Sleep Disorders in Patients with Chronic Kidney Disease

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• Sleep – significance
• Sleep disorders in CKD
• The most frequent sleep problems in CKD patients
• 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

– BUT, how much we sleep does not only depend on how much we worked that day
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

Diagram showing the relationship between cytokines and sleep, including pro-inflammatory and anti-inflammatory cytokines, TNF, IL-1β, IL-10, IL-4, IL-6, NF-κB, and various signaling pathways involving IFN-γ, Muramyl peptides, LPS, and sleep deprivation.
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 HYPERTENSIION

![Bar chart showing sleep time distribution by gender.](chart.png)

- Women
- Men

- Hours: <5, 5-6, 6-7, 7-8, >8

- Percentage distribution

- Graph indicates higher percentages for women in the <5 and 5-6 hours categories, with a decrease in percentages for both genders in the 6-7, 7-8, and >8 hours categories.
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
Would you be willing to do more frequent dialysis?

- If it increased your energy? – 94%
- If you had better sleep? – 57%
- If you lived 1-3 yrs longer? – 19%

Patient preferences for in-center intense hemodialysis

Nirupama RAMKUMAR, Srinivasan BEDDHU, Paul EGGERS, Lisa M. PAPPAS, Alfred K. CHEUNG

Factors contributing to sleep disturbances in patients on dialysis

Treatment-Related Factors
- Premature discontinuation of dialysis
- Cytokine production during treatment
- Rapid changes in fluid electrolyte and acid-base balance
- Abnormalities in melatonin
- Alterations in thermoregulatory
- Medications

Psychological Factors
- Anxiety
- Depression
- Stress
- Worry

Disease-Related Factors
- General health status
- Comorbid conditions
- Anemia
- Symptoms of uremia
- Metabolic changes
- Alterations in neurotransmitter production

Lifestyle Factors
- Coffee intake
- Cigarette use
- Poor sleep hygiene

Sleep Disturbances in Dialysis Patients
- Changes in sleep architecture
- Sleep apnoea syndrome
- Restless legs syndrome
- Periodic limb movement disorder
- Excessive daytime sleepiness

Demographic Factors
- Age
- Male gender
- White race

Diagnostic tools to detect sleep problems

- Sleep diaries
- Self administered questionnaires
  - Insomnia: Pittsburgh Sleep Quality Index, Athens Insomnia Scale
  - SAS: Berlin Questionnaire
  - RLS: Restless Legs Syndrome Questionnaire
  - Epworth Sleepiness Scale
- Clinical interview
- 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
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
RLS
Restless Legs Syndrome

Predictors, etiology

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

Consequences

- Fragmented sleep, „intitiation” 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 patients\textsuperscript{4}

• There is no data regarding the association of RLS, poor sleep and QoL after renal transplantation

\textsuperscript{1} Winkelman et al. (1995)
\textsuperscript{2} Mucsi et al. (2004)
\textsuperscript{3} Molnar et al. (2005)
\textsuperscript{4} Unruh et al. (2004)
RLS in dialysis patients predicts mortality

Table 3. Adjusted Hazards of Severe Symptoms of Restless Legs and by Category of Restless Legs Symptom

<table>
<thead>
<tr>
<th></th>
<th>Severe Restless Legs Symptoms</th>
<th>Category of Restless Legs Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted hazard</td>
<td>1.31 (1.00-1.73)</td>
<td>1.06 (0.97-1.15)</td>
</tr>
<tr>
<td>Model 1, adjusted for age and race</td>
<td>1.42 (1.07-1.97)</td>
<td>1.07 (0.96-1.18)</td>
</tr>
<tr>
<td>Model 2, model 1 and adjusted for ICD, Karnofsky</td>
<td>1.39 (1.05-1.84)</td>
<td>1.06 (0.98-1.16)</td>
</tr>
<tr>
<td>Model 3, model 2 adjusted for clustering of clinics</td>
<td>1.39 (1.08-1.79)</td>
<td>1.06 (0.98-1.16)</td>
</tr>
</tbody>
</table>

Fig 2. Crude cumulative mortality according to severe symptoms of restless legs.

Unruh et al; AJKD; 2004
Restless Legs Syndrome and Mortality in Kidney Transplant Recipients

Miklos Zsolt Molnar, MD, PhD, Andras Szentkiralyi, MD, Anett Lindner, MD, Maria Eszter Cziria, MD, Lilla Szellert, MD, Agnes Zsofia Kovacs, MD, Katalin Fornadi, MD, Andras Szabo, MD, DSc, Laszlo Rosivall, MD, DSc, Istvan Mucsi, MD, PhD, and Marta Novak, MD, PhD

Multivariate Cox-modell

<table>
<thead>
<tr>
<th>Mortality</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of RLS</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, hypertension 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, arrhythmias
- 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%

HTN: 50%

CAD: 30%

J Am Coll Cardiol 2003;41:1429-37
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

OSA
R. Khayat: Heart Failure Reviews, 2008
Leptin resistance
Ventilatory drive
Low HDL
Obesity
Insulin resistance
Hypertension
Glucose intolerance

Adipose vascularisation
Hypoxia
Adiponectin secretion

Endothelial dysfunction
Angiotensinogen, resistin, CRP, TNF-α, PAI-1, leptin

CD40/CD40L
VCAM-1, ICAM-1

↓NO
↑Ang II
↑OxLDL
Snoring and cardiovascular disease (n= 12600)

- **Stroke**
  - Men: Loud snorers (4%), Quiet snorers (3%), Non-snorers (2%)
  - Women: Loud snorers (6%), Quiet snorers (4%), Non-snorers (2%)
  - p < 0.01

- **AMI**
  - Men: Loud snorers (6%), Quiet snorers (3%), Non-snorers (2%)
  - Women: Loud snorers (5%), Quiet snorers (3%), Non-snorers (2%)
  - p < 0.0001, p < 0.005
SAS - HTN


SAS - LVH

Nocturnal Hypoxemia Predicts Incident Cardiovascular Complications in Dialysis Patients

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Fatal and non fatal cardiovascular events

Cumulative Survival

Time (months)

SaO₂ >95%

SaO₂ ≤95%

Clinical management of SAS in CKD

- Weight loss life style changes
- CPAP
  - Long term effects?
  - Compliance?
- Oral devices, Sx
- Transplantation?
- Intensified dialysis
SAS and Nocturnal Home Hemodialysis

Obstructive Sleep Apnea in Patients on Conventional and Short Daily Hemodialysis

Roshline Motta Elias, manual Carlos Martins Castro, Eduardo Lyra de Queiroz, Hugo Abensur, João Egidio Romão-Junior, Geraldo Lorenzi-Filho

**Fig. 1.** Relation between OSA and standard Kt/V. Fisher’s test, p < 0.0001.
Obstructive Sleep Apnea in Patients on Conventional and Short Daily Hemodialysis

Rosilene Motta Elias, Manuel Carlos Martins Castro, Eduardo Lyra de Queiroz, Hugo Abensur, João Egidio Romão-Junior, Geraldo Lorenzi-Filho

Fig. 2. Relationship between neck circumference and risk of OSA, according to dialysis dose (expressed as standard Kt/V). For each 1-cm increase on neck circumference, there is 1.4 sleep apnea risk.
Alleviation of Sleep Apnea in Patients with Chronic Renal Failure by Nocturnal Cycler-Assisted Peritoneal Dialysis Compared with Conventional Continuous Ambulatory Peritoneal Dialysis

Sydney C.W. Tang,*† Bing Lam,‡ Pui Pui Ku,‡ Wah Shing Leung,§ Chung Ming Chu,§ Yiu Wing Ho,‡ Mary S.M. Ip,‡ and Kar Neng Lai*

Prevalence of sleep disorders in Hungarian dialysis and transplanted patients

*: P<0.001, Khi-square test
Sleep Apnea Is Associated with Cardiovascular Risk Factors among Kidney Transplant Patients

Miklos Zsolt Molnar,† Alpar Sandor Lazar,‡ Anett Lindner,† Katalin Fornadi,¶ Maria Eszter Czira,§ Andrea Dunai,† Rezso Zoller,‡ Andras Szentkiralyi,† Laszlo Rosivall,§ Colin Michael Shapiro,|| Marta Novak,†¶ and Istvan Mucsi†¶

Figure 2. Prevalence and severity of OSA in Tx and WL patients (NS).
Severity of OSA vs hypertension in Tx

Apnoe-Hypopnoe Index (/ hour)

- more than 3 antihypertensive drugs

Average systolic RR

Below 5 5 - 15 15 - 30 Over 30

Below 5 5 - 15 15 - 30 Over 30

P<0.05; Linear-by-linear association, both
High risk of OSAS and graft failure

A. Szentkiralyi et al: Sleep medicine – in press
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 under-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!