Evaluation of the relationship between circadian blood pressure profile and natriuresis in patients with chronic kidney disease and renal transplant recipients

Ocena zależności między dobowym profilem ciśnienia tętniczego a natriurezą u pacjentów z przewlekłą chorobą nerek oraz po przeszczepieniu nerki

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Abstract

Introduction. The disturbed circadian rhythm of blood pressure (BP) is more prevalent in patients with chronic kidney disease (CKD). Diminished renal capacity to excrete sodium may result in nocturnal BP elevation in order to enhance pressure natriuresis to compensate for impaired daytime natriuresis. We hypothesized that kidney transplantation (KTx) that restores glomerular filtration should normalize circadian BP profile.

The aim of the study was to assess and compare natriuresis and circadian BP profiles of patients at different stages of CKD and KTx recipients.

Material and methods. Blood pressure was monitored noninvasively for 24 hours and urinary samples were collected during the daytime and night-time to measure natriuresis among 55 patients with stable graft or kidney function: 41 with CKD and 14 patients after KTx.

Results. Mean awake systolic blood pressure (SBP) was lower in KTx recipients than in CKD at all stages. Night-time mean BP was lowest in CKD patients with eGFR > 45 ml/min (126/68 mm Hg vs. KTx 130/75 mm Hg; $p = 0.005$). The prevalence of dipper status was also highest in CKD patients with eGFR > 45 ml/min. 50% vs. 8.3% (CKD 3b), 0% (CKD 4–5) and 7.1% (KTx) ($p < 0.01$), whereas reverse status was the rarest. Nocturnal blood pressure fall correlated inversely with night to day natriuresis ratios in both groups (CKD $r = –0.91$ $p < 0.01$; KTx $r = –0.63$ $p = 0.016$). The dipping profile was present only in KTx patients with eGFR > 60 ml/min, whereas reverse dipping profile only in those with eGFR < 60 ml/min. More than half CKD patients were taking at least 4 antihypertensive medications. In contrast, 64% of KTx recipients were receiving no more than 3 antihypertensive drugs to control BP.

Conclusions. Kidney transplantation improves blood pressure control and reduces a number of antihypertensive drugs used. Normal circadian rhythm could be restored only in the transplant patients with well-functioning renal graft.

Key words: circadian rhythm of blood pressure, chronic kidney disease, kidney transplantation, natriuresis

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Streszczenie

Wstęp. Niedostateczne wydalanie sodu spowodowane upośledzoną czynnością nerek w przewlekłej chorobie nerek (PChN) może być wyrównywane zwiększoną natriurezą w nocy. Wymaga ona zwiększenia systemowego ciśnienia tętniczego, co wyjaśnia częste występowanie zaburzeń rytmu dobowego ciśnienia tętniczego w PChN. Zwiększenie filtracji kłębuszkowej po udanym przeszczepieniu nerki (KTx, kidney transplantation) powinno prowadzić do zmian dobowego profilu ciśnienia tętniczego.

Celem pracy była ocena i porównanie dobowego profilu ciśnienia tętniczego i natriurezy u pacjentów z PChN oraz po KTx.

Materiał i metody. Monitorowano równolegle ciśnienie tętnicze oraz prowadzono zbiórki moczu przez 24h u 55 chorych, w tym 41 z PChN oraz 14 po KTx.

Wyniki. Średnie dzienne skurczowe ciśnienie tętnicze było najniższe po KTx. Natomiast średnie nocne ciśnienie tętnicze było najniższe w grupie z PChN i eGFR > 45 ml/min. (126/68 mm Hg wzgl. KTx 130/75 mm Hg; p = 0,005). Prawidłowy rytm ciśnienia tętniczego obserwowano u 50% chorych z eGFR > 45 ml/min. wzgl. 8,3% w stadium 3b, 0% stadium 4.–5. PChN i 7,1% po KTx (p < 0,01), podczas gdy „reverse dipping" występował w tej grupie najrzadziej. Wartość nocnego spadku ciśnienia tętniczego (NBPF, nocturnal blood pressure fall) korelowała ujemnie z ilorazem nocnej do dziennej natriurezy zarówno w PChN (r = –0,91, p < 0,01), jak i po KTx (r = –0,63, p = 0,016). Prawidłowy profil ciśnienia tętniczego (dipping) po przeszczepieniu stwierdzano tylko u chorych z eGFR > 60 ml/min, natomiast profil „reverse dipping" tylko gdy eGFR < 60 ml/min. Ponad połowa pacjentów z PChN przyjmowała przynajmniej 4 leki hipotensyjne, w przeciwieństwie do pacjentów po KTx, którzy w większości (64%) wymagali nie więcej niż 3 leków.

Wnioski. Przeszczepienie nerki poprawia kontrolę ciśnienia tętniczego i pozwala na zmniejszenie liczby leków hipotensyjnych, jednak poprawę dobowego rytmu obserwuje się jedynie przy dobrej czynności przeszczepu.

Słowa kluczowe: profil ciśnienia tętniczego, przewlekła choroba nerek, przeszczepienie nerki, natriureza

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Introduction

Blood pressure control is a complex physiological function that depends on the interaction of the cardiovascular, renal, endocrine and nervous systems. Kidneys play an essential role in the integrated system of blood pressure control by influencing the fluid-electrolyte balance, sodium metabolism, sympathetic nervous system and neurohormonal systems, including in particular renin-angiotensin-aldosterone system. Kidneys may be both perpetrators and victims of increased blood pressure [1]. The mechanism of blood pressure autoregulation control the renal blood flow, glomerular filtration and the filtered sodium load, depending on the blood pressure. The increase in sodium excretion in response to blood pressure elevation results from the progressive decrease in its tubular reabsorption [2].

In patients with chronic kidney disease (CKD), hypertension, which is one of the first signs of the disease, is very common and blood pressure values increase with the decrease in glomerular filtration rate. The third National Health and Nutrition Examination Survey (NHANES III) showed that 40% of patients with glomerular filtration rate (GFR) between 60 and 90 ml/min/1.73 m^2 had elevated blood pressure values, i.e. above 140/90 mm Hg, whereas in the group with GFR < 30 ml/min/1.73 m^2 high BP was found in as much as 75% [3]. The pathogenesis of hypertension in CKD is multifactorial, but one of the most important causes is retention of sodium and water leading to hypervolaemia. The pressure natriuresis curve is shifted to the right to remove the excess of sodium molecules and, subsequently, water. Blood pressure increase becomes necessary.

Insufficient sodium excretion during daytime, caused by impaired glomerular filtration in CKD, may be compensated by increased natriuresis during better renal perfusion, i.e. at night. However, this requires an additional increase in systemic blood pressure during the night-time hours, which seems to confirm similar prevalence of non-dipping and reverse-dipping circadian BP patterns in CKD patients [4–6].

Increased glomerular filtration following successful kidney transplantation (KTx) should lead to restoration of the normal circadian blood pressure profile. The aim of the study was to evaluate and compare circadian blood pressure and natriuresis profiles in patients with chronic kidney disease and renal transplant recipients.

Material and methods

A prospective, observational study involving blood pressure monitoring and measurements of natriuresis was performed in 55 randomly selected patients, including 41 patients with CKD (19 males, 21 females, mean age 67 ± 10 years; 12 patients with CKD in stages 2 and 3a, 12 patients in stage 3b and 17 patients in stages 4–5) and 14 patients after KTx (8 males, 7 females, mean age 53 ± 10 years, mean time since KTx 5.1 ± 4.7 years). The detailed characteristics of each group are summarized in Table I. Kidney transplant patients were younger and less burdened with internal diseases. Occurrence of potential symptoms, diagnosis of obstructive sleep apnoea or shift work were the exclusion criteria from the study.

Blood pressure was monitored noninvasively using the automatic blood pressure measuring device — BR-102plus ABPM system, Schiller Poland Ltd. zoo. Twenty-four-hour ambulatory blood pressure monitoring (ABPM) was performed on the arm of the non-dominant upper limb. The device recorded blood pressure measurements every 15 minutes during the day, from 7:00 AM to 10:00 PM and every 30 minutes during the night (from 10 PM to 7: 00 AM). At the same time, the patient recorded his/her daily activities in a diary, on the basis of which the time intervals of night rest and daily activity used for the analyses were adjusted. Automatic blood pressure monitoring provided between 50 and 75 measurement results.

Based on the report generated by computer software dedicated to the BR-102 plus, information was obtained about the mean values and standard deviation of the following parameters: systolic blood pressure (SBP), diastolic blood pressure (DBP), BP load, and heart rate (HR) for the 24-hour period and in certain time intervals, i.e. during the daytime (e.g. SBPd, DBPd) and night-time (e.g. SBPn, DBPn). Based on these data, mean arterial pressure (MAP) values were calculated for each time interval, according to the following formula: MAP = SBP + 1/3 (SBP – DBP), and then used for the calculation of nocturnal blood pressure fall (NBPF), using the following formula: NBPF (%) = [(MAPd – MAPn)/ /MAPd] × 100% [7].

Urinary sodium excretion was measured from two urine collections made by patients during their daily activities and night rest.

According to the guidelines of the European Society of Cardiology and the European Society of Hypertension [8], normal values of mean blood pressure were as follows: mean daytime BP < 135/85 mm Hg, mean night-time BP < 120/70 mm Hg and mean diurnal BP < 130/80 mm Hg. The disturbed circadian BP pattern was diagnosed when the reduction in mean night-time blood pressure was less than 10% in relation to the values recorded during the day. According to the values of NBPF, the patients were assigned to the following groups: dippers — those with normal circadian BP pattern, i.e. when the NBPF was 10–20%; extreme dippers — patients with excessive NBPF, when the NBPF was above 20%; non-dippers — patients with NBPF of 0–10% and reverse-dippers — patients with reversed circadian BP pattern, where mean night-time BP values were higher than during the day (the NBPF values were negative). Mean values and standard deviations of the selected parameters were calculated, and the means were compared between the study groups using the Student's t-test for independent values (after checking the normality of their distribution) and one-way analysis of variance. Pearson's test was used to evaluate correlations.

Results

Mean 24-hour systolic blood pressure (SBP) values were 130 mm Hg in kidney transplant patients and

Table I. Characteristics of the study population

	KTx (n = 14)	Stage 2 and 3a CKD (n = 12)	Stage 3b CKD (n = 12)	Stage 4 and 5 CKD (n = 17)
Females (%)	43	33	50	71
Males (%)	57	67	50	29
Mean age (years)	53 ± 10	62 ± 10	69 ± 11	71 ± 9
Mean duration of CKD/time since KTx (years)	5.1 ± 4.7	1.8 ± 0.7	1.7 ± 1.5	4.6 ± 0.8
BMI	25 ± 3	26 ± 5	25 ± 6	22 ± 2
T2DM (%)	21	50	41	53
IHD (%)	14	50	42	71
History of cardiovascular events (%)	21	25	25	36
Mean GFR [ml/min]	46.4	57.7	35.1	27.4

141 mm Hg in patients with chronic kidney disease ($p < 0.001$), whereas DBP values were comparable in both groups. Mean daytime systolic blood pressure was lowest in the group of patients after kidney transplantation — 130 mm Hg vs. 138 mm Hg in the CKD group with eGFR > 45 mL/min ($p = 0.07$); 139 mm Hg in patients with stage 3b CKD; 145 mm Hg in patients with stage 4–5 CKD ($p < 0.05$) (Figure 1). Mean night-time blood pressure was lowest in the CKD group with eGFR > 45 mL/min (126/68 mm Hg vs. 130/75 mm Hg in KTx group; $p = 0.005$) (Figure 2).

Correct circadian BP profile was observed in 50% of patients with eGFR > 45 mL/min vs. 8.3% of patients with stage 3b CKD, 0% of patients with stage 4–5 CKD and 7.1% of patients after KTx ($p < 0.01$), while the proportion of "reverse dippers" was 8.3% vs. 25%, 71% and 42.8%, respectively ($p < 0.01$) (Figure 3).

The association of night-time to daytime BP ratio with night-time to daytime natriuresis ratio and glomerular filtration rate was demonstrated. Night-time BP fall correlated negatively with night-time to daytime natriuresis ratio in both groups of patients: those with CKD ($r = –0.91$, $p < 0.01$) and those after KTx ($r = –0.63$; $p = 0.016$) (Figure 4, 5), and positively with eGFR, but only in patients with chronic kidney disease. The preserved dipping BP profile after renal transplantation was reported only in patients with eGFR above 60 ml/min, while the reverse dipping profile — only in patients with eGFR below 60 ml/min (Figure 6). More than half of patients with CKD received at least four antihypertensive drugs, in contrast to patients after renal transplantation who mostly (64%) required no more than three drugs (Figure 7).

Discussion

Hypertension is not only a frequent symptom of chronic kidney disease, but also a risk factor for its progression to the end-stage kidney disease [9, 10]. In a landmark study, the Modification of Diet in Renal Disease (MDRD) trial, intensive blood pressure control — BP target of 125/75 mm Hg — resulted in a significant prolongation of time to renal replacement therapy by more than 1 year in patients with moderate renal impairment (mean GFR 38.6 mL/min) [11]. In addition to the high prevalence of hypertension in the population of patients with chronic kidney disease [8], which is 80% in patients with end-stage kidney disease, additional problem is treatment resistance [12] and disturbed circadian BP pattern — frequent occurrence of non-dipping and reverse-dipping in this group of patients [13–15] — which was also observed in our study. All patients with chronic kidney disease observed in our study were diagnosed with hypertension and more than 80% had abnormal circadian blood pressure profile. Also the vast majority of the patients (83%) required at least three antihypertensive drugs.

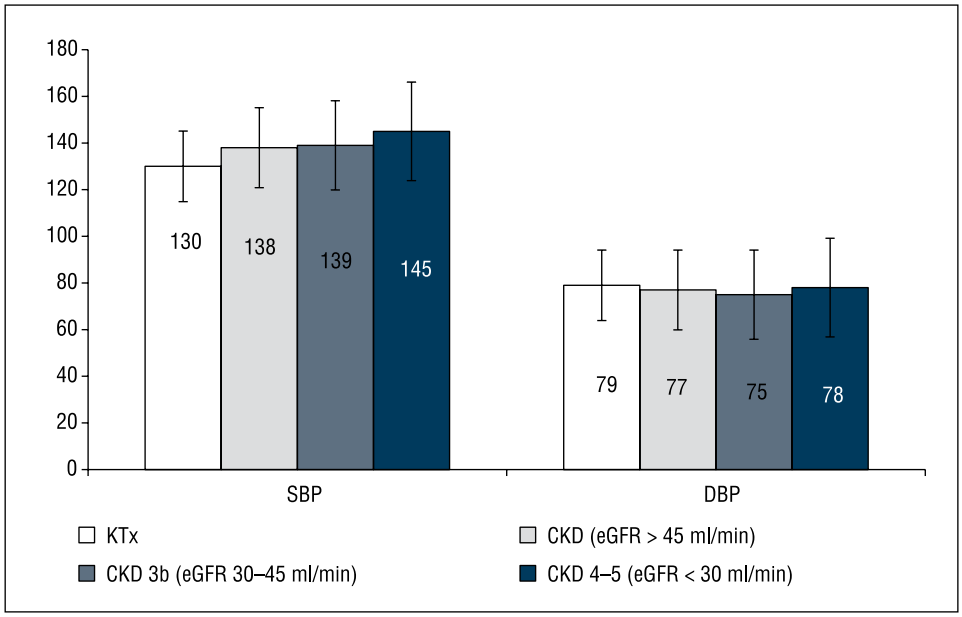

Figure 1. Mean daytime blood pressure values depending on the study group and renal excretion function
KTx — kidney transplantation; CKD — chronic kidney disease; SBP — systolic blood pressure; DBP — diastolic blood pressure

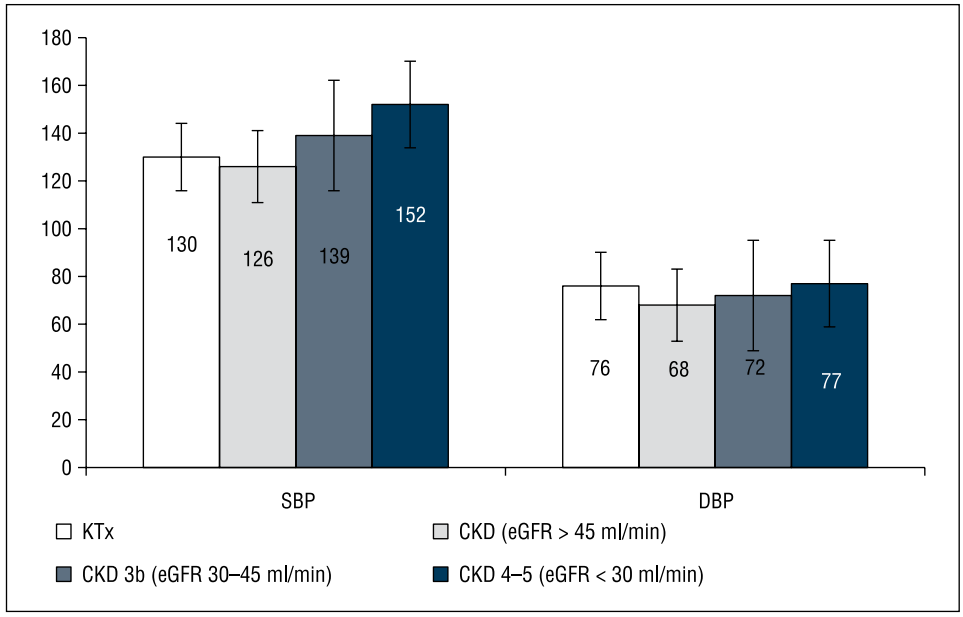

Figure 2. Mean night-time blood pressure values depending on study subgroup and kidney function
KTx — kidney transplantation; CKD — chronic kidney disease; SBP — systolic blood pressure; DBP — diastolic blood pressure

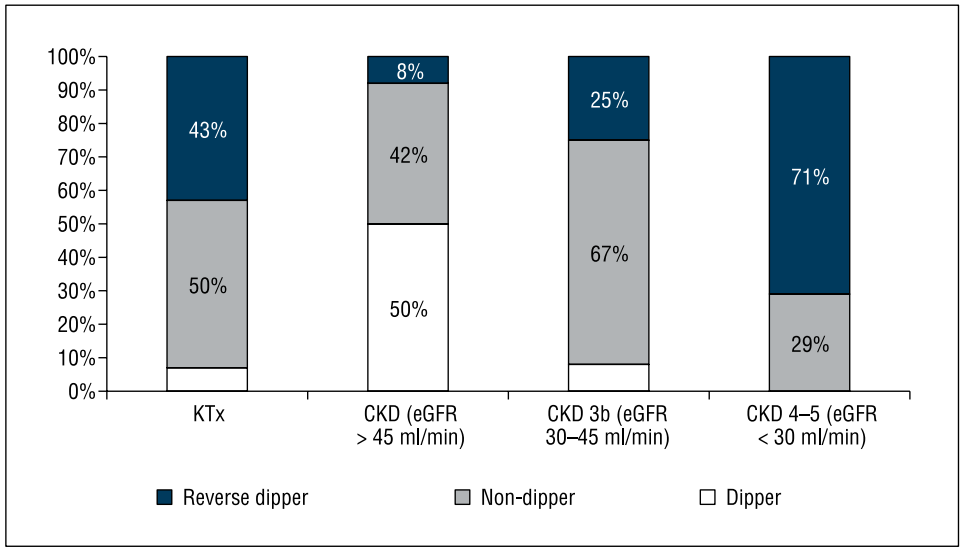

Figure 3. Circadian blood pressure patterns
KTx — kidney transplantation; CKD — chronic kidney disease

After renal transplantation, many disorders associated with chronic kidney disease such as anaemia or electrolyte abnormalities, such as hypocalcaemia or hyperphosphataemia, are gradually compensated [16]. However, hypertension usually does not disappear and occurs in a significant proportion of kidney transplant recipients [17]. Kidney transplantation may improve blood pressure control, but many observational studies report maintenance of abnormal blood pressure profile in these patients [18–20].

The mean circadian and daytime systolic blood pressure values in renal transplant recipients participating in our study were lower than in the chronic kidney disease group. Additionally, in contrast to patients with CKD, the majority of transplant recipients (64%) required no more than three drugs to achieve blood pressure control. Retrospective comparison of 24-hour ambulatory blood pressure monitoring prior to and after transplantation in the evaluated group of patients was, however, impossible, since in most cases it was not carried out before the surgery.

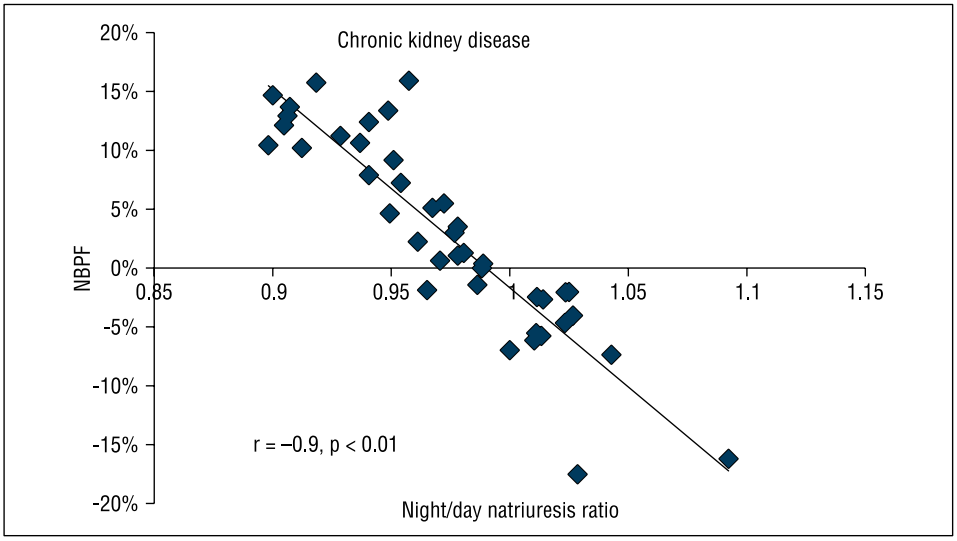

Figure 4. Relationship of blood pressure profiles and natriuresis in patients with chronic kidney disease
NBPF — nocturnal blood pressure fall

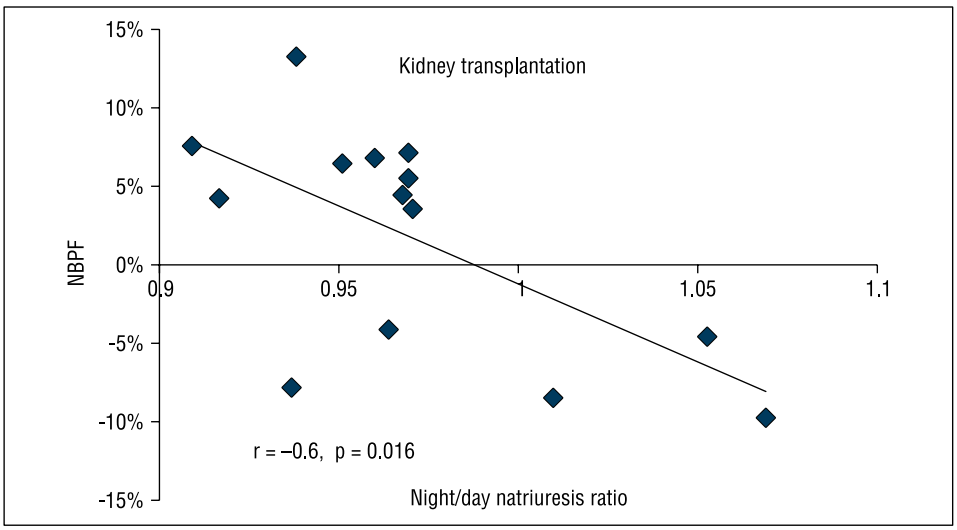

Figure 5. Relationship of blood pressure profiles and natriuresis in patients after kidney transplantation
NBPF — night blood pressure fall

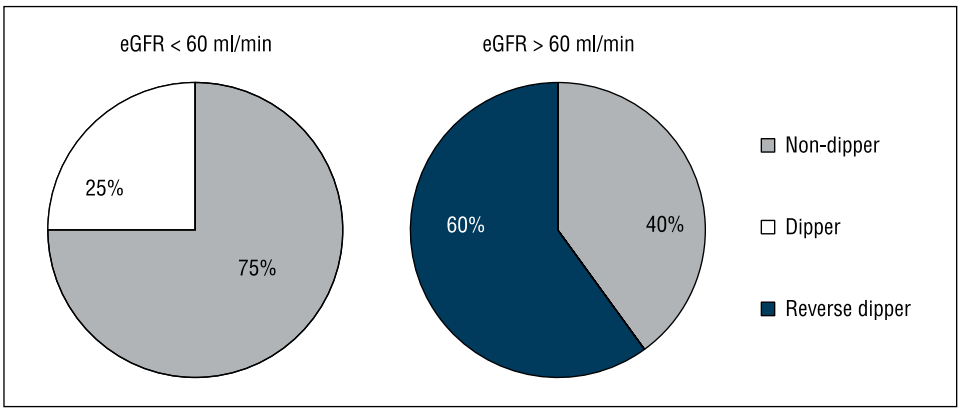

Figure 6. Circadian blood pressure profiles in patients after kidney transplantation with optimal and suboptimal graft function
eGFR — estimated glomerular filtration rate

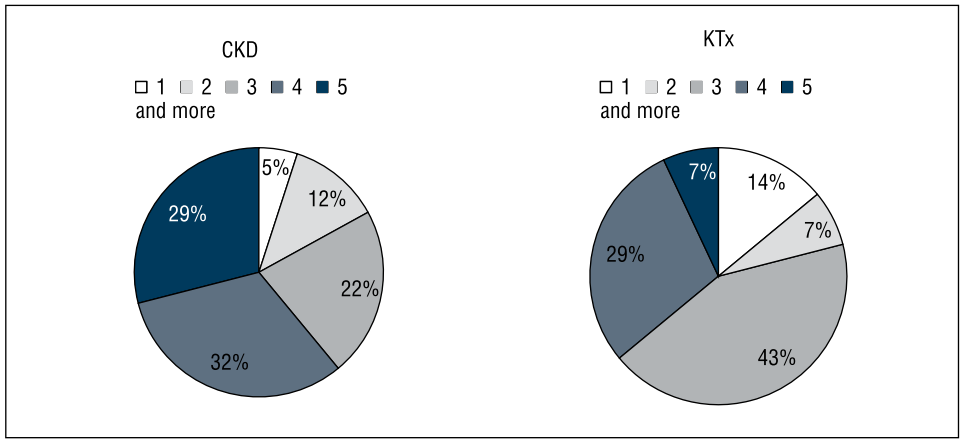

Figure 7. Number of antihypertensive drugs used
KTx — kidney transplantation; CKD — chronic kidney disease

Despite this limitation, our results are consistent with the prospective observation of 48 patients performed before and about 12 months after renal transplantation by Lee et al. [21] who found that mean daytime systolic blood pressure decreased from 125.5 ± 18.7 mm Hg to 120.5 ± 14.1 mm Hg and the average number of tablets per patient decreased from 1.7 ± 1.21 before transplantation to 0.6 ± 0.88 after transplantation. The criterion for a dipping profile, i.e. the reduction in night-time blood pressure above 10% in relation to the values recorded during the day, was fulfilled in only 7% of patients after transplantation observed in our study, similarly to findings reported by Lee et al. (only 10% of patients). The remaining patients, about 90% in both studies, exhibited a disturbed circadian BP pattern with a predominance of the non-dipping profile (58% in the study by Lee et al. and 50% in our study), while reverse dipping was found in 31% and 43%, respectively.

As shown in many studies, all abnormalities of circadian BP profile are associated with increased rates of organ damage and elevated risk of cardiovascular complications and hypertension. Since non-dippers are more likely to have left ventricular hypertrophy, ventricular arrhythmias, adverse structural changes in carotid arteries and peripheral arterioles, increased albuminuria and faster progression of renal failure, the aim of our paper was not only to evaluate the circadian BP profile in patients with chronic kidney disease and kidney transplant, but also to explain the pathophysiological mechanism that may be responsible for the occurrence of this phenomenon. Mechanisms of circadian BP profile disorders are not fully explained. The physiological difference between day and night blood pressure values results from the different activities of the autonomic nervous system, especially in terms of sympathetic-parasympathetic balance during daytime activity and night's sleep. Increased autonomous activity at night should be therefore considered as the cause of the phenomenon of non-dipping. Such a mechanism probably plays a role in people with insomnia or sleep apnoea syndrome. Also in chronic kidney disease, disturbed circadian BP rhythm is thought to be caused by the increased activity of the sympathetic nervous system. The increased sympathetic activity, observed even in early stages of chronic kidney disease, irrespective of its aetiology, is caused by efferent stimuli reaching the central nervous system via renal sensory nerves.

The limitation of our study is the lack of evaluation of the sympathetic system activity in the study population. In literature, abnormal circadian blood pressure rhythm in subjects with hypertension was most often associated with excessive intravascular volume and the phenomenon of sodium sensitivity. Fujii et al. [22] compared night-time to daytime natriuresis ratio between two groups of hypertensive patients: dippers and non-dippers. In the non-dippers group, the rate of urinary sodium excretion in the night compared to day was > 1.0, indicating increased excretion of sodium at night in these patients, while in the dippers group this ratio was below 0.9.

In chronic renal failure with reduced amount of functional renal parenchyma, there is a decrease in glomerular filtration, which leads to sodium and water retention. Fukuda et al. [23] and Bankir et al. [24] showed a significant correlation between night-time to daytime blood pressure ratio and night-time to daytime natriuresis ratio in patients with chronic kidney disease. Increased sodium excretion during night-time was associated with increased blood pressure values compared to daytime hours. On this basis, it was concluded that the impaired ability to

excrete sodium during the day was compensated by increased nocturnal natriuresis, provoked by increased systemic blood pressure. This mechanism was confirmed by the observations obtained in kidney donors in whom circadian BP rhythm became abnormal after removal of a kidney, without significant change in mean blood pressure values.

In our observational study, we also found associations of the ratio of night-time to daytime mean blood pressure values with night-time to daytime natriuresis and the glomerular filtration rate. Nocturnal blood pressure fall was correlated negatively with night-time to daytime natriuresis ratio in both CKD and renal transplantation groups and positively with eGFR, but only in patients with chronic kidney disease. The nonsignificant association between the glomerular filtration rate and the magnitude of nocturnal blood pressure fall in patients after renal transplantation is most likely due to the small group size. However, when analysing only patients undergoing renal transplantation, normal circadian blood pressure pattern (dipping) was only found in patients with eGFR above 60 ml/min, while reverse dipping — only in those with eGFR below 60 ml/min.

Risk factors and potential causes of the lack of nocturnal blood pressure fall are, in addition to autonomic dysfunction or renal failure, African-American origin, coexistence of diabetes or endocrine disorders, such as hyperaldosteronism, hypercortisolaemia and pheochromocytoma, or drugs, such as steroids and calcineurin inhibitors [25]. The mean glomerular filtration rate in patients after kidney transplantation participating in our study was comparable to that in patients with 2–3a stage CKD. Although the proportion of patients with coexisting diabetes was significantly lower in patients after transplantation than in patients with chronic kidney disease in stages 2–3b, normal circadian blood pressure profile was reported only in 7% of kidney transplant recipients, whereas among patients with CKD it was observed in 50% of those in stage 2–3a and 8% of those in stage 3b. Therefore, it can be expected that factors such as immunosuppressive therapy, including in particular steroids and cyclosporin, also affect circadian blood pressure profile in this group of patients after renal transplantation. Data from previous studies provide conflicting conclusions [26].

Conclusions

Poor control of blood pressure value and circadian BP profile is associated with increased risk of cardiovascular events and organ damage, which may lead to faster progression of graft failure [27]. Kidney transplantation improves blood pressure control and reduces the number of antihypertensive drugs taken by the patient, but only properly functioning graft may favourably affect the circadian BP profile. In some patients after kidney transplantation, graft function remains suboptimal and, in addition, glomerular filtration rate decreases with time. Gradual deterioration of kidney transplant function is influenced by the age of the recipient, the burden of concomitant diseases and the process of chronic rejection. Further studies are needed to explain pathogenic mechanisms leading to circadian blood profile disturbances after renal transplantation and establish the principles of adequate blood pressure control in this group of patients.

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