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 depend on how much we worked that day
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

TNF

IL-1β

IL-1R1

IL-10

CRH

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

NF-κB

IL-2

Slow-wave sleep

IL-6

IL-10

IL-18

IL-4

IL-10

IL-1β

TNF-

NF-κB

IL-2

Cortisol

ACTH

GHRH

GH

Prolactin

IL-6

NATURE REVIEWS | IMMUNOLOGY | VOLUME 4 | JUNE 2004
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

% women

% men

hours

<5 5-6 6-7 7-8 >8

50
45
40
35
30
25
20
20
15
10
5
0

women

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

- **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

- **Demographic Factors**
  - Age
  - Male gender
  - White race

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

Diagnostic tools to detect sleep problems

• Sleep diaries
• Self administered questionnaires
  – Insomnia: Pittsburgh Sleep Quality Index, Athen 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
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 sleep problems and renal function across CKD stages]
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, „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 (1.07-1.87)</td>
<td>1.07 (0.98-1.16)</td>
</tr>
<tr>
<td>Model 2, model 1 and adjusted for ICED, 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>1.30 (1.08-1.79)</td>
<td>1.06 (0.98-1.16)</td>
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</table>

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

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Restless legs syndrome, insomnia, and quality of life after renal transplantation

Miklos Zsolt Molnára,b,c, Marta Novaka,d, Lilla Szefert,a, Csaba Anbrusb,c, Andras Keszei,a, Agnes Koczy,a, Anett Lindnera, Szabolcs Bartói,f, Andras Szentkirályia, Adam Remportb, Istvan Mucsi,a,c,h,*

[Diagram showing quality of life metrics for RLS and non-RLS groups.]

Restless Legs Syndrome and Mortality in Kidney Transplant Recipients

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Multivariate Cox-modell

<table>
<thead>
<tr>
<th>Presence of RLS</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Presence of RLS</td>
<td>2</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, 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%
- CAD: 30%
- HTN: 50%
Hypoxia

Hypertension
Heart failure
Arrhythmias
CAD
Cerebrovascular disease

Hypercapnia

Change in the Intrathoracal pressure

Endothelial dysfunction

Oxidative stress

Inflammation

Hypercoagulability

Sympathetic nervous system activity

Mediating processes

Obesity
Gender
Age
Metabolic syndrome
Smoking
Medications

Modifying factors

OSAS

Micro-arrousals
Physiologic non-REM sleep

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

- Parasympathetic activity
Snoring and cardiovascular disease (n= 12600)

**Stroke**

- **Men:**
  - Loud snorers: 6%
  - Quiet snorers: 4%
  - Non-snorers: 2%
  - **p<0.01**

- **Women:**
  - Loud snorers: 8%
  - Quiet snorers: 6%
  - Non-snorers: 2%
  - **p<0.01**

**AMI**

- **Men:**
  - Loud snorers: 6%
  - Quiet snorers: 3%
  - Non-snorers: 2%
  - **p<0.0001**

- **Women:**
  - Loud snorers: 5%
  - Quiet snorers: 2%
  - Non-snorers: 1%
  - **p<0.005**

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 Vasiliou · Stavros Konstantopoulos

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)

SAS and quality of life in dialysis patients

Sanner et al.: NDT, 2002
Clinical management of SAS in CKD

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

Prevalence of sleep disorders in Hungarian dialysis and transplanted patients

OSAS
RLS
Insomnia

Transplanted
Wait-listed

*: P<0.001, Khi-square test
High prevalence of patients with a high risk for obstructive sleep apnoea syndrome after kidney transplantation—association with declining renal function

Miklos Zsolt Molnar\textsuperscript{1,2,3}, Andras Szentkiralyi\textsuperscript{1}, Anett Lindner\textsuperscript{1}, Maria Eszter Czira\textsuperscript{1}, Andras Szabo\textsuperscript{4}, Istvan Mucs\textsuperscript{1,2,5} and Marta Novak\textsuperscript{1,6}

\[ p = 0.004 \]
Prevalence and severity of OSA

p=NS, in all groups

WL
Tx
Severity of OSA vs hypertension in Tx

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

Cumulative survival

Follow up (months)
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!