

Autonomic and arterial function in nondiabetic chronic kidney disease patients

Rama Mohan Pathapati¹, Sree Bhushan Raju Devaraju²

¹Department of Clinical Pharmacology, Narayana Medical College, Nellore, Andhra Pradesh, India.

²Department of Nephrology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.

Correspondence to: Rama Mohan Pathapati, E-mail: pill4ill@yahoo.co.in

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ABSTRACT

Background: Patients with chronic kidney disease (CKD) suffer with both autonomic and cardiac dysfunction. Reports analyzing the correlation between autonomic and vascular dysfunction are fairly accurate. **Aims and Objective:** We correlated vascular sympathetic reactivity to isometric handgrip exercise and vascular stiffness in nondiabetic pre dialysis CKD patients noninvasively. **Materials and Methods:** A total of 52 participants. 28 nondiabetic CKD and 24 normal, were recruited for this study. Blood pressure was measured by oscillometry and vascular sympathetic reactivity. Absolute rise in diastolic blood pressure (ARDBP) was assessed using isometric handgrip test. Pulse wave velocities (PWV) were recorded using automatic waveform analyzer and pressure-standardized elastic vascular resistance (EVR) was derived from it. Carotid-femoral PWV (cf-PWV) > 12 m/s was considered as vascular dysfunction. Serum nitric oxide (NO) and malondialdehyde (MDA) were also measured. **Results:** The patients had lower values of NO and higher values of MDA than the controls. Isometric handgrip exercise, the test performed to detect sympathovagal imbalance suggesting presence of autonomic dysfunction, was observed in 80% of patients vs. 20% of controls, whereas arterial dysfunction was observed only in 34% of patients vs. 14% controls. No correlation was observed between autonomic and vascular dysfunction ($r = 0.13$, $P > 0.05$). **Conclusion:** Our study results demonstrate that nondiabetic CKD patients had increased central artery stiffness (cf-PWV) as compared to controls. It was also observed that reduced vascular compliance was associated with autonomic imbalance, increased oxidative stress, and decreased NO bioavailability. However, no correlation was observed between autonomic and vascular dysfunction. Our study confirms that the multiple complex pathogenesis mechanisms that cause vascular dysfunction coexist in our patient group.

KEY WORDS: Chronic Kidney Disease; Isometric Hand Grip; Carotid-Femoral Pulse Wave Velocity; Malondialdehyde; Oxidative Stress; Pressure Standardized Elastic Vascular Resistance

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD).^[1] In

these patients, cardiovascular disease results from impaired functioning of cardiac, autonomic, and/or vascular systems. Abnormalities in autonomic function, namely sympathetic overdrive and parasympathetic insufficiency, play a key role in the susceptibility to sudden cardiac death in CKD/ESRD.^[2-6] The incidence of sudden cardiac death increases with the advance in the stage of kidney disease (Herzog, 2003; U.S. Renal Data System, 2011).^[7-8]

On the other hand, vascular dysfunction in the context of cardiovascular and renal disease is characterized by vascular endothelial dysfunction and stiffening of the large elastic arteries.^[8-11] In addition, decreased carotid distensibility, increased arterial thickness, and presence of calcifications and plaques often coexist

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in the same subject.^[12] In renal disease, endothelial dysfunction occurs due to decrease in NO bioavailability. Tone of the large arteries is increased in these patients.^[13] as endothelial-dependant nitric oxide (NO) contributes to resting tone.^[14] lowered NO bioavailability due to decreased production of NO due to less substrate availability or increased inactivation of available NO due to the formation of reactive oxygen species (ROS), which cause peroxidation of lipids in the cell membranes and produce malondialdehyde (MDA; oxidative stress marker) and as such, lipid peroxidation products in turn inactivate NO. The above information inspired us to test the hypothesis whether the pathogenesis mechanisms such as increased oxidative stress, decreased NO availability, and sympathovagal imbalance are independently or collectively responsible for increased arterial stiffness in pre-dialysis patients. For this, we evaluated arterial stiffness and sympathetic activity noninvasively in pre-dialysis patients. In addition, we measured serum NO and MDA, the oxidative stress marker.

MATERIALS AND METHODS

This case-controlled study was carried out at the Department of Clinical Pharmacology & Therapeutics, Nizam's Institute of Medical Sciences (NIMS), Hyderabad, after getting approval from the Institutional Ethics Committee. The patients were recruited from the outpatient nephrology clinics and controls were patient attendees. None of the participants had diabetes mellitus, were taking hormone supplements or regular nitrate medications, or were undergoing external exercise sessions or any other etiology that could cause autonomic neuropathy. Participants were informed about the study and written informed consent was obtained from them. After recording the clinical history and demographics, the participants were asked to lie down comfortably in a temperature-controlled laboratory. The baseline blood pressure of the dominant arm was recorded. Mean arterial pressure was calculated using the formula $MAP = DBP + 1/3 (SBP - DBP)$. Carotid-femoral pulse wave velocity (cf-PWV) was recorded by using an automatic waveform analyzer (Periscope, M/s Genesis Medical systems, Hyderabad).^[15-18] Elastic vascular resistance (EVR), a pressure-standardized index of aortic stiffness, was derived using the formula $EVR = (PWV)^2 / MAP$ ($m^2/s^2 \cdot mmHg^{-1}$).^[19-20] A threshold value of aortic PWV (> 12 m/s) was used to stratify cardiovascular risks in these patients.^[21] All patients underwent isometric handgrip exercise, (Canwin, M/s Genesis Medical systems, Hyderabad) a simple, easily applicable, and safe stress test. During sustained isometric handgrip exercise, heart rate, systolic and diastolic BP, left ventricular systolic and end-diastolic pressure, and cardiac output increased.^[22] Blood pressures were recorded at the end of 2 min while the subject was holding the hand dynamometer. Absolute rise in diastolic blood pressure (ARDBP) was used to assess the vascular sympathetic reactivity to isometric handgrip test.^[23] Values were considered, normal (> 16 mmHg), borderline (11–15 mmHg), and abnormal (< 10 mmHg).^[24] Five milliliters of blood was collected from the median cubital vein, centrifuged, and serum was stored in plastic tubes at $-20^\circ C$ till NO and malondialdehyde (MDA) were analyzed.

Statistical Analysis

All data were entered in a spreadsheet. The statistical analysis was carried out in Graph pad Prism, version 4.0, USA. Continuous data were presented as mean and standard deviation and categorical data as actual numbers and percentages. Unpaired *t*-test was used for comparison of clinical parameters between the two groups. Pearson correlation test was used to assess autonomic and arterial dysfunction. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

This study consists of 24 healthy controls and 28 nondiabetic CKD patients. The patients were older than healthy controls (40.91 ± 14.5 vs. 34.4 ± 7.3 years). There was no statistically significant difference in height in patients as compared to controls. (165.91 ± 8.3 vs. 170.9 ± 6.1) The mean duration of disease and serum creatinine was 16.55 ± 18.9 months and 2.67 ± 1.0 mg/dL, respectively. It can be seen from Table 1 that the baseline blood pressures in patients were statistically higher in patients than in controls. Cf-PWV, a surrogate marker of central elastic arterial stiffness was higher in patients than in controls, suggesting the presence of reduced arterial compliance in patients than controls. Pressure-normalized index of aortic stiffness EVR and reflection index (RI), a marker of small artery tone, were significantly higher in patients as compared to controls. The patients had lower values of NO and higher values of MDA than the controls. Isometric handgrip exercise, the test performed to detect sympathovagal imbalance suggesting the presence of autonomic dysfunction in patients, was observed (Table 2) in 80% of patients vs. 20% of controls, whereas arterial dysfunction was observed only in 34% of patients vs. 14% controls. No correlation was observed between autonomic and vascular dysfunction. ($r = 0.13$, $P > 0.05$).

DISCUSSION

Cardiovascular autonomic dysfunction and alterations in vascular elasticity are known complications of several disorders, including diabetes mellitus, hypertension, hypercholesterolemia, aging, and CKD.^[25] Dysfunction of both the parasympathetic and sympathetic divisions of the ANS occurred in chronic renal failure (CRF) patients. Severity of autonomic dysfunction increases with severity of CKD.^[3,26,27] Patients with CKD frequently have the two most abnormal tests, heart rate variation during deep breathing and blood pressure response to hand grip exercise.^[2,28] Nondialysis-dependent nondiabetic CKD patients with decreasing glomerular filtration rate have reduced cardiac baroreceptor sympathetic activity and increased large artery stiffness.^[29] Sanya et al.^[24] showed that abnormal blood pressure response to the handgrip tests in Nigerians with nondiabetic CRF was 28%.[] One study showed that blood pressure rather than sympathetic activity seems to play the major role in modulating the elastic properties of the central arteries.^[30]

Table 1: Clinical characters, changes in blood pressure to ischemic hand grip, indices of vascular stiffness and indices of oxidative stress between healthy controls and chronic kidney disease patients

Clinical parameters	Controls (n = 24)	CKD (n = 28)	P-value
Height (cm)	170.9 ± 6.1	165.91 ± 8.3	ns
Weight (kg)	70.9 ± 11.3	64.90 ± 16.2	<0.05
Age (years)	34.4 ± 7.3	40.91 ± 14.5	ns
Duration (months)	-	16.55 ± 18.9	-
Creatinine (mg/dL)	-	2.67 ± 1.0	-
Blood pressure at baseline			
SBP (mm Hg)	116.1 ± 10.2	146.18 ± 19.9	<0.001
DBP (mm Hg)	72.9 ± 9.9	91.09 ± 11.9	<0.05
MAP (mm Hg)	50.5 ± 3.5	52.6 ± 2.2	ns
Blood pressure after isometric hand grip exercise			
SBP (mm Hg)	134.5 ± 14.2	157.70 ± 20.2	<0.05
DBP (mm Hg)	91.2 ± 14.2	96.20 ± 8.0	ns
Absolute change in blood pressure to isometric hand grip from baseline			
SBP (mm Hg)	18.30 ± 8.1	14.90 ± 13.4	ns
DBP (mm Hg)	18.3 ± 7.4	7.20 ± 6.4	<0.001
Indices of arterial stiffness			
Cf-PWV (m/s)	9.77 ± 192.9	14.43 ± 768.3	<0.001
EVR (m ² .s ² /mm Hg)	1.1 ± 0.4	2.39 ± 1.0	<0.001
Indices of vasomotor tone			
RI%	67.0 ± 13.1	74.47 ± 9.1	<0.001
Indices of oxidative stress			
Serum malondialdehyde nM/mL	4.86 ± 1.19	6.39 ± 0.42	<0.001
Serum nitric oxide μM/L	4.9 ± 1.2	0.75 ± 0.52	<0.001

Table 2: Autonomic and vascular abnormalities and antihypertensive use patterns

Response to IHG N/B/A	N-6(20%), B-9(34%), A-13(46%)	cf PWV > 12 m/s	10 (34%)
Pearson correlation between IHG vs. PWV ($r = 0.13$, $P > 0.05$)			
Antihypertensive drugs			
Beta blockers	6 (20%)	CCB	12(44%)
ACEI	5 (19%)	ARB	8 (28%)
Clonidine	1 (5%)	Diuretic	3 (10%)
One drug	11(38%)	Two drugs	12 (43%)
Three drugs	5 (17%)	Four drugs	1(4%)

N/B/A, normal/borderline/abnormal; ARB, angiotensin-receptor blockers; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors.

Twenty percent and 14% of controls have abnormal IHG response and cf-PWV > 12 m/s, respectively.

Our study results demonstrate that nondiabetic CKD patients had statistically higher baseline blood pressures than controls. Cf-PWV and pressure-normalized index of aortic stiffness EVR, which are surrogate markers of central elastic arterial stiffness, were higher in patients than in controls, suggesting the presence of reduced arterial compliance in patients than in controls. In addition, reflection index (RI), a marker of small artery tone, was also significantly higher in patients as compared to controls suggesting increased resistance in vascular reflection sites and baseline vasomotor tone. It is also observed that reduced vascular compliance was associated with autonomic imbalance, increased oxidative

stress, and decreased NO bioavailability. However, no correlation was observed between autonomic and vascular dysfunction. The multiple mechanisms contributing to arterial dysfunction in these patients are elevated shear stress due to hypertension; heart rate variability due to sympathovagal imbalance; calcium deposition in the arteries due to secondary hyperparathyroidism; vascular inflammation due to stents and catheters; decreased NO bioavailability due to decreased production of NO as a result of less substrate availability; or increased inactivation of available NO due to the formation of reactive oxygen species (ROS), which are the products of various endogenous enzymatic or nonenzymatic reactions.

These ROS also cause peroxidation of lipids in the cell membranes and produce MDA (oxidative stress marker) and as such, lipid peroxidation products in turn inactivate NO.

A recent study showed a stepwise increase of arterial stiffness with increasing disease severity stage in patients with CKD.^[31] Cardiovascular reflex tests mainly characterizing sympathetic function had no correlation with aortic stiffness parameters.^[25] However, peripheral PWV correlated with total autonomic score in patients with type 2 diabetes. when autonomic neuropathy was assessed using heart rate variability with continuous ECG recording during various breathing and postural maneuvers and an overall autonomic score was generated.^[21] Cardiac parasympathetic function is a strong predictor of large arterial stiffness in young, type 1 diabetes patients free of macrovascular and renal complications.^[32]

We observed that RI, a marker of small artery tone, was significantly higher (vasoconstriction) in patients as compared to controls. In addition, these patients had lower values of NO and higher values of MDA than the controls. It is possible that in CKD, angiotensin II enhances central sympathetic tone and peripheral sympathetic action by suppressing NO availability, which in turn enhances the damaging action of sympathetic tone.^[33,34] Moreover, hyperactivation of sympathetic neural activity has proatherogenic effects on the vascular function by increasing vasoconstriction, accumulation of modified lipoproteins in the vascular wall, induction of endothelial dysfunction, and stimulation of oxidative stress and vascular remodeling.^[31] Renin-angiotensin system increases sensitization of calcium and its effect is counterbalanced by nitric oxide, which decreases calcium sensitization.^[35] Endothelial dysfunction occurs in CKD (characterized by blunted endothelial NO release) even early in the course of the disease.^[36] Decreased total NO production in renal disease likely reflects the endothelial dysfunction.^[37] Endothelial function is abnormal even in patients with mild renal insufficiency and those without atherosclerotic vascular disease.^[38]

Vasodilator drugs also exerts beneficial effects that are independent of pressure reduction in cuff blood pressure (BP) and may explain the apparent of drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.^[30,33] In addition, several trials demonstrate that the renoprotective effect of RAS suppression extends beyond BP lowering alone.^[25,39]

Strengths and Limitations

We have assessed the vascular and autonomic dysfunction in nondiabetic predialysis CKD patients noninvasively; such evaluations are convenient to patients at affordable cost. We did not correlate clinical symptoms with vascular and autonomic dysfunction due to nonavailability of data.

CONCLUSION

Our study results demonstrate that nondiabetic CKD patients had increased central artery stiffness (cf-PWV) as compared to

controls. It was also observed that this reduced vascular compliance was associated with autonomic imbalance, increased oxidative stress, and decreased NO bioavailability. Our study confirms that the multiple complex pathogenesis mechanisms that cause vascular dysfunction coexist in our patient group. However, no correlation was observed between autonomic and vascular dysfunction. Assessing these markers provides a scope for early diagnosis and therapeutic interventions. Further studies are needed to understand this complex pathogenic mechanism in large sample sizes and to provide a rationale therapy.

REFERENCES

1. Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol.* 2005;16(2):489-95.
2. Sahin M, Kayatas M, Urun Y, Sennaroglu E, Akdur S. Performing only one cardiovascular reflex test has a high positive predictive value for diagnosing autonomic neuropathy in patients with chronic renal failure on hemodialysis Renal failure. 2006;28(5): 383-7. PubMed PMID: 16825086. Epub 2006/07/11. eng.
3. Klein IH, Ligtenberg G, Neumann J, Oey PL, Koomans HA, Blankestijn PJ. Sympathetic nerve activity is inappropriately increased in chronic renal disease. *J Am Soc Nephrol: JASN.* 2003;14(12):3239-44. PubMed PMID: 14638922. Epub 2003/11/26. eng.
4. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, et al. Sympathetic nerve activity in end-stage renal disease. *Circulation.* 2002;106(15):1974-9. PubMed PMID: 12370222. Epub 2002/10/09. eng.
5. Pun PH, Smarz TR, Honeycutt EF, Shaw LK, Al-Khatib SM, Middleton JP. Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney intl.* 2009;76(6):652-8. PubMed PMID: 19536082. Pubmed Central PMCID: PMC2990680. Epub 2009/06/19. eng.
6. Salman IM. Cardiovascular autonomic dysfunction in chronic kidney disease: a comprehensive review. *Curr Hypertens Rep.* 2015;17(8):59 PubMed PMID: 26071764. Epub 2015/06/15. eng.
7. Herzog CA. Cardiac arrest in dialysis patients: approaches to alter an abysmal outcome. *Kidney Intl Suppl.* 2003;(84):S197-200. PubMed PMID: 12694343. Epub 2003/04/16. eng.
8. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, et al. 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. *Am J Kidney Dis.* 2012;59(1 Suppl 1):A7, e1-420. PubMed PMID: 22177944. Epub 2011/12/30. eng.
9. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol JASN.* 1999;10(7):1606-15. PubMed PMID: 10405218. Epub 1999/07/15. eng.
10. Shamseddin MK, Parfrey PS. Sudden cardiac death in chronic kidney disease: epidemiology and prevention. *Nature Rev Nephrol.* 2011; 7(3):145-54. PubMed PMID: 21283136. Epub 2011/02/02. eng.
11. Hildreth CM. Prognostic indicators of cardiovascular risk in renal disease. *Front Physiol.* 2011;2:121 PubMed PMID: 22294981.
12. Benetos A, Waeber B, Izzo J, Mitchell G, Resnick L, Asmar R, et al. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. *Am J Hypertens.* 2002; 15(12):1101-8.

13. Förstermann U, Münzel T. Endothelial nitric oxide synthase in vascular disease: From marvel to menace. *Circulation*. 2006; 113(13):1708–14.
14. Neuman RB, Hayek SS, Poole JC, Rahman A, Menon V, Kavtaradze N, et al. Nitric oxide contributes to vasomotor tone in hypertensive African Americans treated with nebivolol and metoprolol. *J Clin Hypertension* (Greenwich, Conn). 2015. PubMed PMID: 26285691. Epub 2015/08/20. Eng.
15. Mohan PR, Sujith T, Desai M, Kolla P, Madhavulu B, Ramalingam K, et al. *Jour of Med Sc & Tech* 2013; 2 (1), 8–12.
16. Naidu MU, Reddy BM, Yashmaina S, Patnaik AN, Rani PU. Validity and reproducibility of arterial pulse wave velocity measurement using new device with oscillometric technique: a pilot study. *Biomed Eng*. 2005;4:49 PubMed PMID: 16115324. Pubmed Central PMCID: PMC1224857. Epub 2005/08/24. eng.
17. Pathapati RM, Rajesh Kumar M, Chirra BR, Buchineni M, TR S, Devaraju SR, et al. Acute effects of two angiotensin receptor blockers on vascular hemodynamics, arterial stiffness, and oxidative stress in patients with mild to moderate hypertension: an open label parallel group study. *ISRN Vasc Med*. 2013;2013:5.
18. Pathapati RM, Reddy CB, Buchineni M, Sujith T, Kumar MR, Praveen K. *IJBCP Intl J Basic Clin Pharmacol*. 2015;4(2):219.
19. Breithaupt-Grogler K, Leschinger M, Belz GG, Butzer R, Erb K, de May C, et al. Influence of antihypertensive therapy with cilazapril and hydrochlorothiazide on the stiffness of the aorta. *Cardiovasc Drugs Ther* (sponsored by the International Society of Cardiovascular Pharmacotherapy). 1996;10(1):49–57. PubMed PMID: 8723170. Epub 1996/03/01. eng.
20. Breithaupt-Grögl K, Ling M, Boudoulas H, Belz GG. Protective effect of chronic garlic intake on elastic properties of aorta in the elderly. *Circulation*. 1997;96(8):2649–55.
21. Meyer C, Milat F, McGrath BP, Cameron J, Kotsopoulos D, Teede HJ. Vascular dysfunction and autonomic neuropathy in type 2 diabetes. *Diabet Med*. 2004;21(7):746–51. PubMed PMID: 15209768. Epub 2004/06/24. eng.
22. Kivowitz C, Parmley WW, Donoso R, Marcus H, Ganz W, Swan HJ. Effects of isometric exercise on cardiac performance. The grip test. *Circulation*. 1971;44(6):994–1002. PubMed PMID: 4331419. Epub 1971/12/01. eng.
23. Khurana RK, Setty A. The value of the isometric hand-grip test: studies in various autonomic disorders. *Clin Auton Res*. 1996; 6(4):211–8. PubMed PMID: 8902317. Epub 1996/08/01. eng.
24. Sanya EO, Ogunniyi A. Cardiovascular autonomic neuropathy in non-diabetic Nigerian patients with chronic renal failure. *W Afr J Med*. 2004;23(1):15–20. PubMed PMID: 15171518. Epub 2004/06/03. eng.
25. Kshirsagar AV, Joy MS, Hogan SL, Falk RJ, Colindres RE. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. *Am J Kidney Dis*. 2000;35(4):695–707 PubMed PMID: 10739792. Epub 2000/03/31. eng.
26. Thapa L, Karki P, Sharma SK, Bajaj BK. Cardiovascular autonomic neuropathy in chronic kidney diseases. *JNMA J Nepal Med Assoc*. 2010;49(178):121–8 PubMed PMID: 21485597. Epub 2011/04/14. eng.
27. Grassi G, Quarti-Trevano F, Seravalle G, Arenare F, Volpe M, Furiani S, et al. Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension*. 2011;57(4):846–51 PubMed PMID: 21300663. Epub 2011/02/09. eng.
28. Karnik JA, Young BS, Lew NL, Herget M, Dubinsky C, Lazarus JM, et al. Cardiac arrest and sudden death in dialysis units. *Kidney Intl*. 2001;60(1):350–7 PubMed PMID: 11422771. Epub 2001/06/26. eng.
29. Lacy P, Carr SJ, O'Brien D, Fentum B, Williams B, Paul SK, et al. Reduced glomerular filtration rate in pre-dialysis non-diabetic chronic kidney disease patients is associated with impaired baroreceptor sensitivity and reduced vascular compliance. *Clin Sci* (London, England: 1979). 2006;110(1):101–8 PubMed PMID: 16171454. Epub 2005/09/21. eng.
30. Palatini P, Casiglia E, Gasowski J, Gluszek J, Jankowski P, Narkiewicz K, et al. Arterial stiffness, central hemodynamics, and cardiovascular risk in hypertension. *Vasc Health Risk Manage*. 2011;725–39 PubMed PMID: 22174583. Pubmed Central PMCID: PMC3237102. Epub 2011/12/17. eng.
31. Chistiakov DA, Ashwell KW, Orekhov AN, Bobryshev YV. Innervation of the arterial wall and its modification in atherosclerosis. *Auton Neurosci*. 2015;7–11 PubMed PMID: 26164815. Epub 2015/07/15. Eng.
32. Liatis S, Alexiadou K, Tsiakou A, Makrilakis K, Katsilambros N, Tentolouris N. Cardiac autonomic function correlates with arterial stiffness in the early stage of type 1 diabetes. *Exp Diabet Res*. 2011. 2011;957901. PubMed PMID: 21804819. Pubmed Central PMCID: PMC3143454. Epub 2011/08/02. eng.
33. Koomans HA, Blankestijn PJ, Joles JA. Sympathetic hyperactivity in chronic renal failure: a wake-up call. *J Am Soc Nephrol*. 2004;15 (3):524–37.
34. Park J, Liao P, Sher S, Lyles RH, Deveaux DD, Quyyumi AA. Tetrahydrobiopterin lowers muscle sympathetic nerve activity and improves augmentation index in patients with chronic kidney disease. *Am J Physiol Regul integr Comp Physiol*. 2015;308 (3):208–18 PubMed PMID: 25477424. Pubmed Central PMCID: PMC4313073. Epub 2014/12/06. eng.
35. Brunova A, Bencze M, Behuliak M, Zicha J. Acute and chronic role of nitric oxide, renin-angiotensin system and sympathetic nervous system in the modulation of calcium sensitization in Wistar rats. *Physiol Res*. 2015;64(4):447–57 PubMed PMID: 26291725. Epub 2015/08/21. eng.
36. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet* (London, England). 2000;356(9224):147–52 PubMed PMID: 10963260. Epub 2000/08/30. eng.
37. Landray MJ, Wheeler DC, Lip GY, Newman DJ, Blann AD, McGlynn FJ, et al. Inflammation, endothelial dysfunction, and platelet activation in patients with chronic kidney disease: the chronic renal impairment in Birmingham (CRIB) study. *Am J Kidney Dis*. 2004;43(2):244–53 PubMed PMID: 14750089. Epub 2004/01/30. eng.
38. Thambyrajah J, Landray MJ, McGlynn FJ, Jones HJ, Wheeler DC, Townsend JN. Abnormalities of endothelial function in patients with predialysis renal failure. *Heart*. 2000;83(2):205–9.
39. Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Int Med*. 2001;135(2):73–87 PubMed PMID: 11453706. Epub 2001/07/17. eng.

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