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Change in GFR in relation to pulse rate, dipping blood pressure, anti-hypertensives, NLR and PLR in patients with chronic kidney disease

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Abstract

This study aimed to evaluate the change in glomerular filtration rate (GFR) in chronic kidney disease (CKD) patients in relation to certain 24-h ambulatory blood pressure monitoring (ABPM) parameters and anti-hypertensives and inflammatory markers. This retrospective study included 206 adult CKD patients (mean±SD age: 51.3±17.1 years, 54.9% females). We recorded the data on patient demographics, comorbidity and medications, 24-h ABPM parameters (pulse rate and dipping systolic and diastolic BP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and GFR. We evaluated the change in e-GFR values from baseline concerning study variables. There was a mean -1.5mL/min/1.73m^2(range -80.2 to 18.1) decline from baseline GFR during the study period. The decrease in GFR from baseline was significantly lower in patients with vs without diuretic therapy (median 1.2 vs 0 mL/min/1.73m^2, p=0.017). The GFR change from baseline was positively correlated with the patient age (r=0.145, p=0.040) as well as with the total (r=0.198, p=0.005), day-time (r=0.184, p=0.009) and night-time (r=0.219, p=0.003) pulse rate. We noted no significant difference in the GFR change from baseline concerning gender, anti-hypertensive medications other than diuretics, dipping systolic or diastolic BP values or inflammatory markers. Our findings revealed a significant correlation between age, pulse rate and diuretic usage but not dipping systolic or diastolic BP or inflammatory markers with the GFR change from baseline.

Keywords: chronic kidney disease, hypertension, renal progression, dipping blood pressure, anti-hypertensive medications, inflammatory markers

1. Introduction

Chronic kidney disease (CKD) is an important public health concern in association with an increased risk of adverse outcomes such as the development of end-stage renal disease (ESRD), cardiovascular events, psychiatric problems and mortality in the advanced stage (1-4). Given the continued risk of progression to ESRD and the mortality despite several measures devoted to managing CKD, identifying the risk factors of kidney function decline is considered crucial for patients with CKD (4, 5).

Hypertension leads to an increased risk of CKD development and progression to ESRD, while CKD is also a common cause and a sequel of uncontrolled hypertension (4-6).

Although the exact mechanisms of circadian pattern alterations in CKD patients remain unknown, the diurnal variability of blood pressure (BP) and pulse rate (reduced or absent decrease in nighttime BP levels in particular) is considered likely to be associated with end-organ damage and cardiovascular events in hypertensive CKD patients (7-13).

The 24-h ambulatory blood pressure monitoring (ABPM) is therefore considered the gold standard for assessing hypertension in CKD patients to assess the progression of renal dysfunction and prevent cardiovascular complications (5,14).

In addition, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have also been proposed recently as markers of inflammation and predictors of renal decline in patients with CKD (15-19).

This study aimed to evaluate the change in GFR values in CKD patients in relation to certain 24-h ABPM parameters (pulse rate, dipping systolic and diastolic BP), anti-hypertensive medications and inflammatory markers (NLR, PLR).

2. Materials and Methods

2.1. Study population

We included 206 adult CKD patients (mean±SD age: 51.3±17.1 years, 54.9% females) in this retrospective descriptive study conducted between January 2013 and December 2017.

We obtained written informed consent from each subject, and the institutional ethics committee approved the study (Approval number: 2021/208, approval date: 9.12.2021).

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2.2. Assessments

We recorded each patient's data on demographics (age, gender), body mass index (BMI, kg/m^2), active smoking, comorbid diseases, anti-hypertensive medications, 24-h ABPM parameters, including pulse (bpm, total daytime, nighttime) and dipping systolic and diastolic BP (mmHg) via inflammatory markers (NLR, PLR) and glomerular filtration rate (GFR; baseline, last visit and the change from baseline values).

A decrease of ≥10% in BP value measured at night compared to daytime is considered dipping. We calculated the patients' e-GFR values (mL/min/1.73m^2) using the CKD-EPI formula. We evaluated the change in e-GFR values from baseline concerning demographics, anti-hypertensive medications, pulse, dipping BP and inflammatory markers.

2.3. Statistical analysis

We conducted statistical analyses using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). We used Mann-Whitney U test to analyze the parametric variables and analyzed the correlation of GFR difference from baseline with study parameters via Spearman correlation analysis. We expressed the data as mean ± standard deviation (SD), median (min-max) and percent (%) where appropriate and considered $p < 0.05$ statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Mean±SD patient age was 51.3±17.1 years, and 54.9% of patients were females. Concomitant hypertension was evident in 90.3% of CKD patients, while diabetes in 25.7%. The most commonly used anti-hypertensive medications were calcium channel blockers (CCB, 40.8%), beta-blockers (28.9%) and diuretics (23.3%) (Table 1).

Table 1. Demographic and clinical characteristics

Age (year)	mean±SD	51.3±17.1
	Median (min-max)	52.5(17-86)
Gender, n(%)		
Male		93(45.1)
Female		113(54.9)
BMI (kg/m^2), mean±SD		31.1±6.4
Active smoking, n(%)		46(22.3)
Comorbid diseases, n(%)		
Diabetes mellitus		53(25.7)
Hypertension		186(90.3)
Antihypertensive medications, n(%)		
CCB		84(40.8)
Beta blocker		59(28.9)
Diuretic		48(23.3)
ACEi		44(21.5)
ARB		39(19.0)
Alpha-blocker		34(16.5)

BMI: Body mass index; CCB: Calcium channel blocker; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker

3.2. Cardiac parameters, inflammatory markers and GFR change from baseline

Mean±SD total daytime and nighttime pulse rate values were 74.1±10, 76.3±10.7 and 66.5±8.9, respectively. Median dipping systolic and diastolic BP values were 6.8mmHg (range, -17.5 to 100 mmHg) and 9.7mmHg (range, -14.5 to 100mmHg), respectively (Table 2).

Mean±SD NLR values were 2.3±2.2, while PLR values were 130.2±57.0 (Table 2).

There was a mean -1.5 mL/min/1.73m^2 (range -80.2 to 18.1mL/min/1.73m^2) decline from baseline GFR during study period (Table 2).

Table 2. 24-h ABPM parameters, inflammatory markers and GFR change from baseline

24-h ABPM parameters		
Pulse rate (bpm), mean±SD	Total	74.1±10
	Day-time	76.3±10.7
	Nigh-time	66.5±8.9
Dipping blood pressure (mmHg), median (min-max)	Systolic	6.8 (-17.5-100)
	Diastolic	9.7 (-14.5-100)
Inflammatory markers, mean±SD		
NLR		2.3±2.2
PLR		130.2±57.0
GFR (mL/min/1.73m^2)		
Baseline	mean±SD	74.8±34.6
	Median (min-max)	78.9(0.4-166.1)
Last visit	mean±SD	73.4±33.4
	Median(min-max)	74.5(6.1-147.1)
Change from baseline	mean±SD	-1.5±15.4

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; GFR: Glomerular filtration rate

3.3. GFR change from baseline with respect to study parameters

We noted no significant difference in GFR change from baseline with respect to gender or anti-hypertensive medications other than diuretics. The decrease in GFR from baseline was significantly lower in patients with vs without diuretic therapy (median 1.2 vs 0 mL/min/1.73m^2, p=0.017) (Table 3).

3.4. Correlation of GFR change with continuous variables

GFR change from baseline was positively correlated with patient age (r=0.145, p=0.040) as well as with the total (r=0.198, p=0.005), day-time (r=0.184, p=0.009) and night-time (r=0.219, p=0.003) pulse rate values. We noted no significant change from baseline GFR with the dipping systolic or diastolic BP values or inflammatory markers.

Table 3. GFR change from baseline with respect to gender and antihypertensive medications

		GFR change from baseline (mL/min/1.73m^2) median (min-max)	p value
Gender			
Male		-0.1±13.6	0.444
Female		0(-29.5-18.1)	
Antihypertensive medications			
ACEi	No	0(-80.2-18.1)	0.983
	Yes	0(-49-62.2)	
ARB	No	0(-49.7-18.1)	0.757
	Yes	0(-80.2-17.5)	
Beta blocker	No	0(-80.2-62.2)	0.527
	Yes	0(-22.9-18.1)	
CCB	No	0(-49-62.2)	0.192
	Yes	0(-80.2-18.1)	
Alpha blocker	No	0(-80.2-18.1)	0.295
	Yes	0(-19.8-27.9)	
Diuretic	No	0(-80.2-62.2)	**0.017**
	Yes	1.2(-19.8-18.1)	

ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; GFR: Glomerular filtration rate
Mann Whitney U test

4. Discussion

Our findings revealed that eGFR declined by 1.5 units on average during follow up in CKD patients, along with a significant correlation of age, pulse rate and diuretic usage with the change in GFR over time. The gender, BMI, other types of anti-diabetic medications, dipping systolic or diastolic BP or inflammatory markers (NLR, PLR) had no significant impact on GFR change over time in CKD patients.

Notably, a past study with 190 hypertensive patients reported patients with reduced eGFR (60 mL/minute/1.73 m^2) to have an earlier time of systolic BP to reach a significantly higher level above the midnight systolic BP, to be older and to include more non-dippers (57.8% vs 39.3%) than those with a normal eGFR, while the time course of pulse rate was similar in reduced vs normal GFR groups (9). The 5-year data of APrODiTe-2 study revealed faster eGFR progression and adverse renal outcomes in patients with poor BP control at baseline or over one year and higher systolic BP and pulse pressure (5).

In this regard, the association of total daytime and nighttime pulse rates with the amount of decline in GFR in CKD patients in the current study seems to be in accordance with the consideration of pulse rate as a good surrogate marker of adverse renal outcomes and eGFR progression, as well as the association of lower BP burden over at least one year with increased likelihood of better renal outcomes over five years (5).

Although the non-dipper HT pattern is considered to be more prevalent in CKD patients as a known indicator of rapid end-organ damage, the direct interaction between non-dipper HT and renal progression remains unclear (20,21). Past studies based on 24-h ABPM recording revealed the likelihood of increased DBP variability associated with better renal outcomes (13) and no significant impact of 24-hour systolic and diastolic BP variability on the progression of CKD (21-23). Our findings revealed no association between dipping systolic or diastolic BP and GFR decline from baseline. Likewise, we have previously reported in 186 adult patients with CKD and HT that the dipper HT pattern was prevalent (45.8%) in them, possibly concerning the presence of severe proteinuria and no significant association of BP variability or non-dipper HT pattern with renal progression (21).

However, other studies indicated the increased systolic BP variability to be a significant determinant of increased risk of CKD and ESRD (11,12). Also, a past study with 436 CKD patients reported non-dipper HT as a significant risk factor for CKD progression through an analysis adjusted for 24-hour ABPM, cardiovascular history, proteinuria and other risk factors (10). Similarly, the authors of a past study with 46 CKD patients reported a significant decrease in dipping diastolic BP during the night, whereas there was no change in nighttime systolic dipping, mean BP values or pulse wave velocity after a one-year observation period (7). The authors noted the likelihood of peripheral and central BP not participating in the CKD progression and no change in their levels over a 1-year follow up despite the significant decline of eGFR (7). The authors also suggested that the reduced magnitude of the diastolic dipping had a key role in the pathogenesis of deterioration of kidney function (7). Also, patients with IgA-nephropathy and non-dipping BP patterns were reported to have lower eGFR and more extensive renal tissue damage than those with preserved dipping BP patterns (24). Moreover, 1-year data from the APrODiTe-2 study with 400 CKD patients revealed the association of good BP control and the dipper BP pattern with subtler eGFR and proteinuria changes (25).

Indeed, given the association of non-dipping BP profile and nocturnal hypertension with hypertension-mediated organ damage in CKD patients, ABPM is suggested to be more extensively used for applying individual risk assessment and personalized anti-hypertensive treatment in CKD patients (26), and the daily BP variability on 24-hour ABPM rather than visit-to-visit BP variability is considered more valuable in reflecting the renal survival (5,21). Notably, a past study with 10271 hypertensive patients (3227 with CKD) from the

Hygia Project reported patients with vs without CKD to have older age, higher nocturnal systolic BP, higher ambulatory pulse pressure, and lower daytime ambulatory diastolic BP along with the higher prevalence of non-dipping and the riser BP (elevated asleep systolic BP) pattern (27). The authors emphasized the increased prevalence of a blunted nocturnal BP decline and the riser BP pattern, and the elevated pulse pressure as a marker of increased arterial stiffness. They enhanced CVD risk in hypertensive patients with CKD to indicate a need for ABPM to be considered necessary for proper diagnosis and CVD risk assessment in CKD patients (27).

In fact, our findings on the significant age-dependency of GFR decline seem notable given the reported association of age with SBP or DBP variability in the past studies (21,22,28). In addition, the association of diuretic treatment with GFR change from baseline in our study also seems to support the likelihood of the different impacts of different anti-hypertensive medications on BP variability (i.e., a decline in variability with calcium channel blockers and non-loop diuretics and an increase in variability with ACE inhibitors) (29).

Although previous studies indicated a likelihood of NLR to serve as an independent risk factor for hypertension and renal progression in patients with IgA nephropathy (18,19) and both NLR and PLR to be potential markers for predicting renal outcomes in patients with rapidly progressive glomerulonephritis (RPGN) (15), our findings revealed no correlation of NLR or PLR values with GFR decline during follow up.

In conclusion, our findings revealed a significant correlation between age, pulse rate, and diuretic usage but not dipping systolic or diastolic BP or inflammatory markers with the change of GFR in CKD patients. Future longer-term large-scale studies addressing BP patterns via 24-hour ABPM in CKD patients are needed to understand the exact role of BP variability and dipping status in controlling hypertension and predicting renal progression in CKD patients.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: H.D., Design:H.D., Data Collection or Processing: H.D., Analysis or Interpretation: H.D., Literature Search: H.D., Writing: H.D.

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