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ORIGINAL ARTICLE

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Orthostatic hypotension in kidney transplant recipients

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ABSTRACT

Introduction: Orthostatic hypotension (OH) is associated with increased morbidity and mortality. The prevalence of OH in the general population is 2–26% and is strongly associated with age. The prevalence of OH in kidney transplant recipients (KTRs) is unknown. The study aimed to investigate the prevalence of OH among KTRs and to identify factors associated with this phenomenon.

Material and methods: The study was designed as a cross-sectional analysis in KTRs at a routine visit in an outpatient department. Fifty KTRs aged 60 ± 12 years (21 female and 29 male) were investigated. The kidney transplant follow-up was 72 ± 63 months (range 3–243). All subjects underwent an orthostatic test (OT). Clinical and laboratory data were also analyzed.

Results: OH was diagnosed in 17 (34%) patients (the OH+ group). KTRs with OH were older (63 ± 9 *vs.* 54 ± 13; p = 0.01) and were more often diabetic (53% *vs.* 24%; p = 0.04) than patients without OH. OH+ patients had higher supine systolic blood pressure (152 ± 23 *vs.* 134 ± 16; p = 0.006) and higher supine pulse rate (75 ± 12 *vs.* 68 ± 10; p = 0.047). A higher percentage of OH+ patients were taking beta-blockers (94% *vs.* 70%; p = 0.048) and calcium antagonists (88% *vs.* 52%; p = 0.01). Pulse rate did not change significantly during the OT in patients with OH, while it increased significantly in patients without OH.

Conclusions: Orthostatic hypotension is a common finding among kidney transplant patients, particularly elderly patients with coexisting diabetes. Awareness of such a high prevalence of OH should encourage physicians to perform the orthostatic test in KTRs. Concomitant pulse rate measurement and analysis of current medications may contribute to a better understanding of OH pathogenesis in an individual patient.

Key words: blood pressure, kidney transplant, orthostatic hypotension, pulse rate

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Introduction

Orthostatic hypotension (OH), a drop in blood pressure after taking a vertical position, is associated with an increased risk of mortality and cardiovascular (CV) events [1–4]. Orthostatic hypotension is defined as a reduction in systolic blood pressure (SBP) of ≥ 20 mmHg or diastolic blood pressure (DBP) of ≥ 10 mmHg within 3 minutes of standing [5]. The prevalence of OH in the general population is 5–26 % and is strongly associated with age [3, 4, 6]. In population-based cohorts, the prevalence of OH ranged from 2% among persons aged 45–49 years, 9.4% among persons 60–64 years [4], 14.8% among persons aged 65–69 years, up to 26% in a group of people aged 85 and older [6]. Among elderly patients in nursing homes and geriatric wards, the prevalence of OH is 50% [7, 8]. It should be, however, noted, that OH is asymptomatic in the vast majority (about 90%) of patients [6]. OH frequently affects patients with neurodegenerative disease, diabetes, hypertension, chronic kidney disease, and chronic heart failure [3, 8, 9]. Autonomic neuropathy seems to be the main cause of OH. Several drugs were also identified to be associated with OH. Orthostatic hypotension is considered a risk predictor of falls, disability, and impaired quality of life, however, clinical data are inconsistent [7, 8, 10]. There is a lack of clinical data regarding the epidemiology of OH among KTRs.

Aim of the study

The study aimed to investigate the prevalence of OH among KTRs and to identify factors associated with this phenomenon.

Material and methods

The study was designed as a cross-sectional analysis. Kidney transplant recipients from the Transplantology Outpatient Department of the Jurasz University Hospital in Bydgoszcz, Poland, were recruited to the study. The study was performed in accordance with the ethical standards of the Declaration of Helsinki (Approval of the local Bioethics Committee KB 798/2019). Informed consent was obtained from each participant. Fifty-six KTRs were asked to participate in the study, 6 patients refused. Fifty KTRs aged 31–75 years (mean ± SD: 60 ± 12) were included in the study. There were 29 male and 21 female patients in the study group. The underlying renal disease was (1) glomerulonephritis in 16 (32%), (2) polycystic kidney disease (ADPKD) in 11 (22%), (3) diabetic nephropathy in 7 (14%), (4) hypertensive nephropathy in 6 (12%), (5) interstitial nephritis (including kidney stone disease and gout nephropathy) in 5 (10%), (6) other or unknown in 5 (10%). Detailed anamnesis including the history of diabetes, hypertension, coronary heart disease, stroke, atrial fibrillation, episodes of falls, or fainting was performed. Fasting blood was collected for laboratory analyses. Patients' charts were analyzed for current medical therapy. An orthostatic test (OT) according to the guidelines of the European Cardiac Society/European Hypertension Society (2018) was performed for each participant [11]. SBP, DBP, and pulse rate (PR) recordings were taken using oscillometric blood pressure monitor Microlife BP B3 AFIB (Microlife AG, Widnau, Switzerland). Figure 1 presents the diagram of the OT performed in a study. All OTs were done between 8.00 and 10.00 A.M.

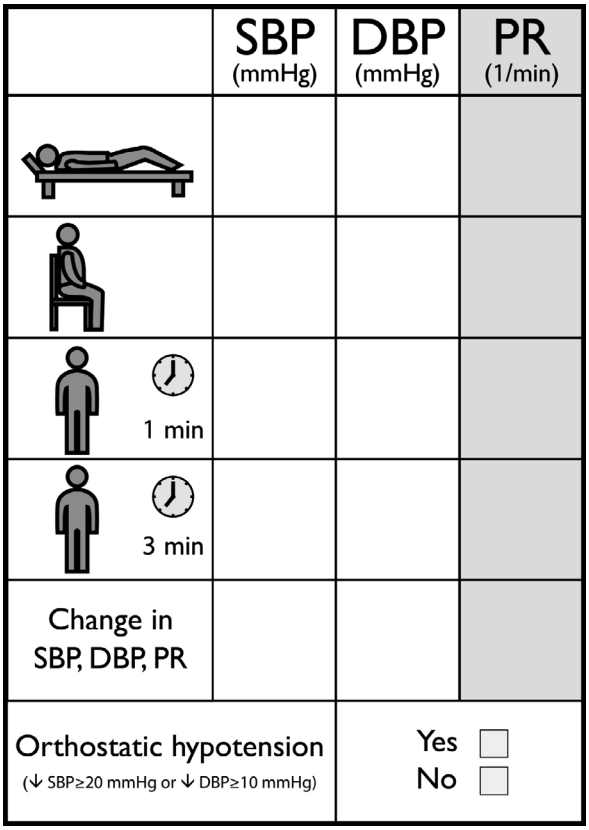

Figure 1. The diagram of orthostatic test with systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) measurements

Laboratory measurements

Laboratory measurements were performed on Abbott Architect ci8200 analyzer using Abbott Laboratories commercial reagents (Abbott Laboratories, Abbott Park, IL, USA). Glomerular filtration rate was estimated (eGFR) using CKD-EPI equation [12].

Statistical analysis

Statistical analysis was performed using the Statistica 13.1 software. The distribution of variables was analyzed using the Shapiro-Wilk test. Normally distributed data are presented as mean ± standard deviation (SD). Not normally distributed data are shown as median and range. Categorical variables are presented as percentages. The comparison between groups was performed using Student's t-test. For not-normally distributed data the Mann-Whitney U-test was used. Qualitative data were compared using χ^2- test. One-way analysis of variance (ANOVA) was used to compare the means in variables with multiple measurements. P-value < 0.05 was considered statistically significant.

Results

OH was diagnosed in 17 (34%) patients (the OH+ group). The clinical and laboratory characteristics of the OH+ group and patients without OH (the OH- group) are presented in Table 1.

KTRs with OH were older (63 ± 9 *vs.* 54 ± 13; p = 0.01) and were more often diabetic (53% *vs.* 24%; p = 0.04). Higher percentage of OH+ patients were taking beta-blockers (94% *vs.* 70%; p = 0.048), calcium antagonist (88% *vs.* 52%; p = 0.01), and statin (77%

Table 1. Characteristics of kidney transplant recipients with orthostatic hypotension (OH+) and without orthostatic hypotension (OH-)

	OH+ (n = 17)	OH- (n = 33)	P-value
Age (years)	63 ± 9	54 ± 13	0.01
Male gender n (%)	9 (53%)	20 (61%)	0.60
Kidney transplant follow-up (months)	56 ± 46	81 ± 69	0.14
Hypertension n (%)	14 (82%)	28 (85%)	0.82
Diabetes n (%)	9 (53%)	8 (24%)	0.04
Coronary heart disease n (%)	2 (11%)	6 (18%)	0.56
Atrial fibrillation n (%)	2 (12%)	4 (12%)	0.97
History of falls n (%)	5 (29%)	7 (21%)	0.52
History of fainting n (%)	7 (41%)	8 (24%)	0.22
History of stroke n (%)	2 (12%)	1 (3%)	0.21
Height (cm)	169 ± 7	172 ± 10	0.34
Body mass (kg)	80 ± 8	79 ± 13	0.62
Body mass index (kg/m^2)	28.0 ± 2.8	26.8 ± 5.0	0.29
Serum creatinine (mg/dL)	1.23 ± 0.52	1.43 ± 0.66	0.26
eGFR (mL/min/1.73m^2)	63 ± 22	58 ± 22	0.45
Hemoglobin (g/dL)	13.4 ± 2.0	13.5 ± 1.6	0.93
Total cholesterol (mg/dL)	188 ± 46	194 ± 39	0.74
LDL-cholesterol (mg/dL)	113 ± 41	125 ± 32	0.45
HDL-cholesterol (mg/dL)	56 ± 16	56 ± 15	0.99
Triglycerides (mg/dL)	146 ± 49	156 ± 73	0.71
Sodium (mmol/L)	141 ± 4	143 ± 3	0.17
Potassium (mmol/L)	4.4 ± 0.5	4.3 ± 0.4	0.44
Uric acid (mg/dL)	7.1 ± 2.2	7.6 ± 1.8	0.59
BUN (mg/dL)	29 ± 12	30 ± 16	0.80
SBP supine (mmHg)	152 ± 23	134 ± 16	0.006
DBP supine (mmHg)	86 ± 10	83 ± 11	0.22
SBP sitting (mmHg)	135 ± 21	137 ± 17	0.53
DBP sitting (mmHg)	81 ± 11	85 ± 12	0.28
SBP standing after 1 minute (mmHg)	128 ± 22	130 ± 17	0.79
DBP standing after 1 minute (mmHg)	77 ± 11	84 ± 11	0.06
SBP standing after 3 minutes (mmHg)	129 ± 24	132 ± 18	0.63
DBP standing after 3 minutes (mmHg)	79 ± 12	86 ± 11	0.06
Pulse rate supine	75 ± 12	68 ± 10	0.047
Pulse rate sitting	78 ± 12	72 ± 11	0.09
Pulse rate standing after 1 minute	81 ± 13	78 ± 11	0.40
Pulse rate standing after 3 minutes	81 ± 12	77 ± 12	0.25
Number of antihypertensive drugs	3,1 ± 0.9	2.6 ± 1.5	0.16
Beta-blocker n (%)	16 (94%)	23 (70%)	0.048
Calcium antagonist n (%)	15 (88%)	17 (52%)	0.01
ACEI n (%)	4 (24%)	14 (42%)	0.19
Sartan n (%)	1 (6%)	3 (9%)	0.69

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Table 1 cont. Characteristics of kidney transplant recipients with orthostatic hypotension (OH+) and without orthostatic hypotension (OH-)

	OH+ (n = 17)	OH- (n = 33)	P-value
Diuretic n (%)	8 (47%)	11 (33%)	0.34
Alfa-blocker n (%)	7 (41%)	13 (39%)	0.90
Other antihypertensives n (%)	1 (6%)	4 (12%)	0.49
Tacrolimus n (%)	14 (82%)	23 (70%)	0.33
Cyclosporine n (%)	2 (12%)	7 (21%)	0.41
Mycophenolate mofetil n (%)	16 (94%)	29 (88%)	0.49
Everolimus n (%)	2 (12%)	1 (3%)	0.22
Azathioprine n (%)	0 (0%)	2 (6%)	0.30
Steroid n (%)	17 (100%)	32 (97%)	0.47
Statin n (%)	13 (77%)	13 (39%)	0.01

ACEI — angiotensin converting enzyme inhibitors; BUN — blood urea nitrogen; DBP — diastolic blood pressure; eGFR — estimated glomerular filtration rate; HDL — high-density lipoprotein; LDL — low-density lipoprotein; SBP — systolic blood pressure

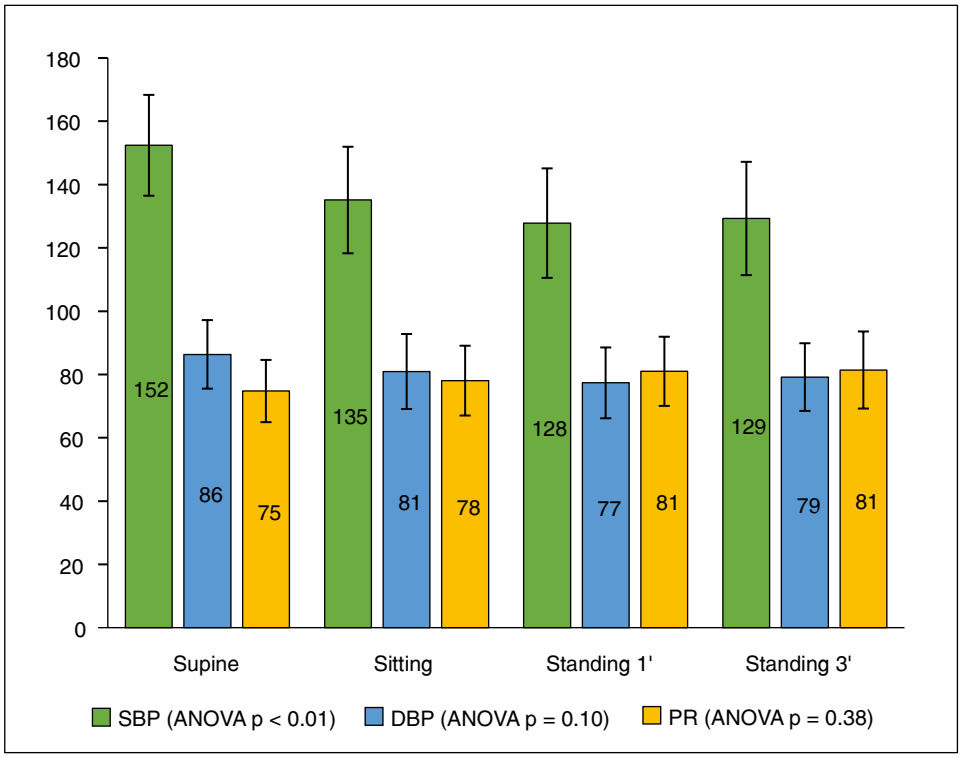

Figure 2. Changes in SBP, DBP, and PR in kidney transplant recipients with orthostatic hypotension (the OH+ Group); DBP — diastolic blood pressure; PR — pulse rate; SBP — systolic blood pressure

vs. 39%; p = 0.01). There were no significant differences in the history of falls (29% *vs.* 21%; p = 0.52) and the history of fainting 41% *vs.* 24%; p = 0.22) between the OH+ and OH- groups. OH+ patients had higher supine systolic blood pressure (152 ± 23 *vs.* 134 ± 16; p = 0.006) and higher supine pulse rate (75 ± 12 *vs.* 68 ± 10; p = 0.047). Pulse rate did not change significantly during the OT in patients with OH, while it increased significantly in patients without OH (ANOVA p < 0.001). Patterns of SBP, DBP and PR changes during the OT in OH+ and OH- patients are shown in Figure 2 and 3, respectively.

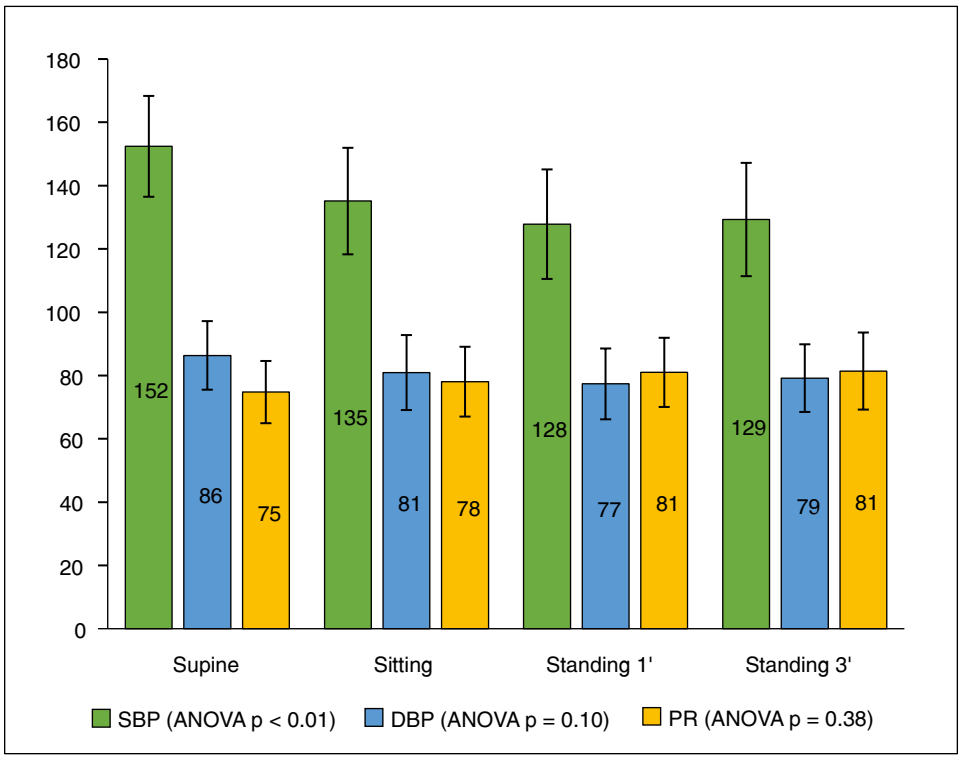

Figure 3. Changes in SBP, DBP, and PR in kidney transplant recipients without orthostatic hypotension (the OH- Group); DBP — diastolic blood pressure; PR — pulse rate; SBP — systolic blood pressure

Discussion

Out of 50 KTRs included in the study, 17 (34%) met the criteria of OH. To our best knowledge, it is the first study documenting such a high prevalence of OH among KTRs. It indicates that the prevalence of OH among KTRs is much higher than in the general population. In a population-based Atherosclerosis Risk in Communities (ARIC) study, the prevalence of OH among the middle-aged population was 4.9%, with 9.4% prevalence among patients aged 60–64 years [4].

The prevalence of OH increases with age [4, 6]. In the general population, OH was more prevalent in patients with diabetes and with hypertension [4]. Chronic kidney disease (CKD) is associated with a high prevalence of OH. In a group of asymptomatic CKD patients (mean age 69 years, eGFR 36 mL/min/1.73m^2), the prevalence of OH was 38% [13]. In the present study, KTRs with OH were older and more often diabetic than patients without OH. There was no difference in the history of falls or fainting between the OH+ and OH- groups. It is in line with earlier studies showing that OH was asymptomatic in the majority of patients [6, 13]. If patients are screened for OH based only on clinical symptoms connected with blood pressure fall after standing, the detected prevalence would underestimate the real prevalence [6, 8]. Our study revealed that every third patient at routine visit presented OH. Thus, it seems reasonable to include an OT into daily clinical practice in KTRs.

In our study different SBP, DBP, and PR patterns were found in the OH+ and OH- groups. In OH+ patients, SBP significantly fell during the orthostatic test, while DBP and PR did not change (Fig. 2). In KTRs without OH, there were no significant changes in SBP and DBP, while PR increased significantly (Fig. 3). Baseline (supine) PR was higher in OH+ patients even though most of them (94%) were being treated with beta-blockers.

Several studies investigating the association between antihypertensive medications and OH found a relationship between antihypertensive therapy per se and specific classes of antihypertensive drugs, like alpha-blockers, diuretics, and beta-blockers [4, 6, 14–16]. Also, nitrates, anti-Parkinson drugs, and tricyclic antidepressants may be involved in OH pathogenesis [8]. In a historical study in KTRs, significant OH was observed after the introduction of alpha-blocker prazosin [14]. Newer data regarding the association between OH and antihypertensive drugs in KTRs is lacking. In our study, it was found that KTRs with OH were more often treated with beta-blockers and calcium channel antagonists. It is of interest that there were no significant differences in alpha-blocker (41% *vs.* 39%, p = 0.90) and diuretic (47% *vs.* 33%; p = 0.34) usage between the OH+ and OH- groups.

In several studies in non-transplant populations association between treatment with beta-blockers and OH was documented [6, 13, 15]. In AASK Trial the risk of OH was higher among patients treated with metoprolol than in patients receiving ramipril or amlodipine [15]. In the ARIC study, there was no difference in the proportion of OH+ and OH- patients using beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, or diuretics among hypertensive subjects. However, in normotensive patients with OH, beta-blockers were more commonly used compared to those without OH [4]. It may suggest that beta-blockers may attenuate the physiological cardiac response to the change from a supine to an upright position.

Autonomic neuropathy, specifically sympathetic autonomous system neuropathy, seems to be the main cause of OH [7, 9, 17]. A change from a lying to standing position normally results in activation of a baroreceptor-initiated, centrally-mediated sympathetic reflex, leading to an increase in peripheral vascular resistance and cardiac acceleration [18]. Gerhardt et al. showed in a group of KTRs that abnormal blood pressure response to active standing up was associated with diminished baroreceptor sensitivity [19].

Elevated resting heart rate (HR) is considered a marker of autonomic dysfunction [18]. Resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients with autonomic neuropathy [18]. The absence of a compensatory PR increase during OTs observed in the present study seems to confirm the role of autonomic neuropathy in OH. On the other hand, exaggerated tachycardia during OTs (increase in heart rate > 15 beats per minute) may suggest volume depletion or other secondary causes rather than a neurogenic form of OH [7, 20].

The authors of the 2018 ESC/ESH Guidelines for the management of arterial hypertension suggest that heart rate should be recorded at the time of blood pressure measurement during the OT [11]. Automatic blood pressure devices allow measuring SBP, DBP, and PR simultaneously. Analysis of PR change during OT gives valuable information about cardiac response to change in body position from supine to standing. Arnold et al. also suggest that measurement of HR during OT allows assessing the integrity of baroreflex function [7]. It is also notable that resting HR is an independent predictor of cardiovascular morbidity and mortality [21].

Research resources on OH among kidney transplant recipients are severely limited. Interestingly, in a study investigating pancreas-kidney transplant (SPKT) recipients, OH developed postoperatively in 28% of patients aged 25–53 years [22]. In a comparative group of diabetic kidney-only transplant recipients, postoperative OH developed in only 1 out of 43 patients (2.3%). In most SPKT patients, postoperative OH was a symptomatic condition and required discontinuation of antihypertensive therapy; most patients also required midodrine for symptomatic relief. In this study, post-transplant OH in SPKT patients resolved within 3 weeks to 9 months in all but 1 patient [22]. The pathogenesis of this transient OH in SPKT is unclear. This type of OH seems to be related not only to pre-transplant neuropathy and post-transplant hypovolemia but also to hyperinsulinemia or vasoactive peptides imbalance associated with pancreas transplantation [22]. Transient postoperative OH in SPKT recipients appears to be a different phenomenon from OH during long-term follow-up in kidney transplant recipients.

It is unclear whether a diagnosis of OH should result in a reduction in antihypertensive treatment. There is a lack of such studies in KTRs. However recent analysis of SPRINT Study patients showed that the prevalence of OH was higher among patients assigned to standard treatment as compared with those assigned to intensive treatment [10]. In this study, OH was not associated with increased risk of CV events, syncope, or injurious falls but was associated with a higher risk of hypotension-related hospitalizations or emergency department visits [10]. The authors of this study concluded that the presence of symptomless OH should not be a reason for the down-titration of antihypertensive medications [10].

The present study has several limitations which arise from a small number of patients and the cross-sectional study design. In our study, the orthostatic test was performed only once in each patient. OT reproducibility (57–79%) is not perfect [23]. As orthostatic response can vary during the day and over time, repeated OTs may result in a better understanding of this phenomenon [8]. Other authors suggest that the most sensitive and consistent measurements are obtained early in the morning when patients are more symptomatic due to nocturnal pressure natriuresis [7, 23]. Thus, in the present study, all OTs were performed in the morning. Higher supine systolic blood pressure found in the OH+ group may also suggest nocturnal hypertension in these patients. Automatic blood pressure monitoring would allow us to analyze this potential association.

All this data confirm the urgent need for further studies investigating the prevalence, pathogenesis, and therapeutic approach to OH among KTRs. Long-term observational studies would elucidate the prognostic significance of OH in kidney transplant recipients.

Conclusions

Orthostatic hypotension is a common finding among kidney transplant patients, particularly elderly patients with coexisting diabetes. Awareness of such a high prevalence of OH should encourage doctors to

perform the orthostatic test in KTR. Concomitant pulse rate measurement and analysis of current medications may contribute to a better understanding of OH pathogenesis in individual patients.

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