Original Article

Cardiac Autonomic Neuropathy: An Emerging Cardiovascular Risk to Hemodialysis and Non-Hemodialysis Chronic Kidney Disease Patients of Primary Renal Diagnosis

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Abstract

Background: **Patients with chronic kidney disease (CKD) are at higher risk of cardiovascular disease. A dysfunctional autonomic nervous system may be the underlying cause. However, very few studies have determined the status of cardiac autonomic neuropathy (CAN) in both non-hemodialysis and hemodialysis CKD patients.**

Objectives: **The present study intended to determine and compare CAN in both non-hemodialysis and hemodialysis CKD patients of primary renal diagnosis only and its correlation with the progression of the disease.**

Methods: **Non-hemodialysis and hemodialysis CKD patients (n = 23 in each group) of both sexes of 18 to 50 years were recruited in this cross-sectional, observational study. Resting blood pressure and heart rate (HR) were measured, and lead II ECG was recorded for analysis of time- and frequency-domain measures of heart rate variability (HRV). Mann-Whitney U test was applied to compare the variables between the two groups. Spearman correlation was conducted to examine the relationship between variables and the stage of the disease (non-hemodialysis and hemodialysis CKD). A 2-tailed p value < 0.05 was taken as the cutoff level of significance.**

Results: **Body mass index (BMI) was significantly higher in non-hemodialysis patients (p = 0.008). Resting HR was significantly higher in the hemodialysis group (p = 0.001). Among HRV measures, standard deviation of RR intervals (SDRR; p = 0.0001), standard deviation of successive differences (SDSD; p = 0.001), and root mean square of successive RR intervals (RMSSD; p = 0.001) were significantly lower in the hemodialysis group. Peripheral blood pressure was not significantly different between the two groups. Resting HR (r = 0.498, p = 0.001) was positively associated with the end-stage renal disease. However, SDRR (r = −0.507, p = 0.001), RMSSD (r = −0.507, p = 0.001), and BMI (r = −0.427, p = 0.004) were negatively associated with end-stage renal disease.**

Conclusion: **Altered autonomic function was more profound in hemodialysis patients as evidenced by increased resting HR and decreased HRV measures (SDRR, SDSD, and RMSSD). Moreover, altered autonomic function was associated with end-stage renal disease. Therefore, CKD patients may be screened for CAN for early detection of cardiovascular disease.**

Keywords: **Cardiac Autonomic Neuropathy, Heart Rate Variability, Chronic Renal Insufficiency, Renal Dialysis.**

Introduction

Patients with chronic kidney disease (CKD) are at higher risk of cardiovascular disease (CVD) development. The mortality from CVD in patients with CKD is 10 times higher than in the general population.[1] It was further documented that sudden cardiac death accounts for about a third of total mortality among dialysis patients.[2] The traditional cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia are essential mechanisms to explain the increased prevalence of CVD in this population of patients. Nevertheless, it cannot explain the answer completely. Other non-traditional risk factors, such as chronic, low-grade inflammation associated with renal disease, enhanced oxidative stress, anemia, and vascular calcification, contribute to the early occurrence of atherosclerosis in these patients.[3] A dysfunctional autonomic nervous system, in particular, cardiac autonomic neuropathy (CAN) is increasingly recognized as one of the major mechanisms contributing to the development of increased cardiac morbidity and mortality in patients with CKD.

It is possible to assess CAN by measuring heart rate variability (HRV), a non-invasive technique to assess beat-to-beat variation in heart rate (HR) in a given subject. Low HRV is documented to be associated with increased cardiovascular morbidity and

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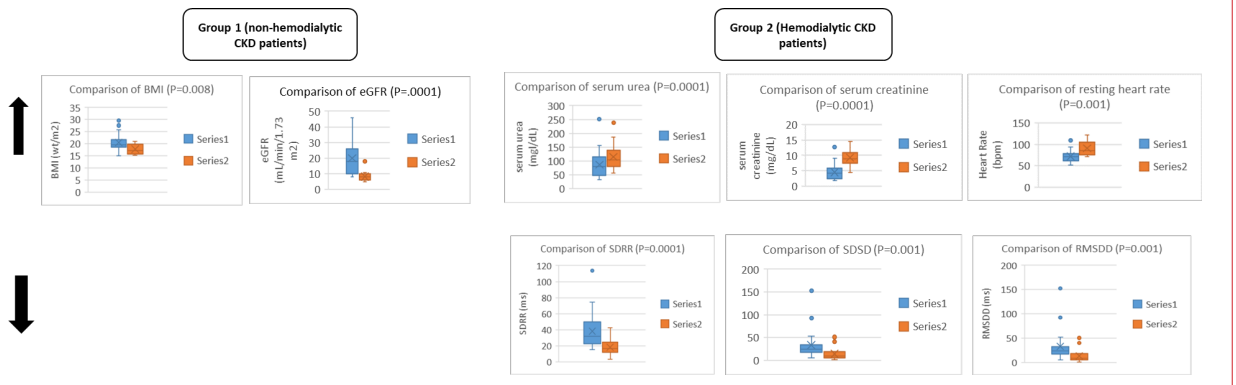
Central Illustration: Cardiac Autonomic Neuropathy: An Emerging Cardiovascular Risk to Hemodialysis and Non-Hemodialysis Chronic Kidney Disease Patients of Primary Renal Diagnosis



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Synopsis of the results of the present study

mortality in various diseases such as diabetes, CVD, and renal disease.[4] Previous studies reported that lower HRV is associated with a higher risk of CVD in patients with CKD on conservative treatment in various stages of CKD.[4] However, very few reports document the assessment of CAN as assessed by HRV in non-hemodialysis CKD patients and hemodialysis CKD patients of primary renal diagnosis. Therefore, the present study intended to determine and compare CAN in non-hemodialysis and hemodialysis CKD patients of primary renal diagnosis only and its correlation with the progression of the disease.

Methods

This was a cross-sectional, single-center, observational study. Diagnosed non-hemodialysis and hemodialysis CKD patients with grade 1 through grade 5 (n = 23 in each group) of 18 to 50 years of age of both sexes were recruited in the present study. This study excluded patients suffering from diabetic nephropathy, congenital renal anomaly, autoimmune diseases and endocrine disorders affecting blood vessels, and peripheral vascular disease. As the present study was part of a larger study, the sample size was calculated on the basis of a cognitive metric, i.e., P300 event-related potential, which is the appearance of positive deflection in event-related brain potentials following 300 ms of presentation of infrequent target stimulus in a series of repeated stimuli. During sample size calculation, the following criteria were considered: power of 90%, level of significance of 0.05, and dropout of 10%. Ethical clearance was obtained from the Institute Ethics Committee (IEC/AIIMS BBSR/PG thesis/2021-22/05). The investigators adhered to the Declaration of Helsinki guidelines for the conduct of the study. The study participants were recruited from the outpatient Department of Nephrology for non-hemodialysis patients and the dialysis unit of the Department of Nephrology for hemodialysis patients, from a single center. A consultant nephrologist diagnosed the patients with CKD based on the criteria laid down by the National Kidney Foundation, USA, KDIGO 2012.

Recording of cardiovascular parameters

The participants were requested to report at the Clinical Physiology Laboratory in the Department of Physiology for recording of cardiovascular parameters. They were asked to refrain from physical exertion, drinking beverages, and smoking 2 to 3 hours before the test. After obtaining their consent in the prescribed proforma, their demographic profile, anthropometric assessment, menstrual and parity history in the case of female subjects, and relevant family and medication history were recorded. Figure 1 displays the research protocol followed in the present study.

Recording of resting blood pressure and pulse rate

Brachial blood pressure of the study participants was measured by digital sphygmomanometer following standard protocol. Mean arterial pressure and pulse pressure were derived from the data. The basal pulse rate of the patients was also recorded.

Recording of lead II ECG for analysis of HRV

Lead II ECG was recorded with PowerLab 4/35 system (AD system, Sydney, Australia) for 5 minutes. The ECG data were digitized at a sampling frequency of 1 KHz. The data were passed through a bandwidth filter in which the low-pass filter was set at 50 Hz, and the high-pass filter was set at 0.3 Hz, with the 50 Hz notch "ON." The software detected R peaks automatically. RR interval bin width was kept at 600 to 1200 ms. The ECG recording was checked visually to detect any motion artifact and any missed R peak. After processing of ECG signal, time-domain metrics, including normalized power of low frequency band, normalized power of high frequency band, and ratio of low frequency to high frequency power,

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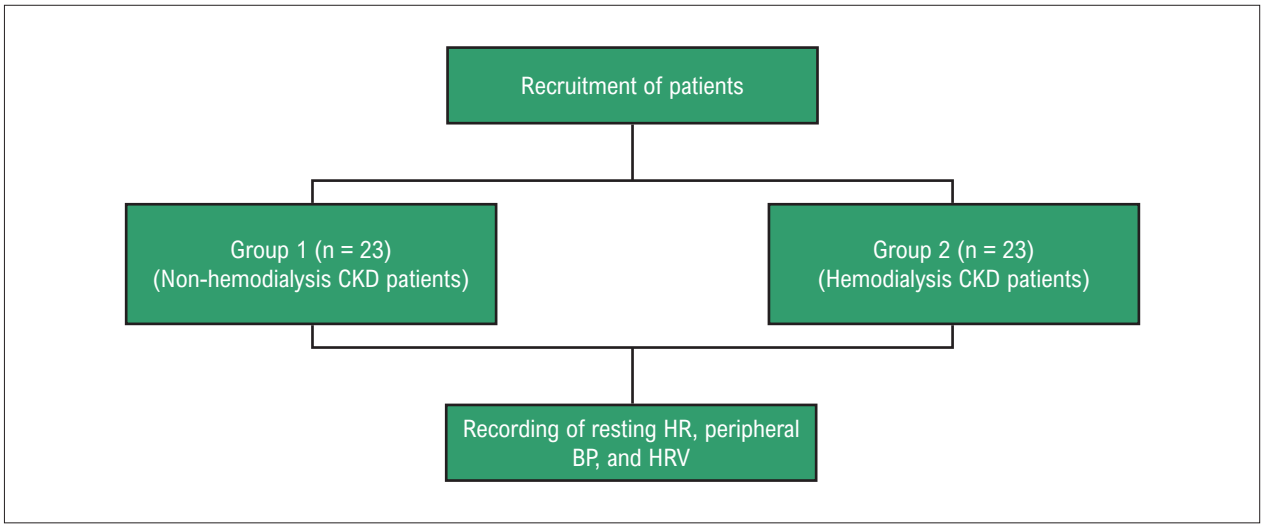

Figure 1 – *The study protocol followed in the present study*

and frequency-domain analyses, including standard deviation of RR intervals (SDRR), root mean square of successive RR intervals (RMSSD), and standard deviation of successive differences (SDSD), were performed by HRV software module inherent to LabChart 8.[5,6]

Statistical analysis

The data were subjected to the Shapiro-Wilk normality test and found to be non-normally distributed. Continuous variables were described using median and range due to the lack of data normality, and categorical variables were expressed as absolute frequencies. The Mann-Whitney U test was applied to the data to compare the variables between the two groups. Spearman correlation was done to examine the relationship between variables and the stage of the disease (non-hemodialysis and hemodialysis CKD). A 2-tailed p value < 0.05 was taken as the cutoff level of significance. The data were analyzed with the help of SPSS software version 26 (SPSS Inc., Chicago, IL, USA).

Results

A total of 46 study participants were recruited in the present study. Out of them, 23 study participants were non-hemodialysis CKD patients, and another 23 subjects were hemodialysis CKD patients. Table 1 show the sex- and age-wise distribution of the study participants.

Body mass index (BMI) in kg/m^2 is an approximate measure of body fat based on height and weight. The stratification of the study participants based on BMI was done following revised guidelines for BMI of Asian Indians.[7] The estimated glomerular filtration rate (eGFR) of the study participants was calculated as per the equation below.

eGFR = ([140 − age] × weight × 0.85 if female) / (72 × serum creatinine)

The equation was adjusted for body surface area (BSA) by 1.73m^2/BSA, where age is in years, weight in kg, and serum creatinine in mg/dl.[8] The anthropometric, clinical, and biochemical data of the study participants were recorded and presented in Table 2.

Table 1 — Sex- and age-wise distribution of the study participants

Parameters	Non-hemodialysis CKD group (n = 23)	Hemodialysis CKD group (n = 23)
Male	17	21
Female	6	2
Obese	4	0
Underweight	5	15
Normal weight	14	8

CKD: chronic kidney disease.

It is evident from Table 2 that BMI was significantly higher in the non-hemodialysis CKD group than in the hemodialysis CKD group ($p = 0.008$). The eGFR was significantly higher in the non-hemodialysis CKD group than in the hemodialysis CKD group ($p = 0.0001$).

The cardiovascular parameters of the study participants were recorded and presented in Table 3.

It is evident from Table 3 that resting HR was significantly higher in the hemodialysis CKD group than in the non-hemodialysis CKD group ($p = 0.001$). Among HRV measures, SDRR ($p = 0.0001$), SDSD ($p = 0.001$), and RMSSD ($p = 0.001$) were significantly lower in the hemodialysis CKD group than in the non-hemodialysis CKD group. The rest of the HRV measures were not significantly different between the two groups. Peripheral blood pressure was also not significantly different between the two groups.

The Spearman correlation analysis has been presented in Table 4.

Table 2 – Anthropometric, clinical, and biochemical data of the study participants

Parameters	Non-hemodialysis CKD group n=23)		Hemodialysis CKD group (n=23)		p value
	Median	IQR	Median	IQR	
Age (years)	42.00	37.00-46.00	32.00	24.00-42.00	0.025
Weight (kg)	49.00	45.00-58.00	49.00	41.40-51.70	0.206
Height (cm)	163.00	154.00-167.00	164.5	160.25-171.75	0.119
BMI (kg/m^2)	19.60	18.70-21.80	17.10	15.80-19.60	0.008
eGFR (ml/min/1.73m^2)	18.20	10.00-26.00	8.00	6.00-9.00	0.0001
Serum urea (mg/dl)	79.00	48.00-115.00	106.00	88.00-139.00	0.010
Serum creatinine (mg/dl)	4.20	2.30-5.90	9.00	7.88-10.96	0.0001
Hemoglobin level	10	8.3-11.0	9.9	8.55-10.50	0.617

The data are displayed as median and interquartile range. BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; IQR: interquartile range.

Table 3 – Cardiovascular parameters of the study participants

Parameters	Non-hemodialysis CKD group (n = 23)		Hemodialysis CKD group (n = 23)		p value
	Median	IQR	Median	IQR	
HR (bpm)	72	62-78	82.50	75-99.75	0.001
PDBP (mmHg)	132	117-147	144	125.50-166.50	0.131
PSBP (mmHg)	86	73-99	95.50	80.25-113.25	0.068
SDRR (ms)	32.15	22.82-49.99	16.91	12.37-26.19	0.0001
SDSD (ms)	24.04	17.33-33.37	10.28	6.03-18.45	0.001
RMSSD (ms)	24.01	17.31-33.33	10.26	6.02-18.43	0.001
LF (nu) (ms^2)	45.06	26.68-62.02	50.07	31.05-64.43	0.512
HF (nu) (ms^2)	54.76	39.67-69.85	42.20	21.41-66.70	0.144
LF/HF ratio	0.82	0.38-1.53	1.29	0.48-3.31	0.242

The data are displayed as median and interquartile range. CKD: chronic kidney disease; HF: high frequency: HR: heart rate; IQR: interquartile range; LF: low frequency; PDBP: peripheral diastolic blood pressure; PSBP: peripheral systolic blood pressure; RMSSD: root mean square of successive RR intervals; SDRR: standard deviation of RR intervals; SDSD: standard deviation of successive differences.

Table 4 – Correlation matrix of Spearman correlation analysis

	Group	BMI	HR	SDRR	SDSD	RMSSD	p value
Group	1.000						
BMI	–0.427	1.000					0.004
HR	0.498	–0.112	1.000				0.001
SDRR	–0.575	0.119	–0.685	1.000			0.0001
SDSD	–0.507	0.080	–0.648	0.868	1.000	1.000	0.001
RMSSD	–0.507	0.080	–0.648	0.868	1.000	1.000	0.001

BMI: body mass index; HR: heart rate; RMSSD: root mean square of successive RR intervals; SDRR: standard deviation of RR intervals; SDSD: standard deviation of successive differences.

The correlation table reveals that resting HR was positively associated with the end-stage renal disease (ESRD). However, SDRR, SDSD, and RMSSD were negatively associated with ESRD. Moreover, BMI was negatively associated with the progression of the disease. The Central Illustration depicts the synopsis of the results of the present study.

BMI: body mass index; eGFR: estimated glomerular filtration rate; RMSSD: root mean square of successive RR intervals; SDRR: standard deviation of RR intervals; SDSD: standard deviation of successive differences.

Discussion

The present study intended to determine CAN as assessed by HRV in non-hemodialysis and hemodialysis CKD patients of primary renal diagnosis. To this effect, 23 non-hemodialysis and another 23 hemodialysis CKD patients were recruited in the present study. HRV was recorded in those patients, and the data were analyzed. BMI was significantly higher in the non-hemodialysis group than in the hemodialysis group. A previous study reported that over 80% of pre-terminal CKD patients were overweight or obese. The same study concluded that higher BMI was not a risk factor for predicting renal replacement therapy in patients with CKD, irrespective of sex.[9]

Among the biochemical parameters, serum urea ($p = 0.010$) and creatinine ($p = 0.000$) were significantly higher in hemodialysis CKD patients than non-hemodialysis CKD patients. An earlier report examined serum urea level's association with adverse cardiovascular events and death before renal replacement therapy in patients with CKD. The study suggested that serum urea predicts cardiovascular outcomes beyond conventional cardiovascular risk factors.[10] High serum urea and creatinine levels may pose a greater cardiovascular risk to hemodialysis CKD patients.

In the present study, both groups recorded resting HR, peripheral blood pressure, and HRV for CAN assessment. Resting HR was significantly higher in hemodialysis CKD patients than in non-hemodialysis patients. This result indicates that decreased parasympathetic activity and increased sympathetic activity were more evident in hemodialysis CKD patients. Among HRV measures, SDRR, SDSD, and RMSSD, which indicate parasympathetic activity, were significantly lower in hemodialysis CKD patients than in non-hemodialysis CKD patients. However, other measures of HRV were not significantly different between the two groups. Previous studies have reported that low HRV is a significant and independent marker of adverse clinical outcomes, encompassing cardiovascular events and possibly even progression to ESRD in patients with CKD.[4]

Furthermore, a study done on dialysis patients suggested that low HRV may predict cardiovascular morbidity and mortality in this cohort.[11,12] A cross-sectional study on patients with CKD stages 3 to 5 analyzed the effects of declining GFR on HRV and nocturnal blood pressure dipping. The study concluded that cardiac sympathetic overdrive and decreased parasympathetic activity were apparent in those patients.[13] A population-based study investigated the relationship between low HRV and renal outcomes. Based on its results, the study suggested that reduced HRV may be a complication of CKD rather than a causal factor.[14] Overall, the results of the present and earlier studies suggest the existence of altered autonomic function in patients with CKD, and more so in hemodialysis CKD patients.

The underlying mechanisms of the altered autonomic function in patients with CKD are speculated to be multifactorial and complex. On the one hand, decreased parasympathetic activity[15] and, on the other hand, heightened sympathetic activity as evidenced by low HRV measures (SDRR, SDSD, and RMSSD) and increased resting HR were found in patients with CKD. This altered autonomic function is more pronounced in hemodialysis CKD patients. The multiple factors that may be responsible for such an altered autonomic function are as follows: (1) a diseased kidney may be responsible for increased activity of the renin-angiotensin-aldosterone system, which may cause enhanced sympathetic activity; (2) there may be enhanced central sympathetic discharge because of chronic disease condition, which is a stressful situation; (3) there may be decreased availability of nitric oxide due to decreased activity of nitric oxide synthase (NOS) enzyme. The increased accumulation of NOS inhibitors (e.g., asymmetrical dimethylarginine) in kidney disease may be responsible for such decreased activity of NOS.[2,16,17] However, further studies are required to establish the underlying mechanisms of deranged autonomic function in patients with CKD.

Correlation analysis of the data showed that resting HR was positively associated with ESRD. However, SDRR, SDSD, and RMSSD were negatively associated with ESRD. These results emphasize that altered autonomic function, as evidenced by heightened sympathetic activity and decreased parasympathetic activity, is associated with the progressive stage of kidney disease. Therefore, CAN associated with the progressive stage of renal disease may act as one of the major cardiovascular risk factors, which may enhance cardiovascular morbidity and mortality in those patients.

There are several limitations of the present study. It is an observational study, so the cause-and-effect relation between the parameters cannot be established based on the result. The result of the present study cannot be generalized, as the sample size is small. Therefore, a more significant number of patients may be included in future studies to confirm the results of the present study.

Conclusion

CAN, as measured by HRV, was determined and compared between non-hemodialysis and hemodialysis CKD patients of primary renal diagnosis only in the present study, and its correlation with the progression of the disease was also examined. The data analysis revealed more altered autonomic function, as evidenced by increased resting HR and decreased HRV measures (SDRR, SDSD, and RMSSD), in hemodialysis than in non-hemodialysis CKD patients. A correlation study showed that altered autonomic function was associated with ESRD. It may be considered as one of the cardiovascular risk factors beyond conventional ones, which aggravate major cardiovascular events in the future. Therefore, it would be beneficial for patients with

CKD to undergo screening for CAN from the initial stage of diagnosis, as preventive measures can be initiated to defer major cardiac events. Furthermore, future studies may be carried out to establish the underlying mechanisms of altered autonomic function in patients with CKD.

Author Contributions

Conception and design of the research: Panda SK, Kannan B, Nanda P, Kar M; acquisition of data: Nair A, Kannan B; analysis and interpretation of the data: Nair A, Panda SK, Kar M; statistical analysis: Nair A, Kar M; writing of the manuscript: Nair A, Nanda P, Kar M; critical revision of the manuscript for intellectual content: Nair A, Panda SK, Kannan B, Nanda P, Kar M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of MD thesis submitted by Aswin PR, from AIIMS, Bhubaneswar.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work

Availability of Research Data and Other Materials

The underlying content of the research text is contained within the manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the AIIMS, Bhubaneswar under the protocol number IEC/AIIMS BBSR/PG thesis/2021-22/05. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Foley RN, Parfrey PS, Sarnak MJ. Clinical Epidemiology of Cardiovascular Disease in Chronic Renal Disease. Am J Kidney Dis. 1998;32(5 Suppl 3):S112-9. doi: 10.1053/ajkd.1998.v32.pm9820470.
2. Herzog CA, Mangrum JM, Passman R. Sudden Cardiac Death and Dialysis Patients. Semin Dial. 2008;21(4):300-7. doi: 10.1111/j.1525-139X.2008.00455.x.
3. Karasavvidou D, Boutouyrie P, Kalaitzidis R, Kettab H, Pappas K, Stagikas D, et al. Arterial Damage and Cognitive Decline in Chronic Kidney Disease Patients. J Clin Hypertens. 2018;20(9):1276-84. doi: 10.1111/jch.13350.
4. Chandra P, Sands RL, Gillespie BW, Levin NW, Kotanko P, Kiser M, et al. Predictors of Heart Rate Variability and Its Prognostic Significance in Chronic Kidney Disease. Nephrol Dial Transplant. 2012;27(2):700-9. doi: 10.1093/ndt/gfr340.
5. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health. 2017;5:258. doi: 10.3389/fpubh.2017.00258.
6. Saeki Y, Atogami F, Takahashi K, Yoshizawa T. Reflex Control of Autonomic Function Induced by Posture Change During the Menstrual Cycle. J Auton Nerv Syst. 1997;66(1):69-74. doi: 10.1016/s0165-1838(97)00067-2.
7. World Health Organization. The Asia Pacific Perspective: Redefining Obesity and Its Treatment. Sydney: Health Communications Australia; 2000.
8. Schwartz GJ, Work DF. Measurement and Estimation of GFR in Children and Adolescents. Clin J Am Soc Nephrol. 2009;4(11):1832-43. doi: 10.2215/CJN.01640309.
9. Wang Z, Zhang J, Chan S, Cameron A, Healy HG, Venuthurupalli SK, et al. BMI and Its Association with Death and the Initiation of Renal Replacement Therapy (RRT) in a Cohort of Patients with Chronic Kidney Disease (CKD). BMC Nephrol. 2019;20(1):329. doi: 10.1186/s12882-019-1513-9.
10. Laville SM, Couturier A, Lambert O, Metzger M, Mansencal N, Jacquelinet C, et al. Urea Levels and Cardiovascular Disease in Patients with Chronic Kidney Disease. Nephrol Dial Transplant. 2022;38(1):184-92. doi: 10.1093/ndt/gfac045.
11. Fukuta H, Hayano J, Ishihara S, Sakata S, Mukai S, Ohte N, et al. Prognostic Value of Heart Rate Variability in Patients with End-Stage Renal Disease on Chronic Haemodialysis. Nephrol Dial Transplant. 2003;18(2):318-25. doi: 10.1093/ndt/18.2.318.
12. Oikawa K, Ishihara R, Maeda T, Yamaguchi K, Koike A, Kawaguchi H, et al. Prognostic Value of Heart Rate Variability in Patients with Renal Failure on Hemodialysis. Int J Cardiol. 2009;131(3):370-7. doi: 10.1016/j.ijcard.2007.10.033.
13. Clyne N, Hellberg M, Kouidi E, Deligiannis A, Höglund P. Relationship between Declining Glomerular Filtration Rate and Measures of Cardiac and Vascular Autonomic Neuropathy. Nephrology. 2016;21(12):1047-55. doi: 10.1111/nep.12706.
14. Thio CHL, van Roon AM, Lefrandt JD, Gansevoort RT, Snieder H. Heart Rate Variability and Its Relation to Chronic Kidney Disease: Results from the PREVEND Study. Psychosom Med. 2018;80(3):307-16. doi: 10.1097/PSY.0000000000000556.
15. Vita G, Bellinghieri G, Trusso A, Costantino G, Santoro D, Monteleone F, et al. Uremic Autonomic Neuropathy Studied by Spectral Analysis of Heart Rate. Kidney Int. 1999;56(1):232-7. doi: 10.1046/j.1523-1755.1999.00511.x.
16. Vonend O, Rump LC, Ritz E. Sympathetic Overactivity--the Cinderella of Cardiovascular Risk Factors in Dialysis Patients. Semin Dial. 2008;21(4):326-30. doi: 10.1111/j.1525-139X.2008.00456.x.
17. 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. doi: 10.1097/01.asn.0000113320.57127.b9.