

Periodic limb movements in sleep are associated with stroke and cardiovascular risk factors in patients with renal failure

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Keywords

cardiovascular risk, dialysis, kidney transplantation, periodic limb movements in sleep, waiting-list for transplantation

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Accepted in revised form 6 August 2011;
received 3 May 2011

DOI: 10.1111/j.1365-2869.2011.00956.x

SUMMARY

Periodic limb movements in sleep (PLMS) is prevalent among dialysed patients and is associated with increased risk of mortality. Our study aimed to determine the prevalence of this disease in a sample of transplanted and waiting-list haemodialysed patients. One hundred transplanted and 50 waiting-list patients underwent polysomnography. Moderate and severe diseases were defined as periodic limb movements in sleep index (PLMSI) higher than 15 and 25 events h⁻¹, respectively. The 10-year coronary heart disease risk was estimated for all patients using the Framingham Score. Moreover, the 10-year estimated risk of stroke was calculated according to the modified version of the Framingham Stroke Risk Profile. PLMS was present in 27% of the transplanted and 42% of the waiting-list group ($P = 0.094$); the proportion of severe disease was twice as high in waiting-list versus transplanted patients (32 versus 16%, $P = 0.024$). Patients with severe disease had a higher 10-year estimated risk of stroke in the transplanted group [10 (7–17) versus 5 (4–10); $P = 0.002$] and a higher 10-year coronary heart disease risk in both the transplanted [18 (8–22) versus 7 (4–14); $P = 0.002$], and the waiting-list groups [11 (5–18) versus 4 (1–9); $P = 0.032$]. In multivariable linear regression models the PLMSI was associated independently with the Framingham cardiovascular and cerebrovascular scores after adjusting for important covariables. Higher PLMSI is an independent predictor of higher cardiovascular and cerebrovascular risk score in patients with chronic kidney disease. Severe PLMS is less frequent in kidney transplant recipients compared to waiting-list dialysis patients.

INTRODUCTION

Periodic limb movements in sleep (PLMS) is a repetitive periodic activity of the anterior tibial muscle resulting in the movement of the big toe and/or ankle. Occasionally, flexion of the knee or the hip can also occur. Polysomnography studies have confirmed that these limb movements are often associated with electroencephalographic arousals, which can

lead to worse subjective and objective sleep quality and may cause impaired daytime functioning, fatigue and sleepiness.

PLMS is common in chronic kidney disease Stage 5 dialysed (CKD5D) patients, with an estimated prevalence of 40–70% among patients on maintenance dialysis (Hanly *et al.*, 2003; Jurado-Gamez *et al.*, 2007; Rijsman *et al.*, 2004) compared to 7–8% in the general population. The Periodic Limb Movement Index (PLMI), i.e. the number of periodic

limb movements per hours during sleep, is higher in haemodialysed compared to the general population, and it is often in the moderate–severe range (Beecroft *et al.*, 2008; Jurado-Gamez *et al.*, 2007; Parker *et al.*, 2005). The only published paper which assessed periodic limb movement before and after transplantation in 18 CKD5_T (CKD5 transplanted, Tx) reported that PLMI was reduced significantly (Beecroft *et al.*, 2008).

It has been suggested that PLMS is associated with increased cardiovascular risk in the general population (Walters and Rye, 2009). Studies have shown an association between PLMS and hypertension as well as congestive heart failure (Hanly and Zuberi-Khokhar, 1996; Javaheri, 2006; Skomro *et al.*, 2009). One possible explanation of this observation is the repetitive sympathetic activation accompanying the PLM events which usually manifest in increased heart rate (Ferrillo *et al.*, 2004; Sforza *et al.*, 1999; Winkelman, 1999) and blood pressure (Allena *et al.*, 2009; Pennestri *et al.*, 2007). The repetitive, long-standing nocturnal sympathetic hyperactivity may, in turn, lead to daytime hypertension. Furthermore, PLMS often accompanies chronic illnesses [e.g. diabetes and renal failure (Hanly and Zuberi-Khokhar, 1996; Jurado-Gamez *et al.*, 2007; Rijsman *et al.*, 2004)] which increase cardiovascular risk (Walters and Rye, 2009). PLMS is associated with obstructive sleep apnoea (OSA), which has also been linked to cardiovascular morbidity and mortality, both in the general population (Young *et al.*, 2008) and in haemodialysed and Tx patients (Masuda *et al.*, 2011; Molnar *et al.*, 2010).

To date, only two studies have examined the association between mortality and PLMS among dialysed patients. Benz *et al.* found that the 20-month survival rate among patients with PLMI <20 was >90% versus 50% among patients with PLMI 20 or higher (Benz *et al.*, 2000). In accord with previous data, higher PLMI predicted mortality during a 48-month-long follow-up in a recent cohort study (Jung *et al.*, 2010). To examine potential confounding, in both studies Cox regression models were applied that included PLMI and one potential confounder at a time, but to date we are not aware of any published study which would have assessed the association between PLMS and cardiovascular risk or mortality using multivariable models, adjusting for multiple clinical and biochemical variables.

Only limited data have been published about the association between PLMS and stroke. Several case reports have described the occurrence of PLMS after cerebrovascular events, but no data have been published about the prospective association of PLMS and stroke. Extrapolation of the published results may suggest a relationship between PLMS versus stroke; however, studies are needed to analyse this potential relationship in detail.

We designed this cross-sectional analysis to examine the association between PLMS and cardio- and cardiovascular risk. Our primary hypothesis was that the presence of PLMS is associated with an increased estimated cardio- and cardiovascular risk both in waitlisted hemodialysis (WL) and

Tx groups. To analyse the association between these factors, we built multivariable linear regression models to adjust for the most important covariables related to cardio- and cardiovascular risk. Our study is the first to use this approach and to control for a large number of potential confounders in order to assess the independent association between PLMS versus the risk of cardiovascular disease and stroke. Furthermore, we determined the prevalence and clinical correlates of PLMS using polysomnography in a sample of stable prevalent Tx patients and a convenience sample of waiting-list dialysed patients (WL). Based on previous reports (Beecroft *et al.*, 2008), we hypothesized that the prevalence of PLMS would be lower in Tx versus WL patients.

METHODS

Sample of patients and data collection

For this study [‘Sleep disorders Evaluation in Patients after kidney Transplantation’ (SLEPT)], potentially eligible patients were selected from all prevalent adult Tx patients (total clinic population; $n = 1214$) who were followed regularly at a single outpatient transplant centre on 31 December 2006. After applying exclusion criteria [previous diagnosis of OSA or PLMS, recent (<3 months) start of dialysis or transplantation, active and acute respiratory disorder, acute infection, hospitalization within 1 month, surgery within 3 months], 1198 patients remained (base population; $n = 1198$) eligible for enrolment. From this base population we randomly selected and approached 150 patients (Tx study sample) using the simple random sampling strategy offered by SPSS version 15.0 (IBM Corporation, Armonk, New York, USA) (Fig. S1). We asked all ($n = 100$) eligible WL dialysis patients who were treated at the four largest dialysis centres in Budapest (listed with the above transplant centre) to participate (WL study sample). Details of medical history such as age, gender, level of education, smoking and aetiology and history of CKD were collected at enrolment.

The primary aim of our study was to assess the association between prevalence of severe PLMI and cardiovascular and stroke risk in our WL and Tx patients. For sample size calculation we used the data of WL and Tx patients with PLMI < 25 h⁻¹. We hypothesized that the calculated risk would be twice as high in patients with PLMI ≥ 25 h⁻¹. We assessed the sample size for WL and Tx patients as 30, 56 for cardiovascular risk and 30 and 79 for stroke risk, respectively.

Our secondary aim was to assess the type of renal replacement therapy associated with presence of severe PLMI in our end-stage renal disease (ESRD) population. Based on previous data we hypothesized that the prevalence of severe PLMI would be 40% in WL haemodialysis patients (Hanly *et al.*, 2003; Jurado-Gamez *et al.*, 2007; Rijsman *et al.*, 2004) and the difference between the two groups was 25%, for which power calculation was performed ($n = 53$ for WL and 79 for Tx patients). Based on the above-mentioned

calculations, our aim was to include at least 150 Tx patients and 100 WL patients, because we expected a refusal rate of 50%.

Laboratory data

Laboratory data [haemoglobin (Hb), C-reactive protein (CRP), intact parathormone (iPTH), serum creatinine, blood urea nitrogen (BUN), serum albumin, serum cholesterol, serum triglyceride, serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol] and single pool (sp) Kt/V (spKt/V) were extracted from the medical records. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula.

Comorbidity

Comorbidity was assessed by the modified Charlson Comorbidity Index (CCI) (Hemmelgarn *et al.*, 2003; Jassal *et al.*, 2005), completed by the most responsible transplant physician. We also collected data about coronary disease and hypertension from the medical records. Atrial fibrillation was diagnosed from the electrocardiogram (ECG) recorded during polysomnography.

Polysomnography

Standard, attended overnight polysomnography was performed in the sleep laboratory at the 1st Department of Internal Medicine, Semmelweis University (SOMNOscreen™ PSG Tele, CE0494; SOMNOmedics GmbH, Germany). The recordings were scored manually by two somnologists (M.Z.M., A.L.). Sleep stages were determined in 30-s epochs according to Rechtschaffen and Kales.

Definition and classification of PLMS

PLMS was defined by the following criteria: limb movement (LM) duration: 0.5–5 s; inter-movement interval: 5–90 s; and separation criteria for LMs occurring in both legs: more than 5 s between onsets. At least four LMs were included in one PLMS cycle (Walters *et al.*, 2007). The PLMI was defined as the number of limb movements per hours during sleep. The patients with PLMS were divided into two categories of severity of PLMS: moderate: $15 \leq \text{PLMI} < 25$ and severe: $\text{PLMI} \geq 25$. The cut-off point of 25 was reported to be clinically relevant in several studies (Rijsman *et al.*, 2004; Skomro *et al.*, 2009). Respiratory related movements were excluded from the PLMI count.

Definition of obstructive sleep apnoea

Apnoea was defined as the absence of airflow for more than 10 s; hypopnoea was defined as a clearly discernible reduction in airflow for more than 10 s associated with an

arousal and/or reduction in oxygen saturation by $> 3\%$. The apnoea–hypopnoea index (AHI) was defined as the number of apnoeas and hypopnoeas per 1 h^{-1} of sleep (American Academy of Sleep Medicine, 1999).

Transplantation- and donor-related data; immunosuppressive therapy

Transplantation-related information included current medications, transplant and dialysis ‘vintage’ (i.e. time elapsed since transplantation or since the initiation of dialysis treatment), time spent on dialysis prior to transplantation, type of transplantation (deceased or living donor), history of acute rejection, human leucocyte antigen (HLA) mismatch, pre-transplant panel reactive antibodies titre (PRA), cold ischaemic time (CIT) and age and gender of donor and history of delayed graft function. Time elapsed since the initiation of the first treatment for end-stage renal disease (ESRD) (cumulative ESRD time) was also calculated. Standard maintenance immunosuppressive therapy generally consisted of calcineurin inhibitor: cyclosporin A microemulsion formulation (CsA) or tacrolimus; combined with mycophenolate-mofetil (MMF); or azathioprine, prednisolone, everolimus or sirolimus.

Framingham risk scores and blood pressure measurement

The 10-year coronary heart disease risk was estimated for all patients using the Framingham score (calculated with LDL-cholesterol) (Wilson *et al.*, 1998). Similarly, the 10-year estimated risk of stroke was calculated according to the modified version of the Framingham Stroke Risk Profile (D’Agostino *et al.*, 1994).

The Framingham Heart Study is a prospective epidemiological cohort study. Subjects returned to the study every 2 years for a detailed medical history, physical examination and laboratory tests. Factors for age, gender, cigarette smoking, blood cholesterol, HDL and LDL cholesterol, blood pressure, left ventricular hypertrophy and diabetes mellitus have been analysed in the Framingham Heart Study for the creation of a model for coronary heart disease (CHD) prediction. Subjects receive a point score based on categorical values of age, total cholesterol, HDL cholesterol, blood pressure, smoking and diabetes.

The Framingham Stroke Risk Profile is based on the following risk factors: age, systolic blood pressure, antihypertensive medication, diabetes, cigarette smoking status, history of cardiovascular disease, atrial fibrillation and left ventricular hypertrophy as determined by ECG. Score sheets were developed for prediction of CHD and stroke risk were developed from the β -coefficients of Cox proportional hazard models, which includes the above-mentioned variables. Point scores are assigned to percentage values which show the risk of coronary heart disease and stroke. We used these percentage values in our analyses.

Ethical approval

The study was approved by the Ethics Committee of the Semmelweis University (4/2007). Patients received detailed verbal and written information about the aims and protocol of the study before enrolment, and signed an informed consent.

Statistical analysis

Statistical analyses were carried out using SPSS version 15.0 software. Results are presented as percentage, mean \pm standard deviation (SD) or medians (interquartile range: IQR). Continuous variables were compared between WL versus Tx recipient patients, and also between patients with versus without severe PLMS, using Student's *t*-test or the Mann–Whitney *U*-test. Categorical variables were analysed with the chi-square test. Spearman's correlation was used to assess the association between PLMI versus continuous variables. To identify factors which were associated independently with the presence of severe PLMS, a logistic regression model was built. The variables entered in the multivariable-adjusted models were selected by theoretical considerations; we included predictors in the models which were known to be associated with PLMS based on external evidence and clinical experience, and which were available in our database. Linear associations between PLMI and Framingham risk score were assessed using fractional polynomials and restricted cubic splines. To assess if PLMI is associated independently with the Framingham risk scores, multivariable linear regression models were built. The variables entered into the multivariable-adjusted models were selected by theoretical considerations; we included predictors in the models which, based on external evidence and clinical experience, were known to be associated with elevated cardiovascular risk and which were available in our database. The risk scores were transformed logarithmically to obtain normal distribution. Variance inflation factors (VIF) were used to indicate collinearity between independent variables. Only two-sided *P*-values were computed and the results were considered statistically significant if *P* was < 0.05 .

RESULTS

Demographic data and baseline characteristics of the sample

Of the 250 eligible patients (Tx study sample + WL study sample, see Methods); 100 individuals, including 50 Tx (33%) and 50 WL (50%) subjects, declined to participate. Consequently, the 'final study sample' included 100 Tx and 50 WL patients (participants) (Fig. S1). Three WL patients were treated with continuous ambulatory peritoneal dialysis and 47 WL patients with intermittent in-centre haemodialysis. There were no significant differences regarding age and gender between participants and those who declined to participate (not shown). The basic characteristics (age, gender, eGFR, haemoglobin, serum albumin) of the 100 participating Tx

patients (Tx study sample) were similar to the characteristics of the total clinic population (not shown).

Baseline characteristics of the Tx and WL patients are shown in Table 1. The two patient groups were similar along most of the parameters analysed. Additionally, we have created subgroups based on GFR of Tx patients and examined baseline characteristics (see Table S1). Six per cent ($n = 3$) of WL patients and 1% ($n = 1$) of Tx patients were taking hypnotics. None of the enrolled patients was treated with dopaminergic agents.

Prevalence and severity of periodic limb movement is sleep in Tx versus WL dialysis patients

The PLMI was similar in the Tx and WL groups (median; IQR: 6.2 (0.7–16) versus 6.2 (0.8–45.1); $P = 0.23$). According to the previously defined criteria, 27% of the Tx and 42% of WL patients had PLMS (PLMI ≥ 15) ($P = 0.094$). The prevalence of moderate PLMS was 11% in the Tx group and 10% in the WL group. The proportion of severe PLMS, however, was significantly higher among WL (32%) versus Tx (16%) patients ($P = 0.034$) (Fig. 1).

Correlates of severe PLMS in the transplanted group

The percentage of males and microarousal index were higher among patients with severe PLMS (PLMI ≥ 25). No other difference regarding sociodemographic, anthropometric and sleep characteristics was observed between patients with and without severe PLMS (Table 2).

Forty-three per cent of the Tx patients had OSA (AHI ≥ 5). PLMI correlated weakly with AHI (Spearman's $\rho = 0.193$; $P = 0.054$), and median AHI appeared to be higher in the group with severe PLMS; however, this difference did not reach statistical significance (median; IQR: 7.6 (2.1–23) versus 2.6 (0.6–13.4); $P = 0.137$).

Correlates of severe PLMS in the dialysed group

Patients with severe PLMS had higher BMI, higher serum triglyceride and LDL levels and the prevalence of iron deficiency was also higher (Table 3).

The prevalence of OSA (AHI ≥ 5) in the WL patient group was 54%. There was no significant correlation between PLMI and AHI (Spearman's $\rho = 0.210$; $P = 0.143$) in the WL group, and similarly there was no difference in AHI between patients with and without severe PLMS (median; IQR: 7.4 (1.6–21) versus 2.6 (0.8–11.8); $P = 0.429$).

Multivariable analysis

Logistic regression analysis was used to determine the independent associations between severe PLMS and the following variables: type of renal replacement therapy, age, gender, presence of diabetes, presence of iron deficiency, AHI and smoking. In this model the type of renal replacement therapy (dialysis versus transplant) was an independent

Table 1 Patient characteristics

	Transplanted (Tx) patients (n = 100)	Waiting-list (WL) patients (n = 50)	P-value
PLMI (events h ⁻¹) (median; IQR)	6.2 (0.7–16)	6.2 (0.8–46)	0.230
Presence of PLMS (%)	27	42	0.094
Male (%)	57	54	0.731
Age (mean±SD) (years)	51 ± 13	50 ± 13	0.599
Level of education (%)			
Primary education or less	21	14	0.213
Skilled workers	15	18	
High school or equivalent university diploma	33	48	
Current smoker (%)	20	20	1
BMI (mean ± SD) (kg m ⁻²)	27 ± 5	25 ± 4	0.058
Ferritin (median; IQR) (ng mL ⁻¹)	196 (74–378)	742 (257–800)	<0.001
Iron deficiency (TSAT <20% and/or ferritin < 100 µg L ⁻¹) (%)	40	25	0.110
Prevalence of hypertension (%)	92	80	0.034
Prevalence of diabetes (%)	19	16	0.822
Charlson Comorbidity Index (median; IQR)	2 (2–3)	3 (2–5)	0.001
Haemoglobin (mean ± SD) (g L ⁻¹)	135 ± 17	116 ± 15	<0.001
Serum albumin (mean ± SD) (g L ⁻¹)	40 ± 3	42 ± 4	0.011
Serum CRP (median; IQR) (mg L ⁻¹)	3.4 (1.4–6)	2.2 (0.7–0.3)	0.417
eGFR (mean±SD) (mL min 1.73 m ⁻²)	52 ± 19	NA	–
spKt/V (mean ± SD)	NA	1.43 ± 0.24	–
Transplant or dialysis ‘vintage’ (median; IQR) (months)	66 (30–113)	34 (16–57)	NA
Cumulative ESRD time (median; IQR) (months)	99 (57–152)	50 (17.5–83.5)	<0.001
Hypnotic drugs (%)	17	22	0.108
Framingham stroke risk (median; IQR) (%)	6 (4–11)	2 (3–10)	0.144
Framingham coronary heart disease based on LDL (median; IQR) (%)	8 (4–15)	5 (2–11)	0.035

PLMI, Periodic Limb Movement in Sleep Index; PLMS, periodic limb movement in sleep; BMI, body mass index; TSAT, transferrin saturation; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; SD, standard deviation; NA, not available; IQR, interquartile range; CRP, C-reactive protein; LDL, low-density lipoprotein; spKtV, single pool (sp) Kt/V.

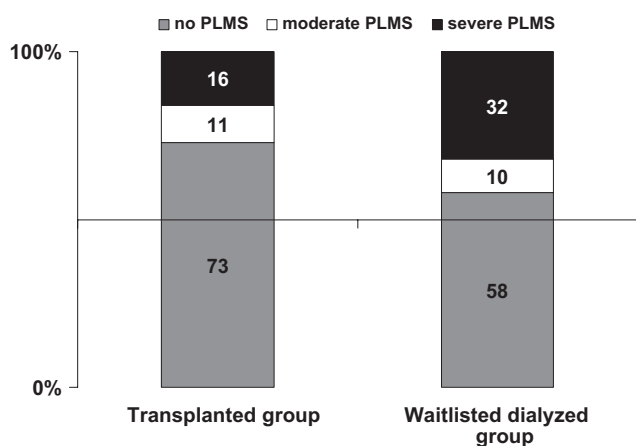


Figure 1. Presence of periodic limb movements in sleep (PLMS) in transplanted group and waiting-list dialyzed group.

predictor of severe PLMS in addition to smoking, male gender and age (Table 4).

Estimated coronary heart disease risk and estimated stroke risk

The 10-year estimated coronary heart disease risk [based on the Framingham score (Wilson *et al.*, 1998)] and the 10-year

estimated stroke risk [based on the modified Framingham stroke risk profile (D'Agostino *et al.*, 1994)] were twofold higher in the severe PLMS group compared to patients without severe PLMS (Table 2) in the Tx group. Both the estimated coronary heart disease (CHD) risk and the estimated stroke risk showed a moderate positive correlation with PLMI (Spearman's rho = 0.265; $P = 0.009$ for CHD and rho = 0.274; $P = 0.006$ for stroke).

Similarly, the estimated 10-year CHD risk was higher in patients with severe PLMS (Table 3), and correlated significantly with the PLMI (Spearman's rho = 0.409; $P = 0.022$) in the WL group. The estimated stroke risk, however, was not associated with the PLMI in this group (not shown).

We assessed the association between Framingham scores and PLMI using restricted cubic splines, which disclose very close similarity between the Tx and the WL groups regarding the association of logarithm of Framingham cardio- and cardiovascular risk scores versus PLMI (Fig. 2). These analyses reveal a similar, linearly increasing, dose–response relationship between the PLMI and the risk scores in both groups.

To assess the independent association between the PLMI versus the Framingham CHD score a linear regression model was built for the total sample (Tx + WL) and Tx as well as WL

Table 2 Patients with and without severe periodic limb movements in sleep (PLMS) in the transplanted group

	PLMI < 25 (n = 84)	Severe PLMS (PLMI ≥ 25) (n = 16)	
Age (mean ± SD) (years)	50 ± 13	55 ± 9	0.138
BMI (mean ± SD) (kg m ⁻²)	26 ± 5	27 ± 4	0.450
Male (%)	50	94	0.001
Transplant 'vintage' (median; IQR) (months)	76 (30–118)	50 (30–98)	0.384
Albumin (mean ± SD) (g L ⁻¹)	40 ± 3	39 ± 3	0.611
Presence of diabetes (%)	15	37	0.075
Haemoglobin (mean ± SD) (g L ⁻¹)	134 ± 17	137 ± 15	0.494
Iron deficiency (TSAT < 20% and/or ferritin < 100 µg L ⁻¹) (%)	38	53	0.392
eGFR (mean ± SD) (mL min 1.73 m ⁻²)	53 ± 18	48 ± 21	0.358
Hypertension (%)	93	87	0.611
Current smoker (%)	19	25	0.733
Charlson comorbidity index (median; IQR)	2 (2–3)	2 (2–3)	0.404
Prevalence of coronary heart disease (%)	9	0	0.348
Prevalence of congestive heart failure (%)	9	0	0.348
Prevalence of peripheral vascular disease (%)	9	3	0.402
Prevalence of cerebrovascular disease (%)	2	0	1
Prevalence of atrial fibrillation (%)	2	6	0.411
Triglyceride (median; IQR) (mmol L ⁻¹)	1.6 (1.2–2.2)	2.2 (1.5–3)	0.076
LDL-cholesterol (median; IQR) (mmol L ⁻¹)	3.2 (2.7–3.7)	3.1 (2.6–3.4)	0.315
HDL-cholesterol (median; IQR) (mmol L ⁻¹)	1.4 (1.1–1.6)	1.1 (0.9–1.3)	0.017
Ferritin (median; IQR) (ng mL ⁻¹)	206 (75–411)	165 (72–334)	0.736
Framingham stroke risk (median; IQR) (%)	5 (4–10)	10 (7–17)	0.002
Framingham Coronary Heart Disease based on LDL (median; IQR) (%)	7 (4–14)	18 (8–22)	0.002
Apnoea–hypopnoea index (event h ⁻¹) (median; IQR)	2.6 (0.6–13.4)	7.6 (2.1–23)	0.137
Microarousal index (event h ⁻¹) (median; IQR)	15 (9–23)	24 (15–41)	0.008
Percentage of Stage 1 (%)	9 (5–14)	12 (7–18)	0.089
Percentage of Stage 2 (%)	44 (33–53)	45 (30–43)	0.785
Percentage of deep sleep (%)	11 (7–18)	11 (5–16)	0.529
Percentage of REM (%)	12 (8–17)	14 (6–20)	0.446
Sleep efficiency (%)	80 (72–87)	82 (62–88)	0.292
Stage shift index (event h ⁻¹) (median; IQR)	18 (12–29)	19 (13–33)	0.888

PLMI, Periodic Limb Movement in Sleep Index; SD, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein; REM, rapid eye movement.

separately (Tables 5–7). In the model for the total sample the PLMI was associated independently with log-transformed Framingham CHD score ($\beta = 0.222$; $P = 0.004$; Table 5). In the WL group PLMI showed a similarly strong relationship with Framingham CHD score ($\beta = 0.357$; $P = 0.015$, Table 6); in the Tx group the model disclosed a clear trend between two variables ($\beta = 0.157$; $P = 0.090$; Table 7).

In the similar linear regression model in the total sample the PLMI was also associated significantly with the log-transformed Framingham stroke risk score, even after adjusting for the above-mentioned covariables ($\beta = 0.154$; $P = 0.031$; Table S2). In WL patients PLMI is related to Framingham stroke risk score ($\beta = 0.312$; $P = 0.033$; Table S3), but in the Tx group did not reach statistical significance ($\beta = 0.098$; $P = 0.234$; Table S4).

We assessed the potential interaction of treatment modality (i.e. dialysis or transplantation) on the association between PLMI versus the risk scores to examine whether the two groups can be combined for the above-mentioned analysis, and no interactions were detected (P -value for

the interaction term was $P = 0.333$ for Framingham cardiovascular risk and $P = 0.106$ for Framingham stroke risk).

DISCUSSION

Our study is the first, to our knowledge, to analyse the complex association between PLMS and cardio- and cardiovascular disease in a relatively large sample of WT haemodialysed and kidney transplanted patients using standard polysomnography. Importantly, we found that PLMS is associated independently with increased estimated cardio- and cardiovascular risk in these populations, albeit in the Tx population a clear trend can be recognized principally. The point estimate suggests an association, and it is likely that with more patients the associations would have been significant. The apparent lack of association between PLMI and cardio- and cardiovascular risk in the Tx group could also be explained, in part, by the relatively fewer severe PLMS cases in this group. We placed great emphasis on building multivariable linear regression models to demonstrate that

Table 3 Patients with and without severe periodic limb movements in sleep (PLMS) in the dialysed group

	PLMI < 25 (n = 34)	Severe PLMS (PLMI ≥ 25) (n = 16)	
Age (mean ± SD) (years)	49 ± 14	53 ± 11	0.255
BMI (mean ± SD) (kg m ⁻²)	24 ± 5	27 ± 5	0.045
Male (%)	47	69	0.225
Dialysis 'vintage' (median; IQR) (months)	32 (16–57)	46 (14–63)	0.739
Albumin (mean ± SD) (g L ⁻¹)	42 ± 5	42 ± 3	0.516
Presence of diabetes (%)	9	31	0.092
Haemoglobin (mean ± SD) (g L ⁻¹)	115 ± 15	119 ± 13	0.300
Iron deficiency (TSAT < 20% and/or ferritin < 100 µg L ⁻¹) (%)	12	60	0.006
spKt/V (median; IQR)	1.4 (1.2–1.7)	1.32 (1.2–1.5)	0.238
Hypertension (%)	77	88	0.468
Current smoker (%)	12	38	0.056
Charlson comorbidity index (median; IQR)	3 (2–4)	3 (2–5)	0.485
Prevalence of coronary heart disease (%)	15	25	0.442
Prevalence of congestive heart failure (%)	9	0	0.542
Prevalence of peripheral vascular disease (%)	15	19	0.699
Prevalence of cerebrovascular disease (%)	6	6	1
Prevalence of atrial fibrillation (%)	3	6	0.542
Triglyceride (median; IQR) (mmol L ⁻¹)	1.6 (0.9–2.3)	2.32 (1.6–3.2)	0.042
LDL-cholesterol (median; IQR) (mmol L ⁻¹)	1.8 (1.4–2.9)	3.14 (2.6–3.3)	0.015
HDL-cholesterol (median; IQR) (mmol L ⁻¹)	1.1 (1–1.2)	0.99 (0.9–1.2)	0.272
Ferritin (median; IQR) (ng mL ⁻¹)	796 (303–835)	310 (129–762)	0.078
Framingham stroke risk (median; IQR) (%)	5 (2–9)	6 (5–11)	0.173
Framingham Coronary heart disease based on LDL (median; IQR) (%)	4 (1–9)	11 (5–18)	0.008
Apnoea–hypopnoea index (event h ⁻¹) (median; IQR)	2.6 (0.8–11.8)	7.4 (1.6–21)	0.429
Microarousal index (event h ⁻¹) (median; IQR)	21 (13–28)	22 (14–41)	0.382
Percentage of Stage 1 (%)	10 (8–14)	12 (7–18)	0.394
Percentage of Stage 2 (%)	36 (28–43)	38 (30–43)	0.533
Percentage of deep sleep (%)	13 (8–19)	11 (5–16)	0.253
Percentage of REM (%)	11 (7–17)	12 (6–20)	0.884
Sleep efficiency (%)	75 (66–84)	75 (62–88)	0.677
Stage shift index (event h ⁻¹) (median; IQR)	27 (21–30)	22 (13–33)	0.519

PLMI, Periodic Limb Movement in Sleep Index; IQR, interquartile range; REM, rapid eye movement; BMI, body mass index; SD, standard deviation; TSAT, transferrin saturation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; spKtV, single pool (sp) Kt/V.

PLMS is independent predictor of cardio- and cardiovascular risk even after adjusting for other important risk factors. Although we clearly cannot claim causality between PLMS and cardiovascular risk, together with the published evidence our results contribute to the question of whether treating PLMS successfully would reduce cardiovascular risk.

In our sample about one-third of the participants had PLMS. The prevalence of severe PLMS was significantly lower in Tx patients. Furthermore, we also demonstrated that age, male gender, current smoking and dialysis treatment (compared to transplant) are risk factors for PLMS in dialysed and transplant patients.

Patients in our sample with severe PLMS had higher estimated cardiovascular and cerebrovascular risk scores in the Tx group and higher cardiovascular risk score in the WL group compared to patients with lower PLMI. It has been established previously that PLMS, even without microarousals, leads to sympathetic activation and increased heart rate variability. In addition, PLMS may contribute to diminish the nocturnal 'dipping' of blood pressure and pulse rate. This and

the sympathetic overactivity associated with PLMS may contribute to the pathomechanism of cardiovascular and cerebrovascular diseases. Potentially leading to transient nocturnal rise of heart rate and arterial blood pressure, PLMS may contribute to this association (Sforza *et al.*, 1999).

Previously reported evidence suggests that patients with PLMS have sympathetic overactivity during sleep (Ferrillo *et al.*, 2004). Due to this effect, long-term PLMS might be associated with higher daytime blood pressure in the general population (Espinar-Sierra *et al.*, 1997). Patients with versus without severe PLMS had similar blood pressure in our study. A possible explanation for this could be the very high prevalence of hypertension and the fact that the majority of dialysed and Tx patients received antihypertensive treatment.

Previous studies have repeatedly suggested an association between PLMS and OSA. Thus, the well-known association between OSA and cardiovascular risk may contribute to the relationship between PLMS and cardiovascular risk. In our sample, however, there was only a weak correlation

Table 4 Binary logistic regression model in the total population [dependent variable: severe periodic limb movements in sleep (PLMS)]

	Odds ratio (OR)	95% Confidence interval for OR		P-value
		Lower	Upper	
Gender (male)	15.302	3.084	75.932	0.001
Age (1-year increase)	1.046	1.001	1.094	0.047
Diabetes (presence)	0.395	0.113	1.384	0.147
BMI (1 kg m ⁻² increase)	1.022	0.906	1.152	0.723
Current smoker (smoker)	3.916	1.035	14.828	0.044
Type of renal replacement therapy (dialysis)	4.113	1.265	13.489	0.019
Presence of iron deficiency (TSAT <20% and/or ferritin < 100 µg L ⁻¹) (%)	2.558	0.873	7.463	0.087
Apnoea-hypopnoea index (1 event h ⁻¹ decrease)	0.902	0.961	1.023	0.602

Nagelkerke *R* = 0.388. BMI, body mass index; TSAT, transferrin saturation.

between AHI and PLMI in the Tx group, and no association was detected in the dialysed group. This could possibly be explained by the potential disease-modifying effect of uraemia. The association between PLMI and the Framingham scores remained significant even after adjusting for AHI in addition to other important covariables in the multivariable models. Importantly, these findings suggest that PLMS is not simply a marker of OSA in this patient population, and it may

carry an independent cardiovascular risk component in transplant and dialysed patients. In our study, sleep macrostructure was similar in patients with versus without PLMS similar to the epidemiological study by Scofield *et al.* (2008), which involved the most patients to date.

Only limited information has been published about the epidemiology of PLMS in patients on chronic haemodialysis (Hanly *et al.*, 2003; Jurado-Gamez *et al.*, 2007; Rijsman *et al.*, 2004). Beecroft *et al.* reported that the PLMI was decreased significantly after transplantation in a substantial proportion of the patients (Beecroft *et al.*, 2008). We also found a trend towards different prevalence of PLMS in the Tx and WL groups, but this difference did not reach statistical significance. It is possible that this is due to the relatively low power of our analysis. In the study by Beecroft *et al.* PLMS improved in all patients after transplantation. It is possible that more severe PLMS improves more significantly with transplantation, while less severe PLMS may not change. This assumption is compatible with our results, as we also found that severe PLMS was twice as frequent in dialysed patients as in the Tx group. The main difference between our study and that by Beecroft and colleagues is that our patients had a longer median transplantation vintage (66 months versus 5 months). A potential explanation for the observed difference could be that PLMS improves immediately after transplantation, but the disorder gradually returns subsequently, as has been suggested previously for restless legs syndrome (Winkelmann *et al.*, 2002). Importantly, however, transplant vintage was not associated with the severity of PLMS in our sample.

Although previous studies did not show an association between PLMS and age in ESRD populations (Benz *et al.*,

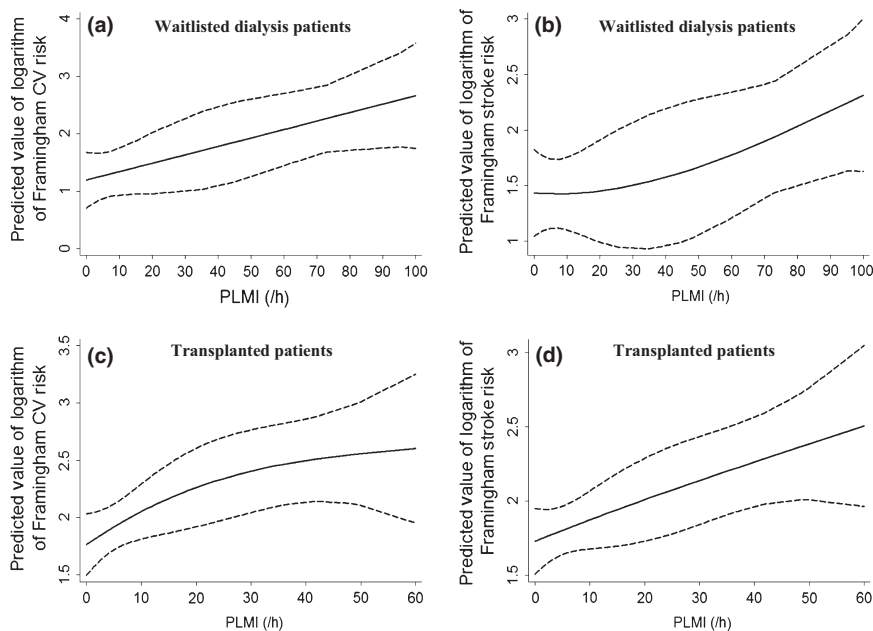


Figure 2. The association of PLMI and logarithm of Framingham cardiovascular and stroke risk in the waitlisted dialysis (WL) and transplanted (Tx) populations.

Table 5 Linear regression model in the total population (dependent variable: logarithm of Framingham cardiovascular risk)

	B	Beta	95% Confidence interval for B		P-value
			Lower	Upper	
PLMI (1 h ⁻¹ increase)	0.007	0.222	0.002	0.012	0.004
Type of renal replacement therapy (transplantation)	0.511	0.227	0.109	0.913	0.013
Haemoglobin (1 g L ⁻¹ increase)	0.002	0.033	-0.008	0.011	0.703
Albumin (1 g L ⁻¹ decrease)	0.066	0.253	0.025	0.107	0.002
Gender (male)	0.531	0.271	0.218	0.844	0.001
AHI (1 event h ⁻¹ increase)	0.013	0.197	0.003	0.023	0.010
Charlson Comorbidity Index (1 increase)	0.155	0.245	0.061	0.249	0.001

Adjusted R^2 : 0.356. AHI, apnoea-hypopnoea index; PLMI, Periodic Limb Movement in Sleep Index.

Table 6 Linear regression model in the waitlisted dialysis (WL) group (dependent variable: logarithm of Framingham cardiovascular risk)

	B	Beta	95% Confidence interval for B		P-value
			Lower	Upper	
PLMI (1 h ⁻¹ increase)	0.009	0.357	0.002	0.016	0.015
AHI (1 event h ⁻¹ increase)	0.027	0.343	0.002	0.051	0.034
Haemoglobin (1 g L ⁻¹ decrease)	0.001	0.015	-0.020	0.022	0.917
Albumin (1 g L ⁻¹ decrease)	0.041	0.148	-0.059	0.141	0.411
Charlson Comorbidity Index (1 increase)	0.182	0.296	0.003	0.361	0.046
Gender (male)	1.059	0.492	0.339	1.779	0.006

Adjusted R^2 : 0.488. AHI, apnoea-hypopnoea index; PLMI, Periodic Limb Movement in Sleep Index.

2000), the relationship is well documented in the general population. Increasing age was associated with the presence of severe PLMS in our sample, which included more dialysed and transplant patients than previous published studies. Furthermore, we focused on severe PLMS, and this may

Table 7 Linear regression model in the transplanted (Tx) group (dependent variable: logarithm of Framingham cardiovascular risk)

	B	Beta	95% Confidence interval for B		P-value
			Lower	Upper	
PLMI (1 h ⁻¹ increase)	0.006	0.157	0.000	0.013	0.090
AHI (1 event h ⁻¹ increase)	0.011	0.178	0.000	0.022	0.058
Haemoglobin (1 g L ⁻¹ increase)	0.005	0.090	-0.006	0.016	0.378
Albumin (1 g L ⁻¹ decrease)	0.086	0.318	0.038	0.135	0.001
Charlson Comorbidity Index (1 increase)	0.140	0.212	0.024	0.255	0.018
Gender (male)	0.350	0.188	-0.037	0.738	0.076

Adjusted R^2 : 0.294. AHI, apnoea-hypopnoea index; PLMI, Periodic Limb Movement in Sleep Index.

have increased the sensitivity of our analysis. Interestingly, we found that severe PLMS was associated independently with male gender. Previous studies did not report gender differences regarding PLMS among dialysed patients (Benz *et al.*, 2000; Jurado-Gamez *et al.*, 2007; Parker *et al.*, 2005; Rijsman *et al.*, 2004). The explanation for this observation is not immediately obvious. Dialysed patients are generally older; they have substantially more comorbidities and take more medications than individuals in the general population. Some of these factors, or potentially other characteristics related to uraemia, may contribute to the differences in the associations observed between dialysed patients compared to the general population.

To our knowledge, this polysomnographic study has enrolled the largest sample of Tx and dialysed patients. Furthermore, we measured a large number of important sociodemographic and clinical covariables that make our analyses more reliable. Finally, we enrolled comparable groups of WL and Tx patients to assess and compare the epidemiology of PLMS in these patient groups.

Limitations of this report, however, should also be noted. The cross-sectional design precludes any directional or causal conclusions. Patients were exclusively Caucasians, and they were enrolled from a single centre; therefore, our results are not to be generalized without further considerations. Furthermore, the Framingham risk prediction index might be skewed in patients with kidney failure. When we were planning this study there were no available data about the prevalence of PLMS in Tx population using polysomnography, therefore we had little information to use for sample size considerations. Due to the expensive nature of the method and the burden it imposes on the patients, feasibility

was a major concern. This study had power to detect a 25% difference in the prevalence of PLMS (90% power) between the WL and Tx groups. To detect 15% difference with 90% power, approximately 500 patients would have been necessary.

Finally, a substantial proportion of both WL and Tx patients declined to participate. We cannot rule out that symptomatic patients were more likely to accept the burden of polysomnography, whereas 'good sleepers' may have opted to avoid this test. This type of selection bias affects all studies of sleep disorders based on polysomnography, and refusal rate was similar in other studies using PSG in the ESRD population (Unruh *et al.*, 2006). Although we did not find any difference between participants and non-participants, it is therefore unlikely that the high refusal rate would have distorted our results significantly; the bias that might have been caused by refusal cannot be ruled out completely. This potential bias, however, does not invalidate our findings about the association between PLMS and increased cardio- and cerebrovascular risk in the Tx population.

In our cross-sectional study we found an independent association between the severity of PLMS (PLMI) and the risk of cardiovascular and cerebrovascular disease. Furthermore, we found that severe PLMS is less frequent in stable prevalent kidney transplant recipients compared to WL dialysis patients. Further studies are needed to analyse the association between PLMS and cardio- and cerebrovascular morbidity in the general population to analyse if PLMS is also an independent risk factor for stroke and cardiovascular disease.

ACKNOWLEDGEMENTS

The authors thank the patients and the staff in the Department of Transplantation and Surgery, Semmelweis University Budapest. This study was supported by grants from the National Research Fund (OTKA) (F-68841; KTIA-OTKA-EU 7KP-HUMAN-MB08-A-81231), ETT (206/09), the Hungarian Kidney Foundation, Hungarian Society of Hypertension, Hungarian Society of Nephrology and the Foundation for Prevention in Medicine. This paper was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (Marta Novak and Miklos Zsolt Molnar). M.Z.M. received grants from the National Developmental Agency (KTIA-OTKA-EU 7KP-HUMAN-MB08-A-81231) from the Research and Technological Innovation Fund, and was also supported by Hungarian Kidney Foundation. The research by M. Novak has been supported by an unrestricted research grant from Canadian Home Healthcare Inc. and the Center for Integrative Mood Research, Toronto, Canada. The authors thank Dr Arthur Walters for the critical reading of this manuscript.

DECLARATIONS OF INTEREST

Zoltan Kiss is employed by Amgen Ltd, Hungary. The other authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flowchart of the patient selection.

Table S1. Subgroups based on estimated glomerular filtration rate (eGFR) in the transplantation (Tx) group.

Table S2. Linear regression model in the total population (dependent variable: logarithm of Framingham stroke risk).

Table S3. Linear regression model in the waitlisted hemodialysis group (dependent variable: logarithm of Framingham stroke risk).

Table S4. Linear regression model in the transplantation (Tx) group (dependent variable: logarithm of Framingham stroke risk).

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