RESEARCH

The Effect of Treatment on Pulse Wave Indices of Proteinuira Cases*

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Abstract: In proteinuria patients, the most significant reason of mortality is cardiovascular diseases caused by increased atherosclerosis. This study seeks to reveal the effects of the changes in the amount of proteinuria on the pulse waves of patients with proteinuria in a period of treatment of six months. 15 voluntary patients with proteinuria that applied to the outpatient clinic of Department of Nephrology, Faculty of Medicine, Cumhuriyet University for the first time enrolled in the study. PWV and AI measurements of the patients were taken by using a pressure-sensitive transduser by a single operator at the moment of diagnosis, third month, and six months after the diagnosis. Ten of the patients were female (66.7%), 5 were male (33.3%). The mean age of the patients was found to be 48.13±11.96 years. When the average of the patients' micro total proteinuria (MTP), Pulse wave velocity (PWV) and augmentation index (AI) measurement are examined, it is observed that at the moment of diagnosis MTP: 4937,76 mg/day PWV: 7,07 m/s AI: 25,07 %, in the third month MTP: 2260,27 mg/day PWV: 6,79 m/s AI: 22,53 % and in the sixth month MTP: 2469,71 mg/day PWV: 7,18 m/s AI: 32,53 %. With our patients, there was a negative correlation between MTP and PWV in the third month ($r=-0.621$ $p=0.014$) and sixth month ($r=-0.664$ $p=0.007$), and the result is found to be statistically significant ($p<0.05$). In the first three-month period, it's seen that MTP is decreased by treatment, and therefore PWV is decreased, also, and after that time, chronic stage occurs, and renal damage continued depending on the high proteinuria amount. We also observed an increase in PWV and atherosclerosis. In order to demonstrate the relationship between proteinuria with PWV and atherosclerosis more clearly, there is a need for further studies which are long-term prospective and have a large number of patients.

INTRODUCTION

Proteinuria; The amount of protein in 24-hour urine is over 150 mg/day in repeated measurements. Proteinuria; is one of the most important clinical manifestations of kidney disease, and recurrent proteinuria is associated with progressive kidney disease. Proteinuria; develops due to primary and secondary glomerular diseases. Depending on the severity of the disease in patients with proteinuria, hypoalbuminemia, hyperlipidemia, inflammation, hypertension, and edema are observed [1].

The first approach in patients with proteinuria is to find the underlying cause. Specific treatments such as steroid therapy and immunosuppressive treatments are performed for renal pathology. In addition, the other approach is conservative treatments to reduce proteinuria. Treatments reducing proteinuria; blood pressure control and dietary regulation. In addition, in patients with proteinuria; Non -specific treatments are performed for complications such as hyperlipidemia, edema, hypoalbuminemia, hypercoagulability [2].

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. Half of deaths in developed countries and 25% of deaths in developing countries are due to coronary artery disease (CAD) [3]. The higher the proteinuria level, the greater the cardiovascular risk and progression to chronic kidney disease (CKD). Identifying cardiovascular risk factors and their early treatment is essential in preventing CAD in asymptomatic people and in preventing recurrent events and mortality in patients with CAD.

Arterial stiffness; decrease in viscoelastic properties and compliance of the artery wall due to many factors such as age, hypertension, diabetes mellitus (DM), hyperlipidemia, smoking, oxidative stress, inflammation [4]. Increased arterial stiffness leads to significant clinical consequences. These; Increase in systolic blood pressure, an increase in pulse pressure, and left ventricular hypertrophy. These changes are significant determinants of cardiovascular morbidity and mortality in the general

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population and renal patient population [5, 6].

With the developing technology, we can evaluate atherosclerosis that develops due to arterial stiffening by non-invasive methods. Pulse wave velocity measurement is the most widely used non-invasive measurement method in assessing arterial stiffness [7]. Increased pulse wave velocity (PWV), a reflection of arterial stiffness, is an indicator of atherosclerosis.

In this study, we aimed to compare the amount of proteinuria and the reflection of the change in cardiovascular risk factors on the parameters of PWV by following up 15 patients who underwent renal biopsy and started treatment for six months due to proteinuria.

METHOD

Fifteen patients who volunteered among those who applied to Cumhuriyet University Medical Faculty Hospital Nephrology Polyclinic for the first time with proteinuria between October 2015 and April 2016 were included in our study. Our study was conducted with the decision of the Cumhuriyet University Faculty of Medicine ethics committee, dated 27.10.2015 and numbered 2015-10 / 02.

Measurement using pressure-sensitive, Mobil-O-Graph 24 h ABPM NG® pulse wave analysis and ambulatory blood pressure monitor based on the brachial-radial artery trace (PWA Dongle, IEM GmbH, Cockerillstr.69, D-52222 Stolberg, Germany) done. Patients were measured at least 30 minutes after resting before measurement. Before the measurement, he did not take any cigarettes or caffeinated drinks in the last 30 minutes, and the measurements were made by sitting on a chair in a quiet area reserved for measurement, avoiding external stimuli. The device made two measurements in total and took the average of the other operations in the 3rd place. When the results were reported as reliable, the results of the patients were recorded. The results were not recorded in patients whose results were not reliable, and the procedure was repeated until reliable results were obtained.

The data obtained from our study were loaded into the SPSS (version 22.0) program. When the parametric test assumptions were fulfilled in the evaluation of the data (evaluated with the Kolmogorof-Simirnov test); In repeated measures, the analysis of variance, Bonferans test, the significance test of the difference between the two means, and when the parametric test assumptions could not be fulfilled, the Kruskal Wallis test, Friedman test, Man Whitney U Test, Chi-Square test and Correlation analysis were used. Results were obtained at a significance level of $p < 0.05$ with 95% confidence.

FINDINGS

Fifteen voluntary patients who underwent renal biopsy for proteinuria were included in the study. Ten of the patients were female (66.7%), 5 were male (33.3%). All patients received antihypertensive, antiaggregant, immunosuppressive, and treatment for hyperlipidemia. The mean age of the patients was found to be 48.13±11.96 years. The mean age of male patients was 42.40 ± 14.29 years, and the average age of female patients was 51.00±10.21 years. When our patients were examined in terms of age and gender, it was seen that there was no statistically significant difference between them ($p > 0.05$). When the patients' height, weight, and BMI were compared according to their gender, it was observed that women were overweight than men, and there was no statistically significant difference ($p=0.510$). When the patients were compared according to their height, the average height of the males was 173.40±4.39 cm, and the average height of the females was 156.50±5.99 cm. It was observed that males were taller than females, and there was a statistically significant difference ($p=0.003$) (Table 1).

Table 1: Demographic characteristics of the patients

		n	Mean±SD	p-value
Age	Female	10	51,00±10,21	0,200
	Male	5	42,40±14,29	
	Total	15	48,13±11,95	
Height	Female	10	156,50±5,99	0,003*
	Male	5	173,40±4,39	
	Total	15	162,13±9,83	
BMI	Female	10	33,87±8,68	0,058
	Male	5	25,39±3,22	
	Total	15	31,04±8,28	
Weight	Female	10	82,80±20,61	0,510
	Male	5	76,20±8,59	
	Total	15	80,60±17,46	

* $p<0,005$

Considering the comorbidities of the patients; While 6 patients (40%) had DM, 9 patients (60%) did not have DM. While 7 (46.7%) of the patients had HT, 8 (53.3%) did not have HT (Table 2).

Table 2: Chronic diseases of the patients according to their gender

	Female	Male	Total
DM	5 (%33,3)	1 (%6,7)	6 (%40)
HT	6 (%40)	1 (%6,7)	7 (%46,7)

When the histopathological diagnoses of our patients who underwent renal biopsy for proteinuria were examined; 6 (40%) had Focal Segmental glomerulosclerosis (FSGS), 4 (26.7%) had Membranous Glomerulonephritis (MGN), 2 had Systemic lupus erythematosus (SLE) nephritis, 1 had Membraneuproliferative glomerulonephritis (MPGN), 1 Amyloidosis was observed in 1 and Chronic tubulointerstitial nephritis in 1 (Table 3).

Table 3: Renal biopsy results of the patients

Pathological Diagnosis	Total
Focal Segmental glomerulosclerosis	6 (%40,0)
Membranous Glomerulonephritis	4 (%26,7)
Systemic Lupus Erythematosus Nephritis	2 (%13,3)
Membraneuproliferative Glomerulonephritis	1 (%6,7)
Amyloidosis	1 (%6,7)
Chronic Tubulointerstitial Nephritis	1 (%6,7)
Total	15 (%100)

When the ambulatory blood pressure measurements of the patients at 0 and 6 months are examined, the mean systolic blood pressure; 0. month 122.67/76.47 mmHg, 6. month 117.21/72.71 mmHg, mean diastolic blood pressure 0. month 76.47±9.19 mmHg 6. month 72.71±9.68 mmHg It was measured, and there was no statistically significant difference ($p>0.05$). When the heart rate measurements of the patients at 0 and 6 months were examined; 0. month 122.67/76.47 mmHg, 6. month 117.21/72.71 mmHg, mean diastolic blood pressure at 0. month 77.40±12.65 minutes / beat at 6. months 79.86±9, It was measured as 69 minutes/beat, and there was no statistically significant difference ($p>0.05$) (Table 4).

Table 4: Comparison of blood pressure and heart rate measurements of the patients.

		0. Month (Mean ±SD)	6. Month (Mean ±SD)	p-value
Cystolic Blood Pressure	Female	124,70±17,67	115,50±14,68	>0,05
	Male	118,60±19,59	121,50±21,33	
	Total	122,67±17,87	117,21±16,19	0,123
Diastolic Blood Pressure	Female	76,80±9,26	70,20±6,81	>0,05
	Male	75,80±10,09	79,00±13,88	
	Total	76,47±9,19	72,71±9,68	0,096
Pulse	Female	81,90±11,52	80,20±9,14	<0,005*
	Male	68,40±10,48	79,00±12,46	
	Total	77,40±12,65	79,86±9,69	0,593

* p<0,005

Laboratory values of the patients at 0, 3 and 6 months are compared in Table 5. Albumin values; between 0th months and 3rd months (p=0.022) and 0th months to 6th months (p=0.022), Na values between 0th months and 6th months (p=0.008), K values with 0th months between the 6th month (p=0.01) and between the 0th month and the 3rd month (p=0.011) in the Ca value, between the 0th month and the 6th month in the sedimentation value (p=0.029), with the 0th month in the MTP value a statistically significant difference was observed between the 3rd month (p=0.008) and between the 0th month and the 6th month (p=0.015) (p <0.05). There was no difference in terms of other laboratory parameters (p>0.05).

When the PWV measurements of the patients were examined, it was observed that women had higher PWV than men, and there was no statistically significant difference between them (p>0.05). When the PWV measurements of the patients at 0, 3, and 6 months were compared; there was no statistically significant difference between the 0th month and the 3rd month (p=0.078), between the 0th month and the 6th month (p=0.305), and between the 3rd month and the 6th month (p=0.065) (p>0.05).

Table 5: Laboratory values of the patients at 0, 3, and 6 months.

	0. Month (Mean±SD)	3. Month (Mean ±SD)	6. Month (Mean ±SD)	p-value
Glucose	109,33±64,12	110,66±56,98	92,80±33,54	>0,05
Triglyceride	221,00±112,90	208,84±96,63	202,53±87,26	>0,05
LDL	168,64±67,98	142,38±40,08	149,20±35,19	>0,05
BUN	19,36±5,68	17,42±6,07	17,96±8,12	>0,05
Creatine	0,88±0,34	0,80±0,29	0,76±0,26	>0,05
Uric acid	5,78±1,66	5,94±2,01	5,85±1,73	>0,05
Total protein	5,69±1,22	5,82±0,93	6,08±0,84	>0,05
Albumin	2,98±0,90	3,43±0,77	3,55±0,66	<0,05[1]
ALT	24,06±14,59	25,60±14,61	20,86±9,89	>0,05
AST	25,40±10,64	24,73±17,61	19,73±4,51	>0,05
Cl	104,66±5,48	104,00±4,20	104,20±4,72	>0,05
Na	136,73±2,60	137,86±4,15	138,73±3,67	<0,05[2]
K	4,40±0,40	4,19±0,25	4,12±0,34	<0,05[3]
Ca	8,40±0,58	8,92±0,80	9,16±0,66	<0,05[4]
P	3,18±0,50	3,30±0,83	3,43±0,67	>0,05
Mg	1,78±0,18	1,74±0,19	1,73±0,18	>0,05
WBC	8,61±4,17	8,23±3,30	8,64±3,32	>0,05
HGB	13,22±1,88	12,70±2,08	13,22±1,34	>0,05
PLT	280733,33±72950,53	276466,66±65883,95	298600,00±84740,61	>0,05
Sedimentation	41,53±28,54	40,93±35,02	27,66±14,10	<0,05[5]
CRP	5,31±3,46	6,54±3,68	4,97±2,94	>0,05
Microalbuminuria	1110,57±581,26	867,74±475,39	938,71±853,33	>0,05
Micrototal Proteinuria	4937,76±4545,68	2260,27±2191,06	2469,71±3249,93	<0,05[6]

1: 0-3. month p=0,022 0-6. month p=0,022
2: 0-6. month p=0,008
3: 0-6. month p=0,010
4: 0-3. month p=0,011 0-6. month p=0,006
5: 0-6. month p=0,029
6: 0-3. month p=0,008 0-6. month p=0,015

When AI measurements of the patients were examined as women/ men, it was observed that AI measurements of women were higher than men, and there was no statistically significant difference between them at 0 and 6 months (p>0.05) and at 3 months (p=0.012). There was a significant difference (p<0.05). When AI measurements of the patients at 0, 3, and 6 months were compared, statistically; there was no significant difference between 0 months and 3 months (p=0.532) (p>0.05), between 0 months and 6 months (p=0.020) and between 3 months and 6 months (p=0.041) was found to be statistically significant (p<0.05) (Table 6).

Table 6: Comparison of patients' PWV parameters

		0. Month (Mean ±SD)	3. Month (Mean ±SD)	6. Month (Mean ±SD)	p-value
PWV	Female	7,39±1,03	7,13±0,89	7,47±1,08	>0,05
	Male	6,44±1,31	6,12±1,54	6,62±1,85	
	Total	7,07±1,18	6,79±1,19	7,19±1,38	>0,05
AI	Female	29,20±12,21	28,40±8,54	34,50±11,88	<0,05[1]
	Male	16,80±10,57	10,80±15,34	28,00±6,52	
	Total	25,07±12,82	22,53±13,71	32,33±10,63	<0,05[2]

1: Between men and women in the 3rd month p=0,012

2: 0-6. month p=0,020 3-6. month p=0,041

There was a positive correlation between MTP and PWV at 0 months (r=0.039 p=0.889) and a negative correlation at 3 months (r=-0.621 p=0.014) and 6 months (r=-0.664 p=0.007). It was monitored and it was found that there was a statistically significant difference (p<0.05). When our patients were compared with MTP and AI (0, 3 and 6 months, respectively; r=0.407 p=0.132 / r=-0.385 p=0.156 / r=0.112 p=0.690), it was observed that there was no statistically significant difference (p>0,05) (Table 7).

Table 7: Correlation analysis of PWV measurements of the patients and proteinuria results

0.month		**Microalbuminuria**	**Micrototal Proteinuria**
PWV	r	-0,252	0,039
	p	0,365	0,889
AI	r	0,303	0,407
	p	0,272	0,132
3.month			
PWV	r	-0,474	-0,621
	p	0,119	0,014*
AI	r	-0,249	-0,385
	p	0,435	0,156
6. month			
PWV	r	-0,671	-0,664
	p	0,006*	0,007*
AI	r	0,224	0,112
	p	0,423	0,690

* p<0,005

DISCUSSION

Proteinuria; is one of the most important clinical manifestations of kidney disease, and recurrent proteinuria is associated with progressive kidney disease. Studies have shown that proteinuria level at the time of diagnosis alone can predict kidney disease prognosis, independent of the underlying disease. According to this, the progression of ESRD in proteinuria below 2g/day was 4.3%, while the progression of ESRD was 34.7% in proteinuria above 3.5g/day [8].

In patients with proteinuria, ESRD and atherosclerotic heart disease are the leading causes of morbidity and mortality. Cardiovascular diseases constitute the most important cause of morbidity and mortality in all stages of chronic kidney disease. Arterial stiffness; is a decrease in the viscoelastic property and compliance of the artery wall. Among the known classical risk factors in the development of atherosclerosis there are age, male gender, smoking, family history, physical inactivity, obesity, HT, DM, and dyslipidemia. In many studies, arterial stiffness; is an independent indicator of hypertension, cerebrovascular accident, atherosclerosis, cardiovascular events, and mortality [9, 10].

Hypoalbuminemia and edema develop in patients with proteinuria due to protein loss, hyperlipidemia due to decreased lipid catabolism, susceptibility to infection, and increased inflammatory values are observed due to the deterioration of the complement system. These parameters predispose patients to atherosclerosis.

It is thought that the immune system is involved in the pathogenesis of many glomerular diseases. Therefore, immunosuppressive therapy is planned according to the histopathological diagnosis and active/sclerotic lesion status. Corticosteroid (1 mg/kg/day maximum 80 mg methylprednisolone) treatment regimens are tried as the first step. In histopathological diagnoses unresponsive to steroid therapy, frequent relapses after steroid therapy, steroid addiction and known to be insufficient steroid therapy; Other immunosuppressive treatments such as cyclophosphamide (2 mg/kg/day), cyclosporine (5 mg/kg/day), mycophenolate mofetil (15 mg/kg/day), tacrolimus, monoclonal antibodies (ritiksumab etc.) are planned. The duration of these immunosuppressive treatments varies according to the histopathological diagnosis. In our study, all patients were given conservative treatments such as antihypertensive, treatment for hyperlipidemia and antiaggregant treatment, and immunosuppressive treatments according to histopathological diagnosis. There is no difference between patients in terms of treatment.

Many factors are affecting PWV. These; age, gender, blood pressure, heart rate, obesity, height, and weight [11]. With advancing age, the elastic tissue of the aorta decreases and leaves its place to collagen tissue, as a result, the width of the aorta increases, and its flexibility decrease. In our study, when the patients are examined without gender discrimination, it is seen that PWV increases as the age increases, and there is a statistically significant difference between them. In our study, when the patients were compared according to their gender, it was observed that the average PWV of women was higher than that of men, and it was observed that there was no difference between them.

The most critical factor affecting PWV after age is blood pressure. Hypertension is a significant risk factor for CAD and accounts for 35% of atherosclerotic events. In patients with hypertension, vascular wall thickness increases, and arterial compliance decreases. When the blood pressure measurement of our patients was compared with PWV

and AI, it was observed that there was a positive correlation but no statistically significant difference. The reason for the lack of statistical difference between blood pressure and PWV is due to the fact that blood pressure is not high, and the result is consistent with the literature.

Many studies show a direct relationship between hypoalbuminemia and ESRD, atherosclerosis, and cardiovascular mortality [12, 13]. Hypoalbuminemia shows both the severity of the disease and inflammatory response. Hypoalbuminemia and proteinuria are cardiovascular risk factors, both directly and indirectly, due to increased inflammatory and atherogenic lipid profile, elevated blood pressure, and decreased GFR. Another reason why hypoalbuminemia is a cardiovascular risk factor because there is an inverse relationship between albumin level and lipid levels. Our study observed a negative correlation between total protein and triglyceride, between total protein and LDL, between albumin and TG, and between albumin and LDL, and there was a statistically significant difference.

In the RENAAL study, it was shown that 85% of patients with proteinuria over 3g/day had an increase in creatine values, and 44% developed CAD [14]. Many studies have shown that cardiovascular risk decreases with proteinuria treatment and that cardiovascular risk increases in ongoing proteinuria. Continuation of inflammation, nephron damage, and endothelial dysfunction have been shown as the reason for this. In the REIN study, it was observed that patients with proteinuria at the nephrotic level had a decrease in GFR by 10% annually, and ESRD developed in 30% at the end of the 3rd year [15]. In patients with proteinuria, development of hypertrophy in healthy nephrons, vasodilation in afferent arterioles, increased glomerular plasma flow, and consequently increase in glomerular filtration rate glomerular capillary pressure are observed in order to compensate for the nephron loss that develops in the later stages. This adaptation mechanism causes damage to intact nephrons even if the underlying disease is treated [16].

Chronic kidney damage; structural and/or functional disorders, regardless of the underlying kidney disease, whether there is a decrease in GFR for more than 3 months or not [17]. In patients with proteinuria, the first 3 months is critical in terms of response to treatment, chronicity of the disease, and reversal of cardiovascular risks. In our study, when our patients were compared with the initial MTP and the MTP in the 3rd month, it was observed that there was a decrease in inflammatory parameters, hyperlipidemia, PWV, and AI measurement in correlation with this. MTP follow-ups at 3 and 6 months remained stable and were found to be higher than the normal range (>2g/day). Although the patients' inflammatory parameters and lipid levels decreased after the 3rd month, it was observed that renal damage and atherosclerosis continued due to ongoing proteinuria. In our patients, it was observed that there was a negative correlation between MTP and PWV measurements after the 3rd month due to chronic kidney damage, and although there was a decrease in the 6th month compared to the MTP initial value, PWV was a value above the initial value.

Conclusion

With the development of non-invasive diagnostic methods, the sensitivity and specificity of the tests used to predict atherosclerosis and coronary artery disease are insufficient to predict the whole patient group due to insufficient studies, and more studies with more patient groups and new methods are needed. More extended studies are needed to understand whether a reduction in the amount of proteinuria in patients with proteinuria lasting more than 3 months can reduce arterial stiffening and whether initiated endothelial damage and inflammation will return to normal.

Conflict of interest

The authors declare that there are no conflict of interest.

Financial disclosure

The authors declare no financial support for his study.

Ethical approval

Our study was conducted with the decision of the Cumhuriyet University Faculty of Medicine ethics committee, dated 27.10.2015 and numbered 2015-10 / 02. Our study was carried out in accordance with the principles of the Declaration of Helsinki.

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REFERENCES

1. Appel GB, Radhakrishnan J. Glomerular disorders and nephrotic syndromes. *Goldman's Cecil Medicine*: Elsevier; 2012:761-771.
2. Floege J, Feehally J. Introduction to glomerular disease. *Comprehensive Clinical Nephrology E-Book.* 2018:182.
3. Mathew RO, Bangalore S, Lavelle MP, et al. Diagnosis and management of atherosclerotic cardiovascular disease in chronic kidney disease: a review. *Kidney international.* 2017;91:797-807.
4. Safar ME, Nilsson PM, Blacher J, Mimran A. Pulse pressure, arterial stiffness, and end-organ damage. *Current hypertension reports*. 2012;14:339-344.
5. Bonarjee VV. Arterial stiffness: a prognostic marker in coronary heart disease. available methods and clinical application. *Frontiers in Cardiovascular Medicine.* 2018;5:64.
6. Gusbeth-Tatomir P, Covic A. Causes and consequences of increased arterial stiffness in chronic kidney disease patients. *Kidney and Blood Pressure Research.* 2007;30:97-107.
7. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *European heart journal.* 2006;27:2588-2605.
8. Ruggenenti P, Perna A, Mosconi L, et al. Proteinuria predicts end-stage renal failure in non-diabetic chronic nephropathies. *Kidney International Supplement.* 1997.
9. Laurent S, Katsahian S, Fassot C, et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke.* 2003;34:1203-1206.
10. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation.* 2002;106:2085-2090.
11. Nandini H, Pandey A. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *International Archives of BioMedical and Clinical Research.* 2018;4:29-31.
12. Peng W, Zhang C, Wang Z, Yang W. Prediction of all-cause mortality with hypoalbuminemia in patients with heart failure: a meta-analysis. *Biomarkers.* 2019;24:631-637.
13. Kirushnan B, Rao BS, Annigeri R, et al. Impact of malnutrition, inflammation, and atherosclerosis on the outcome in hemodialysis patients. *Indian Journal of Nephrology.* 2017;27:277.
14. De Zeeuw D, Remuzzi G, Parving H-H, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney international.* 2004;65:2309-2320.
15. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *The Lancet.* 2005;365:939-946.
16. Chiang WC, Lai CF, Su CT, et al. Angiopoietins modulate endothelial adaptation, glomerular and podocyte hypertrophy after uninephrectomy. *PloS one.* 2013;8:e82592.
17. Levey AS, Coresh J, Bolton K, et al. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *American Journal of Kidney Diseases.* 2002;39:i-ii+ S1-S266.