

**ADHERENCE TO ANTIHYPERTENSIVE DRUG TREATMENT IN KIDNEY
TRANSPLANT RECIPIENTS: ~~A PILOT STUDY~~**

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Abstract

Purpose. Hypertension is a common cardiovascular co-morbidity after kidney transplantation and contributes to shortened graft and patient survival outcomes. However, by contrast with adherence to immunosuppressive drugs, adherence to antihypertensive treatment in kidney transplant recipients has been seldom explored. The aim of the current study was to assess adherence to antihypertensive drugs in kidney transplant recipients from the Cliniques universitaires Saint-Luc and to look for demographic and clinical ~~and psychological~~ characteristics associated with drug adherence.

Methods. Demographic and clinical data were collected from medical files in a standardized case report form. Blood pressure was measured in the sitting position after 5 minutes rest, using validated oscillometric devices. Drug adherence was assessed by drug dosage in urine using liquid chromatography coupled with tandem mass spectrometry.

Results. Our analysis included 53 kidney transplants recipients (75% of men, mean age: 57.2 ± 12.6 years, time since kidney transplantation: 9.5 ± 7.3 years, blood pressure: $130 \pm 16 / 78 \pm 11$ mmHg on 2.1 ± 1.1 antihypertensive drugs). The proportion of patients showing full drug adherence, partial drug adherence and total non-adherence to antihypertensive drugs was 79% (N=42), 15% (N=8) and 6% (N=3), respectively. Adherent patients did not differ from less or non-adherers in any of analyzed characteristics.

Conclusion. The proportion of patients adhering to antihypertensive drug treatment among kidney transplant recipients appears similar to that reported for immunosuppressive drugs in renal transplanted patients (~70%), but much higher than that observed in patients with drug-resistant hypertension (30-40%). Our results need further confirmation in a large, multicenter, prospective cohort.

Keywords: kidney transplantation, hypertension, drug adherence, antihypertensive treatment, LC-MS/MS

Introduction

Hypertension is a common clinical problem in kidney transplantation, affecting 50% to 80% of kidney transplant recipients (KTRs), and is associated with a shortened graft survival and an increased cardiovascular morbidity and mortality.¹ Detection of antihypertensive drugs in blood and urine with Liquid Chromatography coupled to tandem Mass Spectrometry (LC-MS/MS) is now considered as a gold standard and increasingly used to assess drug adherence in patients with essential hypertension.² However, to our knowledge, this method has not been applied to assess adherence to antihypertensive treatment in KTRs. More generally, ~~in~~^{by} contrast ~~to~~^{with} adherence to immunosuppressive drugs, adherence to antihypertensive treatment in KTRs remains largely unexplored.^{1,3,4}

As non-adherence is frequent in hypertensive patients at large, and a high proportion of KTRs develop hypertension³, it seemed appropriate to assess adherence to antihypertensive drugs in this specific population, and to compare these results with adherence to immunosuppressive drugs.^{5,6}

The objectives of the current study were to assess adherence to antihypertensive drugs in KTRs on antihypertensive treatment followed at the Kidney Transplantation outpatient Clinic of the Cliniques universitaires Saint-Luc (Brussels, Belgium), to compare it to adherence to a frequently used immunosuppressive drug, mycophenolic acid (MPA) and to look for factors associated with drug adherence.

Methods

Study population

In order to be eligible, patients had to be at least 18-year-old, to be on one or more antihypertensive drug and to have an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m (CKD-EPI), in the absence of history of graft arterial stenosis and acute graft

rejection within 3 months before inclusion. Demographic and clinical data were collected from medical files in a standardized case report form on the occasion of the yearly follow-up visit.

~~Furthermore, 5 validated questionnaires were administered to the patients in order to assess different aspects of their psychological profile as well as past traumas and possible subsequent posttraumatic stress disorders (see below).~~² Blood pressure was measured in the sitting position

after 5 minutes rest, using the validated oscillometric device Omron HEM 907 (Omron Health Care, Kyoto, Japan) as recommended.⁷ Three measurements were obtained and the mean blood pressure was used in subsequent analysis. For each patient, a 10 mL-urine sample was collected on the day of signature of the written informed consent. **This was a compromise between the**

ethical need to correctly inform the patient and the necessity to avoid interfering in the medication-taking behaviour. The whole procedure (BP measurement, blood, urine and data collection) was done on the same day and all of the procedure (BP measurement, blood, urines and data collection) was done the same day.² This study is part of a larger research program

investigating the main determinants of drug adherence and on-treatment blood pressure level, approved by the Comité d’Ethique hospitalo-facultaire des Cliniques Universitaires Saint-Luc (Brussels). It was performed according to the principles of the Declaration of Helsinki and its subsequent modifications.

Evaluation of drug adherence

Detection of antihypertensive drugs in the urine was performed on a research basis using a liquid chromatography system coupled with a tandem mass spectrometer as detector (LC-MS/MS). Briefly, an ethyl acetate extraction (1 mL) of 200 µL aliquots of urine was performed after adding internal standards. After mixing and centrifugation the organic phase was evaporated. The dry residue was reconstituted with 100 µL 0.1 % formic acid/acetonitrile (80:20, v/v) and analyzed by LC-MS/MS for 64 antihypertensive drugs and metabolites (including all medications prescribed in this study).⁸ Full drug adherence, partial drug

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adherence and total non-adherence were defined as presence of all, part or none of the prescribed drugs in the urine, respectively. Detection of mycophenolic acid (MPA) was performed in plasma by liquid chromatography coupled with mass spectrometry, as part of routine clinical practice and was reported as “present” or “absent”.⁹

Psychological analysis

~~In order to investigate patients’ psychological profile and past life experience, we used five validated questionnaires exploring dimensions previously associated with drug adherence and drug resistance in patients with refractory hypertension: the Cognitive Emotion Regulation Questionnaire (CERQ) assessing emotion regulation strategies, the Toronto Alexithymia Scale (TAS-20) measuring alexithymia, the Brief Symptom Inventory (BSI) exploring patients’ general psychopathological profile and the Posttraumatic Diagnostic Scale (PDS).¹⁰~~

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, New York). Categorical variables are reported as percentages and continuous data as mean ± standard deviation (SD). Independent t-tests and univariate ANOVAs were used to highlight significant correlations involving categorical variables. Pearson’s (for normally distributed variables) and Spearman’s correlations (for those that were not) were used to study the associations between adherence level ~~and~~ demographic and health-related ~~and psychological~~ variables. Correlations were also run between demographic and health-related ~~and psychological~~ variables and the residuals of systolic and diastolic BP, regressed on the number of antihypertensive drugs per day and adherence level, considered as reflecting the severity of hypertension.^{11,12}

Results

Patient characteristics

Fifty-three patients were enrolled between July 2018 and May 2019. Seventy-five percent were men and 81% were Caucasian. Mean age at enrollment was 57.2 ± 12.6 years, mean time since kidney transplantation 9.5 ± 7.3 years and mean blood pressure $130 \pm 16 / 78 \pm 11$ mmHg. Participants were on 9.4 ± 3.0 drugs including 2.1 ± 1.1 antihypertensive drugs (one antihypertensive drug: 36%; 2 drugs: 32%; 3 drugs or more: 32%). The proportion of patients on different drug classes was the following: RAS-inhibitors: 83%; beta-blockers: 55%; calcium antagonists: 38%; diuretics: 25%; central antihypertensives: 9%. Mean urine protein-creatinine ratio ($\pm$ SD) was 0.17 ± 0.12 g/g. Nineteen percent of patients suffered from type 2 diabetes (Table).

Drug adherence

The proportion of KTRs showing full drug adherence, partial drug adherence and total non-adherence to antihypertensive drugs according to LC-MS/MS was 79% (N=42), 15% (N=8) and 6% (N=3) respectively. In view of the reduced number of patients in the two last categories, in subsequent analysis, patients showing partial non-adherence and total non-adherence were grouped in a single category of poorly adherent patients. Adherent and poorly adherent patients did not differ in terms of demographic and clinical (Table) and psychological (data not shown) characteristics, except for the mean daily number of antihypertensive drugs and the mean daily number of tablets, which were significantly higher in poorly adherent patients (2.7 ± 1.0 vs. 1.9 ± 1.1 , in adherent patients, p -value=.033 and 2.73 ± 1.04 vs. 1.879 ± 0.879 in adherent patients, p -value=.001, respectively).

In addition, 34 out of 50 patients on MPA (68%) were found to be adherent to this medication. The level of patients adherent to both antihypertensive drugs and MPA was further lowered to 58% (n=29). Twenty percent of patients (n=10) were found to be adherent to

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antihypertensive treatment but not to MPA, 10% (n=5) were adherent to MPA but not to anti-hypertensive ~~regimen and~~ regimen and a further 12% (n=6 patients) were non-adherent both to MPA and antihypertensive drugs.

Discussion

We report for the first time the proportion of fully-adherent, partly adherent and non-adherent patients to antihypertensive drugs in KTRs using the state-of-the-art LC-MS/MS method. Overall, the proportion of patients fully adhering to antihypertensive drug treatment in KTRs (79%) was similar to that reported for immunosuppressive drugs in KTRs, both in our study (68% pour MPA) and in the literature (72%)³ and to that documented for antihypertensive drugs in essential hypertensive patients on a mean of 2 drugs (~70%)¹³, but much better than that observed in patients with resistant and difficult-to-treat hypertension (30 to 40%).^{2,10} In view of the large number of drugs prescribed in KTRs (9.4 ± 3.0 in this study), these results may be considered as quite reassuring. However, possibly due to a lack of power, KTRs adherent to antihypertensive treatment did not differ from poor or non-adherers in terms of demographic; ~~or clinical or even psychological~~ characteristics.

Limitations of this study include the relatively small number of participants, monocentric and cross-sectional nature of the study and possible selection bias - the patients who accepted to take part in the study being potentially more likely to adhere to their treatment regimen. Evaluation of drug adherence by LC-MS/MS is mostly qualitative, cannot avoid the so-called “toothbrush effect” and may misdiagnose patients with irregular adherence on long-acting drugs as fully adherent.² Renal function may also have an impact on drug elimination and thus on the results of LC-MS/MS. In particular, adherence level may be overestimated for drugs with predominantly renal excretion, especially in patients with the lowest renal function. ~~Also~~Furthermore, though similar, the method used for evaluation of adherence to antihypertensive drugs and MPA is not identical and dosages were performed in different body fluids (urine and blood, respectively). Finally, though in line with the literature, the results from adherence to MPA, a drug associated with digestive side effects, do not necessarily reflect overall adherence to immunosuppressive regimen.^{1,3}

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Our study paves the way to investigate more in depth drug adherence in KTRs, and hopefully, to identify strategies to enhance it, and therefore to improve prognosis. Future studies should aim at assessing adherence to both antihypertensive and immunosuppressive drugs, using state-of-the art methods in a large and diverse multicenter cohort of KTRs, and to correlate prospectively adherence levels to patient and kidney graft outcomes.

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None

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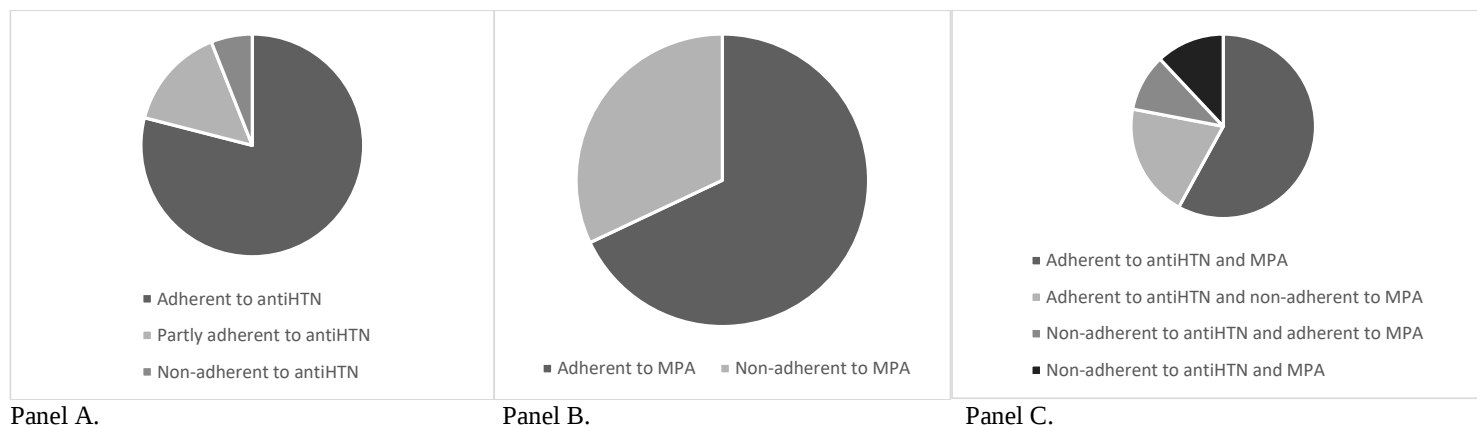
Table: Summary of the main characteristics of kidney transplant recipients

Main characteristics	Proportion (% (N)) or Mean ± SD			
	Total group	Adherent	Poorly adherent	p-value
Number of patients (%)	53	42 (79)	11 (21)	-
Age (years)	57.2 ± 12.6	57.9 ± 11.5	54.7 ± 16.6	.459
Women (%) (N))	26.4 (14)	28.7 (12)	18.2 (2)	.487
Caucasians (%) (N))	81.1 (43)	80.9 (34)	81.8 (9)	.946
Body Mass Index (kg/m²)	26.0 ± 4.1	25.5 ± 4.0	27.7 ± 4.0	.111
eGFR (mL/min/1.73m²)	58 ± 16	59 ± 16	54 ± 18	.373
Time since transplantation (years)	9.5 ± 7.3	9.3 ± 7.3	10.3 ± 7.6	.690
First transplantation (%) (N))	96.2 (51)	97.6 (41)	90.9 (10)	.305
Preemptive transplantation (%(N))	17.0 (9)	16.6 (7)	18.2 (2)	.907
Time on hemodialysis (months)	30 ± 30	30 ± 31	31 ± 29	.924
Live donor (%) (N))	15.1 (8)	14.3 (6)	18.2 (2)	.750
Systolic Blood Pressure (mmHg)	130 ± 16	130 ± 17	133 ± 14	.573
Diastolic Blood Pressure (mmHg)	78 ± 11	76 ± 10	83 ± 14	.064
Urine protein-creatinine ratio (g/g)	0.17 ± 0.12	0.16 ± 0.12	0.22 ± 0.14	.159
Number of antihypertensive drugs prescribed/day	2.1 ± 1.1	1.9 ± 1.1	2.7 ± 1.0	.033
Number of antihypertensive tablets /day	2.01(96 ± 0.92)	1.87(9 ± 0.879)	2.73 ± 1.04	.001
Total number of drugs prescribed/day	0.92	0.879	10.4 ± 3.9	.192
Number of years with treated hypertension (years)	9.4 ± 3.0	9.1 ± 2.6	17.0 ± 12.5	.480
Type 2 diabetes (%) (N))	19.2 ± 11.6	19.8 ± 11.4	9.1 (1)	.358
Dyslipidemia (%) (N))	18.9 (10)	21.4 (9)	63.6 (7)	.699
Smokers (%) (N))	58.5 (31)	57.1 (24)	9.1 (1)	.968
Higher education level (%) (N))	9.4 (5)	9.5 (4)	72.7 (8)	.080
Education level	49.0 (26)	42.8 (18)	0	.615
- Elementary school	2.0 (1)	2.3 (1)	27 (3)	.105
- High school	49.0 (26)	54.7 (23)	73 (8)	.079
- Degree	49.0 (26)	43.0 (18)		
Employment status			36.5 (4)	.966
- Active worker	35.8 (19)	35.8 (15)	0	.462
- Unemployed	3.8 (2)	4.8 (2)	36.5 (4)	.305
- Unable to work	24.6 (13)	21.4 (9)	27.0 (3)	.502
- Retired	35.8 (19)	38.0 (16)	72.7 (8)	.555
Living with a partner (%) (N))	79.2 (42)	80.9 (34)		

eGFR: estimated Glomerular Filtration Rate.

[illegible]

Figure. Distribution of kidney transplant recipients according to drug adherence



Panel A: proportion of kidney transplant recipients (KTRs) fully adherent, partly adherent or non-adherent to antihypertensive drug treatment (antiHTN)
 Panel B: proportion of KTRs adherent or not to mycophenolic acid (MPA)
 Panel C: proportion of KTRs adherent to both antiHTN and MPA, one or none of them.
 For readability, patients partly and totally non-adherent to antihypertensive drug treatment have been grouped in a single category.

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