Sleep Disorders in Patients with Chronic Kidney Disease

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University of Toronto, Canada
Why sleep?

My wife is a sleep specialist …
• Sleep – significance
• Sleep disorders in CKD

• Restless legs syndrome (RLS)/Periodic leg movements in sleep (PLMS)
• Sleep disordered breathing - Obstructive sleep apnea syndrome (OSAS)
Why do we sleep?

Repair and Restoration Theory

- sleep enables the body and brain to repair after activity during the day – homeostatic balance
- memory

- Sleep deprivation leads to irritability, impaired concentration and hallucinations
C. R. Soldatos & T. J. Paparrigopoulos

International Review of Psychiatry, August 2005; 17(4): 213–228
Consequences of Chronic Sleep Deprivation

Sleep is a vital and necessary function, and sleep needs (like hunger and thirst) must be met.
• 40-70 million Americans experience either chronic or intermittent sleep-related problems.

• Untreated sleep disorders have a profound impact nationally in terms of reduced quality of life, lower productivity, increased morbidity and mortality, and decreased public safety.

• Lack of awareness among health care professionals and the public.
Cytokines and sleep

Pro-inflammatory cytokine
Anti-inflammatory cytokine

Muramyl peptides, LPS and sleep deprivation

IFN-γ

IL-10
TNF-receptor fragment
TNF-specific antibody
IL-1R1
IL-4
IL-10
IκB
IL-6
IL-15
IL-18

TNF
IL-1β
NF-κB
TNF antagonists
IL-β-specific antibody
IL-4
IL-13

IL-1R1
IL-10
CRH

IL-1R1
IL-10
CRH

TNF antagonists
IL-β-specific antibody
IL-4
IL-13

GH
Prolactin
GHRH

Cortisol
ACTH

IL-6

Slow-wave sleep
Sleep and the Cardiovascular System

- Sleep deprivation increases concentrations of cytokines and C-reactive protein
- This inflammation can lead to endothelial damage, leading to possible stroke or heart disease
- Blood pressure and heart rate are higher following sleep deprived nights (Voelker, 1999)
- Sleep deprivation increases risk of heart disease in women (Josefson, 2003)
SLEEP TIME AND HYPERTENSION

The graph shows the percentage of women and men who sleep for different durations. The x-axis represents the number of hours slept, with categories for <5, 5-6, 6-7, 7-8, and >8 hours. The y-axis represents the percentage (%). The data indicates that a significant portion of the surveyed group sleeps for less than 5 hours, with a notable difference between women and men.
Sleep in CKD
Sleep disorders in CKD – why is it important?

- Sleep problems are one of the most common complaints of patients in the dialysis unit.
- Sleep Apnea Syndrome (SAS) may contribute to the pathogenesis of hypertension, CV morbidity.
- Sleep disorders may impair quality of life.
- Poor sleep is a predictor of morbidity and mortality in this patient population.
- Sleep disorders are treatable – successful treatment may improve clinical outcomes.
Sleep disorders in dialysis patients (30-80%)

- **Insomnia**
  - 4-29% vs 15-70%

- **Sleep apnea syndrome (SAS)**
  - 2-4% vs 20-70%

- **Restless legs syndrome (RLS)**
  - 5-15% vs 15-80%

Little is known about sleep problems in „predialysis” and transplanted patients
Factors contributing to sleep disturbances in patients on dialysis

Diagnostic tools to detect sleep problems

- Clinical interview
- Sleep diaries
- Self administered questionnaires
  - Insomnia: Pittsburgh Sleep Quality Index, Athen Insomnia Scale
  - SAS: Berlin Questionnaire
  - RLS: Restless Legs Syndrome Questionnaire
  - Epworth Sleepiness Scale
- Actigraphy
- Polysomnography (SAS, PLMS)
  - MSLT, MWT – daytime effects
Polysomnography

- neurophysiologic variables (electrooculography, EEG, submental myogram) – sleep stages
- Measurement of resp. effort
- Art. O2 sat., pCO2 – transdermal pulsoxymetry
- ECG
- Limb movements
Prevalence of sleep disorders in Hungarian dialysis and transplanted patients

*: P<0.001, Khi-square test
Sleep problems and renal function in transplant patients (n=920)

![Graph showing prevalence of different sleep problems across CKD stages](image-url)
Restless legs syndrome
Restless legs syndrome (RLS)

• Restless legs syndrome (RLS) is characterized by an urge to move the legs that is often hard to resist and is usually but not always associated with disagreeable leg sensations

• Main symptoms:
  – 1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
  – 2. The unpleasant sensations begin or worsen during rest or inactivity
  – 3. The unpleasant sensations are partially or totally relieved by movement
  – 4. The unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night
Restless Legs Syndrome

Predictors, etiology

• Altered CNS dopamin metabolism
• Iron deficiency (cerebral versus peripheral)
• Uremia – uremic toxins?
• Anemia
• Neuropathy

Consequences

• Fragmented sleep, „intitation” insomnia
• Fatigue, tiredness
• Daytime sleepiness
• Impaired QoL
• Incr. mortality?
• Prevalence of RLS: 12-20% in dialysed\textsuperscript{1,2} and 4.5% in kidney transplanted populations\textsuperscript{3}

• RLS is associated with increased risk of insomnia and impaired quality of life (QoL) in dialysed and transplanted patients\textsuperscript{4}

\textsuperscript{1} Winkelman et al. (1995)
\textsuperscript{2} Mucsi et al. (2004)
\textsuperscript{3} Molnar et al. (2005)
\textsuperscript{4} Unruh et al. (2004)
Table 3. Adjusted Hazards of Severe Symptoms of Restless Legs and by Category of Restless Legs Symptom

<table>
<thead>
<tr>
<th>Severe Restless Legs Symptoms</th>
<th>Category of Restless Legs Symptom</th>
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</thead>
<tbody>
<tr>
<td>Unadjusted hazard</td>
<td>1.31 (1.00-1.73)</td>
</tr>
<tr>
<td>Model 1, adjusted for age and race</td>
<td>1.42 (1.07-1.87)</td>
</tr>
<tr>
<td>Model 2, model 1 and adjusted for ICED, Karnofsky</td>
<td>1.39 (1.05-1.84)</td>
</tr>
<tr>
<td>Model 3, model 2 adjusted for clustering of clinics</td>
<td>1.39 (1.08-1.79)</td>
</tr>
</tbody>
</table>

Unruh et al; AJKD; 2004

Fig 2. Crude cumulative mortality according to severe symptoms of restless legs.
Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis

Istvan Mucsi\textsuperscript{1,3}, Miklos Zsolt Molnar\textsuperscript{1,2,4}, Csaba Ambrus\textsuperscript{2,4}, Lilla Szeifert\textsuperscript{1}, Agnes Zsofia Kovacs\textsuperscript{1}, Rezső Zoller\textsuperscript{1}, Szabolcs Barótfi\textsuperscript{1}, Adam Remport\textsuperscript{5} and Marta Novak\textsuperscript{1,6}

Restless Legs Syndrome in Patients After Renal Transplantation

Miklos Zsolt Molnar, MD, Marta Novak, MD, Csaba Ambrus, MD, Lilla Szeifert, Agnes Kovacs, Judit Pap, Adam Remport, MD, and Istvan Mucsi, MD, PhD

<table>
<thead>
<tr>
<th>Table 2. Characteristics of Patients With or Without RLS in the Tx Group</th>
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</thead>
<tbody>
<tr>
<td>RLS (n = 39)</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
</tr>
<tr>
<td>Number of comorbid conditions, median (range)</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Cyclosporin A</td>
</tr>
<tr>
<td>Tacrolimus</td>
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<tr>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>Imuran</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
</tr>
<tr>
<td>Serum Hb (g/dL)</td>
</tr>
<tr>
<td>Serum transferrin (mg/dL)</td>
</tr>
<tr>
<td>Iron deficiency TSAT&lt;20%</td>
</tr>
<tr>
<td>Time since transplantation (mo)</td>
</tr>
</tbody>
</table>

American Journal of Kidney Diseases, Vol 45, No 2 (February), 2005; pp 388–396
Restless legs syndrome, insomnia, and quality of life after renal transplantation

Miklos Zsolt Molnar\textsuperscript{a,b,c}, Marta Novak\textsuperscript{a,d}, Lilla Szeifert\textsuperscript{a}, Csaba Ambrus\textsuperscript{b,c}, Andras Keszei\textsuperscript{e}, Agnes Koczy\textsuperscript{a}, Anett Lindner\textsuperscript{a}, Szabolcs Barotfi\textsuperscript{f}, Andras Szentkiralyi\textsuperscript{a}, Adam Remport\textsuperscript{g}, Istvan Mucsi\textsuperscript{h,i,*}

Restless Legs Syndrome and Mortality in Kidney Transplant Recipients

Miklos Zsolt Molnar, MD, PhD,1,2,3 Andras Szentkiralyi, MD,1 Anett Lindner, MD,1 Maria Eszter Cziria, MD,1 Lilla Szellert, MD,1 Agnes Zsofia Kovacs, MD,1 Katalin Fornadi, MD,4 Andras Szabo, MD, DSc,5 Laszlo Rosivali, MD, DSc,6 Istvan Mucsi, MD, PhD,1,2,6,7 and Marta Novak, MD, PhD1,8

Multivariate Cox-modell

<table>
<thead>
<tr>
<th>Presence of RLS</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2</td>
<td>1.03-3.95</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adjusted for: age, gender, eGFR, albumin, hemoglobin, CRP, diabetes, hypertonia and transplant vintage

Clinical management of RLS in CKD

- Adequate dialysis/renal transplantation
- Iv iron/anemia management (Dose?)
- Drugs
  - Ropirinole, pramipexole, carbidopa/levodopa,
  - Benzodiazepines - efficacy??
  - Gabapentin, carbamazepine – efficacy??
Sleep apnea syndrome

- intermittent episodes of breathing cessation during sleep,
  - airway collapse (obstructive sleep apnoea, OSA)
  - cessation of respiratory effort (central SA)
  - or both (mixed SA)

- The severity of the SAS is usually characterized by the number of apneic events per hour of sleep (AHI, RDI) (RDI>5 is considered pathological), severity of desaturation and by the presence and severity of daytime sleepiness.

- SAS is associated with disturbances of sleep initiation and maintenance as well as daytime sleepiness.

- A potential link is suggested between SAS and HTN, CAD, CHF and arrhythmias
OSAS

- Upper airway obstruction
- Anatomical problems
- Decreased muscle tone ↓ + weakness of pharyngeal wall

Dynamic collapse during inspiration
Apnea leads to micro-arousals and fragmented sleep
Sleep Apnoe Syndrome

Predictors, correlates

• Age
• Obesitas (BMI, neck circumference)
• Male gender/menopause
• Alcohol
• Uremic toxins?
• Anemia
• Altered metabolic state

Consequences

• Daytime sleepiness
• Accidents
• Cognitive impairment
• Depression
• Sexual dysfunction
• Hypertension, LVH, CAD, arrhythmiyas
• Impaired QoL
• Increased morbidity, mortality?
CKD specific factors potentially contributing to the pathogenesis of SAS

- Hypocapnia, acid-base disorders
- Uremic toxins – effects on CNS
- Soft tissue edema
- Anemia
- Endocrine problems (menopause – gender difference)
- Dialysis modality (HD-cytokines, type of PD)
Prevalence of OSA in CV diseases

- CHF: 25%
- CAD: 30%
- HTN: 50%
Physiologic non-REM sleep

• Sympathetic nerve activity
• BP
• HR
• PVR
• Stroke volume

• Parasympathetic activity
Obstructive Sleep Apnea (OSA) During REM Sleep

Sympathetic Nerve Activity

Respiration

Blood Pressure, mm Hg
OSAS

Mediating processes
- Hypoxia
- Hypercapnia
- Change in the Intrathoracal pressure
- Micro-arrousals

Sympathetic nervous system activity
Endothelial dysfunction
Oxidative stress
Inflammation
Hypercoagulability

Modifying factors
- Obesity
- Gender
- Age
- Metabolic syndrome
- Smoking
- Medications

Hypertension
Heart failure
Arrhytmias
CAD
Cerebrovascular disease
Snoring and cardiovascular disease (n= 12600)

Stroke

- Loud snorers (men: 6%, women: 8%)  p<0.01
- Quiet snorers (men: 4%, women: 4%)  p<0.01
- Non-snorers (men: 2%, women: 2%)

AMI

- Loud snorers (men: 6%, women: 5%)  p<0.0001
- Quiet snorers (men: 3%, women: 2%)  p<0.005
- Non-snorers (men: 1%, women: 1%)

Note: Percentages for each category and statistical significance levels (p-values) are indicated.
Sleep-Disordered Breathing in Nondialyzed Patients with Chronic Renal Failure

Nikolaos Markou · Maria Kanakaki · Pavlos Myrianthefs · Dimitrios Hadjiyanakos · Dimosthenis Vlassopoulos · Anastasios Damianos · Konstantinos Siamopoulos · Miltiadis Vasiloiou · Stavros Konstantopoulos

High prevalence of patients with a high risk for obstructive sleep apnoea syndrome after kidney transplantation—association with declining renal function

Miklos Zsolt Molnar¹,²,³, Andras Szentkiralyi¹, Anett Lindner¹, Maria Eszter Czira¹, Andras Szabo⁴, Istvan Muci⁴,⁵ and Marta Novak¹,⁶

(Nephrol Dial Transplant (2007))
SAS and quality of life in dialysis patients

Sanner et al.: NDT, 2002
Nocturnal Hypoxemia Predicts Incident Cardiovascular Complications in Dialysis Patients

CARMINE ZOCCALI, FRANCESCA MALLAMACI, and GIOVANNI TRIPEPI
CNR, Centre of Clinical Physiology and Division of Nephrology, Ospedali Riuniti, Reggio Calabria, Italy.

Fatal and non fatal cardiovascular events

Cumulative Survival

Time [months]

Clinical management of SAS in CKD

- Weight loss lifestyle changes
- CPAP
  - Long term effects?
  - Compliance?
- Oral devices, Sx
- Transplantation?
- Intensified dialysis

photo courtesy of the American Sleep Apnea Association
CPAP (Continuous Positive Airway Pressure)
SAS and Nocturnal Home Hemodialysis

Prevalence of sleep disorders in Hungarian dialysis and transplanted patients

* : P<0.001, Khi-square test
High risk of OSAS and graft failure

Graft survival

Follow up (months)

Cumulative survival

OSAS
No OSAS
Sleep disorders in CKD patients - summary

- The prevalence of sleep disorders is much higher in patients with CKD than in the average population.
- The prevalence of these conditions is the lowest in transplanted patients (except OSAS).
- Age, gender, renal function and co-morbidity is associated with sleep disorders in kidney transplanted patients.
Sleep disorders in CKD patients - summary

• Patients with sleep disorders have more fatigue/daytime sleepiness, increased illness intrusiveness and impaired QoL

• OSAS is a predictor of graft loss, RLS is associated with mortality in transplanted patients
Conclusions

- Sleep disorders are underdiagnosed and un(der)treated in the CKD population

- Close collaboration between sleep specialists and nephrologists

may improve management of these treatable disorders and may improve QoL of renal patients
Yawning Apprentice

Mihály Munkácsy

(1844 – 1900)

THANK YOU!