, a venous blood sample was taken immediately prior to the start of hemodialysis from each patient for routine hematology—including red blood cell, white blood cell, count, and platelet count; inflammatory markers (C-reactive protein [CRP] and albumin); and potassium monthly.

The patients in the case group, after each hemodialysis session, were given 25 mg of spironolactone by a nurse, who was unaware of the grouping of the patients. Spironolactone used in this protocol was acquired on the market as Aldactone 25 mg. The patients in the second group were given no medication.

In order to follow up the patients and measure the study variables at baseline and after 9 months, echocardiography was conducted by a single examiner, who was unaware of the study procedure and the allocation of the patients. The echocardiographic examinations determined the patients' ejection fractions (EFs) and LV mass indices. The equipment used was a Vivid S6 GE (General Electric), equipped with a multi-frequency ultrasonic transducer (2.0–3.5 MHz) and a recording system.

The data recorded were the heart rate, the systolic and diastolic dimensions of the LV, and the diastolic thickness of the posterior wall and the septum. These data were used to calculate the ventricular mass via the following formula:

$$\text{LV mass (g)} = 0.8 \times \{1{:}04\,[(\text{LVDD} + \text{EDPW} + \text{EDS})3 - (\text{LVDD})\,3]\} + 0.6$$

where the LVDD is the left ventricular diastolic dimension and the EDPW and the EDS represent the thickness of the end-diastolic posterior wall and the interventricular septum, respectively.

During the study, the systolic and diastolic blood pressures before and after dialysis were measured using a sphygmomanometer at each dialysis referral. The blood samples were sent for monthly tests. The patients were excluded from the study in the event of any adverse effects from spironolactone or any condition causing injury to the patients' health or any disruption in the study results. All the patients received pharmaceutical care and nutritional counseling in addition to that provided routinely.

Means, standard deviations, minimums, maximums, first quartiles, medians, and third quartiles were reported for the descriptive analysis of the quantitative data, as well as frequencies and percentages for the descriptive analysis of the qualitative data. The independent *t*-test or its Mann–Whitney nonparametric equivalent test (depending on the data distribution status) was used to compare

the continuous variables between the 2 groups under study. The χ^2 test or the Fisher exact test (depending on the data distribution status) was applied to check the relationship between the nominal variables. The data were analyzed with the SPSS 20.0.0 software, and all tests were 2-ways. A *P* value of 0.05 was considered statistically significant.

RESULTS

Forty-eight patients (24 patients in each group) were enrolled in this study. Two patients in the control group and 1 patient in the intervention group were withdrawn because of death. Additionally, 1 patient in the intervention group and 1 patient in the control group were withdrawn from the study because of gynecomastia and changing the dialysis center, respectively. The general characteristics of the patients are presented in Table 1.

The groups did not differ in terms of age, sex, height, and body weight. The groups were homogeneous with respect to the duration of dialysis, the causes of end-stage renal disease (ESRD), and the use of angiotensin-converting enzyme inhibitors and/or beta-blockers and calcium channel blockers.

The laboratory data are presented in Table 2. All the laboratory variables tested were homogeneous between the groups at baseline and moments within the groups.

The results of the LVM, the EF, and the central blood pressure are presented in Table 4. The data showed a significant decrease in the LVM and increase in the EF in the spironolactone group by comparison with the control group after treatment.

Table 1. Clinical characteristics of the patients with chronic kidney diseases on hemodialysis undergoing treatment with spironolactone or controls

Characteristic	Intervention	Control	*P*
Sex, n (%)			
Male Female	12(52%) 10(43%)	13(41%) 8(58%)	>0.05
Age (y)	69.2±13.5	67.5±10	>0.05
Time in hemodialysis treatment (y)			
<1 1-2 2-5 >5	2 1 8 11	2 2 7 10	>0.05
ESRD cause, n			
Diabetes mellitus Hypertension Glomerulonephritis Others	10 8 3 1	8 10 2 1	>0.05
Medication			
1)ACEI+/or ARB 2)CCB 3)BB 1+2 1+3 2+3 1+2+3 Others None	1 4 2 2 0 4 0 0 9	2 3 4 1 1 0 1 1 7	>0.05

P, comparison of both groups
ARB, Angiotensin receptor blocker; ESRD, End-stage renal disease; ACEI, Angiotensin-converting enzyme inhibitors; CCB, Calcium channel blocker; BB, Beta-blocker

Table 2. Laboratory variables of the patients with chronic kidney diseases on hemodialysis in both groups

	Intervention		Control		*P*
	Baseline	**Post-study**	**Baseline**	**Post-study**	
Hemoglobin (g/dL)	9.8±1.5	11.6±1.3	10.1±1.5	10.7±1.7	>0.05
Albumin (g/dL)	4.1±0.6	3.9±0.38	4.09±0.45	3.7±0.26	>0.05
Potassium (K^+) (mEq/L)	4.6±0.8	5±0.6	4.8±0.9	4.9±0.5	>0.05
CRP					
Negative	12	11	13	10	>0.05
1+	9	7	9	8	
2+	0	2	0	2	
3+	0	1	0	2	

P, comparison of both groups and moments
CRP, C-reactive protein

Table 3. Blood pressure monitoring data of the patients with chronic kidney diseases on hemodialysis in both groups during a 9-month period

	Intervention		Control		
	Before Dialysis	**After Dialysis**	**Before Dialysis**	**After Dialysis**	***P***
Week 0					
SBP (mmHg)	125.81±25.60	123.86±20.29	123.82±26.14	123.18±25.12	>0.05
DBP(mmHg)	65.61±13.08	68.80±12.49	66.81±14.19	69.09±15.13	
Week 4					
SBP(mmHg)	126.62±29.62	129.48±33.94	122.50±25.62	122.50±25.62	>0.05
DBP(mmHg)	72.85±12.76	75.90±15.41	73.33±18.25	67.66±11.27	
Week 8					
SBP(mmHg)	122.50±25.31	122.50±19.90	120.90±22.29	120.00±22.60	>0.05
DBP(mmHg)	66.25±12.69	66.95±9.82	71.60±13.45	68.00±11.35	
Week 26					
SBP(mmHg)	120.23±15.92	126.64±20.50	129.00±26.43	123.50±27.08	>0.05
DBP(mmHg)	66.86±7.18	68.04±5.9	74.00±19.55	71.00±17.91	
Week 36					
SBP(mmHg)	118.05±22.99	128.42±27.33	120.91±15.78	118.64±17.04	>0.05
DBP(mmHg)	73.68±16.40	80.00±17.63	74.09±13.19	78.00±15.23	

P, comparison of all groups and moments
SBP, Systolic blood pressure; DBP, Diastolic blood pressure

Table 4. Echocardiographic data in the patients with chronic kidney diseases on hemodialysis in both groups

	Control		Intervention		
	Pre	**Post**	**Pre**	**Post**	***P***
LV	283.08±138.1	274.58±127.8	265.23±114.4	205.30±40.5	*0.04
EF	53.33±7.4	48.83±10.3	53.33±7.4	60.00±7.1	0.006

P, comparison of all groups and moments * *P*<0.05, comparison of post intervention LV in both groups
P<0.05, comparison of post intervention EF in both groups
LV, Left ventricular volume; EF, Ejection Fraction

DISCUSSION

The present study was conducted to investigate the effects of spironolactone on the LVM and the EF in hemodialysis patients. Our echocardiographic findings showed that the use of spironolactone over the 9-month period of the study significantly improved the echocardiographic features in the intervention group in comparison with the control group (Table 4).

Long-term kidney failure is associated with complications. One of these changes in the patients with ESRD is a significant increase in the LVM. Previous research has attributed one of the mechanisms of this increase in the LVM during kidney failure to an increased afterload in these patients. [16] One of the problems affecting a significant number of patients with ESRD is hypertension following increased intravascular volumes, the activation of the

renin-angiotensin-aldosterone system (RAAS), high sympathetic activities, secondary hyperparathyroidism, and endothelium-derived factors. [17] In addition, arterial calcification is followed by abnormalities in bone mineral metabolism and tissue collagen cross-linking formation, and then reduced venous compliance, which causes hypertension and reduced arterial compliance. This mechanism, in the long term, causes an increase in the afterload and the LVM, creating an eccentric pattern of LVH. [18,19]

Additionally, studies have identified other factors in patients with CKDs that lead to increased afterload and LVM. One of these factors is the commonly occurring anemia in patients with advanced CKDs, which leads to increased afterload, decreased arterial resistance, and increased LV contraction due to sympathetic hyperactivity. Acute heart failure is also particularly associated with an increased arterial blood volume, resulting in increased LV volume, impulse volume, diastolic blood pressure, and LVH. [20,21] An increased venous return in patients with arteriovenous fistulae can also exacerbate these hemodynamic changes. [20] On the other hand, the permanent activation of the RAAS and elevated aldosterone levels in patients with ESRD can stimulate afterload and preload factors and then hypertrophy patterns, creating a unique cardiac structure in these patients. [17,19,20]

The results of the current study evaluating the effects of spironolactone on echocardiographic indices are consistent with those of a larger randomized trial performed in Japan on 158 chronic peritoneal dialysis patients. That study investigated the echocardiographic indices of the case group undergoing mineralocorticoid receptor antagonist (MRA) treatment, with the initial dose of 25 mg of spironolactone per day, and the control group (placebo) within 2 years. During the study period, an overall increase in the LVM was observed in the control group, while the LVM was decreased in the MRA group and showed a significant difference with the control group in the sixth month (P=0.03), 18th month (P=0.004), and 24th month (P=0.01). In addition, the LVEF was decreased in the control group, while it increased in the case group, with the change being significant in the 24th month (P=0.002). [20]

Recent studies have shown that LV echocardiography features such as the EF and LVH are suitable predictors of cardiovascular events in patients with hypertension or CKDs, and the subsequent repercussions have a positive effect on reducing mortality in these patients. [22, 23] In line with our study, Matsumoto et al [24] recently reported that the use of spironolactone in their dialysis patients increased the EF and reduced the LV volume in the long term, resulting in a longer lifespan in the patients with ESRD. Similarly, other clinical trials aiming to assess the effects of using spironolactone on the LV volume and the EF in patients with ESRD undergoing dialysis have suggested that the RAAS inhibitor could significantly increase the EF and decrease LVH when compared with the control group. [20,25,26]

The positive effect of spironolactone appears to occur through the inhibition of aldosterone, which is one of the direct causative factors of LVH and has a hemodynamic impact on cardiomyocytes. The effects of endogenous cardiac glycosides (endogenous ouabain and marinobufagenine) have been proven in the onset of uremic cardiomyopathy. [27,28] It has also been confirmed that the level of these glycosides increases in patients with CKDs, which causes the proliferation of cardiomyocytes and thereby a change in the morphology of the heart in the long term. [29]

The stable potassium behavior points favorably to the safety of spironolactone in hemodialysis patients. However, it is important to stress that these patients were submitted to rigorous pharmacotherapeutic monitoring throughout the treatment.

The homogeneity and stability of the laboratory data is an important finding because these variables could influence the cardiac structure.

If, for example, hemoglobin levels had dropped in the spironolactone group, this could explain the obtained results for the LVM and the EF, instead of a spironolactone effect on aldosterone. It can, therefore, be argued that these factors are not important in the behavior of the cardiac mass because of the stability demonstrated in the laboratory data. Aldosterone also showed a drop in our control group following treatment. Thus, in spite of this favorable situation of cardiac mass regression in the control group, this group did not demonstrate any LVM reduction. This bias also corroborates the conclusion rather than contradict it.

CONCLUSIONS

The results obtained from the present study generally suggest that the use of angiotensin-system inhibitors, along with the benefits for the renal system, can play a crucial role in controlling and, in some cases, improving cardiovascular complications caused by kidney failure in patients undergoing dialysis and can lead to an increase in the life expectancy of these patients.

REFERENCES

1. Benjamin IJ G, Robert C, Wing, Edward J, Fitz, J Gregory. Andreoli and Carpenter Cecil essential of Medicine. 9th ed. United States: Philadelphia: Elsevier/Saunders; 2015.

2. Lameire N. Handbook of Dialysis J. T. Daugirdas, P. G. Blake, T. S. Ing (Editors). Nephrology Dialysis Transplantation. 2007;22(6):1784-.

3. Bonow DMDZPLR. Renal disorder and heart disease in: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Single Volume 10th Edition18th September 2014.

4. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The New England journal of medicine. 2000;342(3):145-53.

5. Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke. 2005;36(6):1218-26.

6. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet (London, England). 2002;359(9311):995-1003.

7. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. The New England journal of medicine. 1999;341(10):709-17.

8. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. New England Journal of Medicine. 2003;348(14):1309-21.

9. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. The New England journal of medicine. 2011;364(1):11-21.

10. Dorrance AM, Osborn HL, Grekin R, Webb RC. Spironolactone reduces cerebral infarct size and EGF-receptor mRNA in stroke-prone rats. American journal of physiology Regulatory, integrative and comparative physiology. 2001;281(3):R944-50.

11. Osmond JM, Dorrance AM. 11beta-hydroxysteroid dehydrogenase type II inhibition causes cerebrovascular remodeling and increases infarct size after cerebral ischemia. Endocrinology. 2009;150(2):713-9.

12. Matsumoto Y, Kageyama S, Yakushigawa T, Arihara K, Sugiyama T, Mori Y, et al. Long-

term low-dose spironolactone therapy is safe in oligoanuric hemodialysis patients. Cardiology. 2009;114(1):32-8.

13. Kes P, Drusko D, Rupcic V. Cardiovascular complications in end-stage renal disease and hemodialysis patients. Acta medica Croatica : casopis Hravatske akademije medicinskih znanosti. 1996;50(4-5):199-208.

14. Lopez-Gomez JM, Verde E, Perez-Garcia R. Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patients. Kidney international Supplement. 1998;68:S92-8.

15. Anthony J. Trevor BGK, Marieke Kruidering-Hall. Katzung & Trevor's Pharmacology: Examination & Board Review, 11e United States McGraw-Hill Education; 2015.

16. Vukusich A, Kunstmann S, Varela C, Gainza D, Bravo S, Sepulveda D, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Spironolactone on Carotid Intima-Media Thickness in Nondiabetic Hemodialysis Patients. Clinical Journal of the American Society of Nephrology : CJASN. 2010;5(8):1380-7.

17. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol. 2009;4 Suppl 1:S79-91.

18. London GM. Cardiovascular disease in chronic renal failure: pathophysiologic aspects. Seminars in dialysis. 2003;16(2):85-94.

19. Gross ML, Ritz E. Hypertrophy and fibrosis in the cardiomyopathy of uremia--beyond coronary heart disease. Seminars in dialysis. 2008;21(4):308-18.

20. Ito Y, Mizuno M, Suzuki Y, Tamai H, Hiramatsu T, Ohashi H, et al. Long-term effects of spironolactone in peritoneal dialysis patients. Journal of the American Society of Nephrology : JASN. 2014;25(5):1094-102.

21. Sica DA. The risks and benefits of therapy with aldosterone receptor antagonist therapy. Current drug safety. 2007;2(1):71-7.

22. Matsumoto Y, Mori Y, Kageyama S, Arihara K, Sugiyama T, Ohmura H, et al. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. Journal of the American College of Cardiology. 2014;63(6):528-36.

23. Taheri S, Mortazavi M, Shahidi S, Pourmoghadas A, Garakyaraghi M, Seirafian S, et al. Spironolactone in chronic hemodialysis patients improves cardiac function. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2009;20(3):392-7.

24. Taheri S, Mortazavi M, Pourmoghadas A, Seyrafian S, Alipour Z, Karimi S. A prospective double-blind randomized placebo-controlled clinical trial to evaluate the safety and efficacy of spironolactone in patients with advanced congestive heart failure on continuous ambulatory peritoneal dialysis. Saudi journal of kidney diseases and transplantation: an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2012;23(3):507-12.

25. Bagrov AY, Shapiro JI. Endogenous digitalis: pathophysiologic roles and therapeutic applications. Nature clinical practice Nephrology. 2008;4(7):378-92.

26. Hamlyn JM, Hamilton BP, Manunta P. Endogenous ouabain, sodium balance and blood pressure: a review and a hypothesis. Journal of hypertension. 1996;14(2):151-67.

27. Schoner W, Scheiner-Bobis G. Role of endogenous cardiotonic steroids in sodium homeostasis. Nephrology Dialysis Transplantation. 2008;23(9):2723-9.

28. Fedorova OV, Shapiro JI, Bagrov AY. ENDOGENOUS CARDIOTONIC STEROIDS AND SALT-SENSITIVE HYPERTENSION. Biochimica et biophysica acta. 2010;1802(12):1230-6.

29. Bernini G, Galetta F, Franzoni F, Bardini M, Taurino C, Bernardini M, et al. Arterial stiffness, intima-media thickness and carotid artery fibrosis in patients with primary aldosteronism2009. 2399-405 p.