Sleep disorders in kidney disease

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Sleep disorders are common in patients with end stage renal disease receiving hemodialysis or peritoneal dialysis. However also a well functioning renal graft does not cure the poor sleep pattern which now emerges as a problem even in early chronic kidney disease (CKD). When patients are made aware for the first time of a disease such as CKD, which may brink to dialysis or at the best to a renal transplant patients begin to experience a disordered sleep. Sleeping disorders include insomnia (I), sleep apnoea (SAS), restless legs syndrome (RLS), periodic limb movement disorder (PLMD), excessive daily sleeping (EDS), sleepwalking, nightmares, and narcolepsy. Disordered sleep did not meet the clinical and scientific interest it deserves, in addition and we do not have a well defined solution for sleeping complaints. However, awareness that a poor sleep is associated with poor quality of life and carries an increase in mortality risk has recently stimulated interest in the field. There are many putative causes for a disordered sleep in chronic kidney disease and in end-stage renal disease. For a unifying hypothesis demographic factors, lifestyles, disease related factors, psychological factors, treatment related factors, and social factor must be taken into consideration.

Key words: **Sleep disorders - Restless legs syndrome - Somnambulism - Narcolepsy - Dialysis - Transplantation - Hypertension.**

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Among the many physical human needs sleep is a special one since is *conditio sine qua non* for maintaining health and a state of wellness. After sleep an individual is ready to start again his routine. Poor quality of sleep characterizes many diseases and causes tiredness, exhaustion, difficulty on concentration, decreased pain threshold, loss of appetite, nervousness, anxiety and depression.[1]

One third of the population living in Western countries reports a temporarily disordered sleep: either in falling asleep, or because of frequent awakenings, or in going back to sleep after awakenings. Chronic insomnia (*i.e.* more frequent that thrice a week and longer than one month) has a 20-30% prevalence in Western countries, and is associated with daytime dysfunction.[2] chronic insomnia has a high persisting-relapse rate, is associated with poor physical health, frequent accidents at work and on the road, and high social and medical costs and is asso-

ciated with mental disease.[3] The prevalence of persistence-relapse rate was estimated around 40% at one year in a population study.[4] Chronic insomnia is associated with poor health, absenteeism, poor job satisfaction, and work efficiency. Chronic insomnia causes more frequent use of medical and nursing services, drugs, and days of hospitalization. It is also associated with affective disorders, anxiety, psychosomatic diseases, depression (it is considered a precursor of the disease) and negatively affects [3, 4] overall quality of life (QoL).

Chronic insomnia coexists with chronic disease, namely arthritis, gastroesophageal reflux disorder, coronary artery disease, congestive heart failure, diabetes mellitus, kidney disease (patients with early CKD), on maintenance dialysis, renal transplanted patients, obstructive airway obstruction, psychiatric disorders (40% of patients with chronic insomnia have a psychiatric disorder), neurological disorders including Alzheimer's disease and Parkinson's disease. It negatively affects QoL and causes more use of health care resources, and is considered a precursor of depression.[2-4]

TABLE I.—*Uremia associated losses and dependencies.*[4]

Losses	
Loss of urinary function	Loss of good mood
Loss of the capacity to concentrate	Loss of life expectancy
Loss of work place	Loss of capability of practicing a sport
Loss of the freedom to select of to find a job	Loss or limitation in mobility
Loss of the role in the family	Loss of freedom in selecting beverages
Loss of the family dynamics	Loss of body weight
Loss of role in social relationships	Loss of muscle mass
Loss of quality of life	Loss of body imaging
Loss of the sense of femininity	Loss of skin colour
Loss of menstruation	Loss of weight stability
Loss of the capability of having an orgasm	Loss of sleep hours
Loss of the sense of masculinity	*Dependencies*
Loss of erectile function	On dialysis staff
Loss of libido	On physicians
Loss of capability to set constructive goals	On medications
	On family
	On a machine
	On dialysis shifts
	On dialysis calendar

Sleep disorders in patients on chronic dialysis

Sleep complaints have been reported just a few years after Scribner introduced in 1963 maintaining hemodialysis. This seemed to represent the results on a machine-dependent life associated with many losses - not only the loss of renal function - and many dependencies.[3] The list of the losses includes the role in the family, loss of the job, loss of autonomy, loss of time, liberty in selecting foods, beverages, place of vacation. The list of dependencies includes the drugs and their schedule, the dialysis and physician staff, the dialysis schedule and shift, the dialysis machines (Table I).

A 20-100 prevalence of sleep disorders has been reported in dialyzed patients [5-32] in whom it is associated with mortality and is not cured by transplantation. It affects children and adults, it occurs in hemodialysis as well as in peritoneal dialysis. Nocturnal hemodialysis, as we will se later is associated with an improvement of sleep disorders. Sleep disorders are common (Table II) in patients on dialysis who complain of I, restless leg syndrome (RLS), obstructive sleep apnoea syndrome (OSAS), periodic limb movement disorder (PLMD), excessive daytime sleepiness (EDS), narcolepsy, sleepwalking, nightmares, rapid eye movement behaviour (RBD).

Table II is a synopsis of 27 studies performed in the years 1982-2009. The list is obviously incomplete but it tells us that initially sleep related reports in patients on hemodialysis/peritoneal dialysis referred data collected in small series of patients. Only in the last fifteen years the number of investigated patients became relevant.

In a well performed regional study [17] in Italy, as outlined Table III, the prevalence of sleep disorders in 832 hemodialysis patients, was 80.2 % (N=708). Alcohol intake, cigarette smoking, polyneuropathy and morning dialysis shift were significant and independent predictors of sleep disorders. Possible causes for chronic insomnia included restlessness (26.9%), pain (24%), cough (20.8%), worriness (8.9%), bursts of heath (5.8%). The morning

TABLE II.—*Insomnia in hemodialyzed patients in 27 studies published in the years 1982-2009.*[6-32]

Author	Study No.	Year	Patients No.	Treatment	%Prevalence of Sleep Disorders
Strub *et al.*[6]	1	1982	22	HD	63.0
Holley [7]	2	1992	70	HD, PD	52.0/50.0
Walker [8]	3	1995	54	HD	83.3
Stepanski [9]	3	1995	81	PD	73.0
De Vecchi [1]	5	2000	171	HD, PD	56/49
De Santo *et al.*[11]	6-9	2001-2008	294	HD	86.06
Sabbatini *et al.*[15]	10	2002	694	HD	44.8
Iliescu *et al.*[16]	11	2003	89	HD	71.0
de Barbieri [17]	12	2004	112	HD	48.2
Mucsi [18]	13	2004	78	HD	49.0
Kurella [19]	14	2005	78	HD	34.0
Merlino *et al.*[20]	15	2006	883	HD, PD	80.2
Chen *et al.*[21]	16	2006	700	HD	66.0
Unruh *et al.*[22]	17	2006	909	HD, PD	75.0
Noda [23]	18	2006	252	HD	59.1
Bastos *et al.*[24]	19	2007	100	HD	75.0
Hui [25]	20	2007	201	PD	73.0
Yang [26]	21	2007	190	PD	86.0
Güney *et al.*[27]	22	2008	124	PD	53.5
Sabbagh *et al.*[28]	23	2008	46	HD	76.0
Elder *et al.*[29]	24	2008	6321	HD	49.0
Eryavuz [30]	25	2008	104	HD, PD	88.5/78.0
Bornivelli [31]	26	2008	45	HD	20
Pai [32]	27	2008	164	HD	74.4

TABLE III.—*Sleep disorders in 832 dialyzed patients in the study of Merlino et al.*[16]

Sleep disorder	Prevalence
Insomnia	69.1
Obstructive sleep apnoea syndrome	23.6
Restless leg syndrome	18.4
Nightmares	13.3
Excessive daytime sleepiness	11,8
Rapid eye movement behaviour	2.3
Sleepwalking	2.1
Possible narcolepsy	1.4

dialysis shift was the only parameter related to chronic insomnia. This is well organized study which has a major role in history of studies on sleep disorders in end stage renal disease (ESRD). chronic insomnia with daytime dysfunction is more frequent in hemodialysis than in general population. It has been suggested that particular care is needed in patients "with tiredness on awakening, morning headache, transient memory and concentration disturbances could be expression of chronic insomnia or OSAS and not as consequences of dialysis.

There is a scarce level of attention of nephrologists to this problem. Sleep disorders are prevalent in renal disease and have a significant negative impact on functional status on uremic patients. Treatment of sleep disorders can restore QoL of these patients. Concerning nightmares it should be stressed that nearly 50% of the adult population report an occasional frightening dream associated with awakening from sleep, whereas the prevalence of recurrent nightmares is around 1.0%. In this study recurrent disturbing dreams were present in 13.3% of the cases. Narcolepsy prevalence in the general population is 0.02-0.95% whereas in hemodialysis patients 1.4% was reported.

As stated by Parker "sleep disturbances are very prevalent in dialysis patients and appear to have important adverse effects on their overall health and well being. Therefore the effective assessment and management of these sleep disturbance has the potential to significantly enhance patient outcomes. In addition research designed to identify the mechanisms underlying these sleep prob-

lems would expand both the clinical and basic sciences. Thus the dialysis population presents clinicians and researchers alike with an extraordinary opportunity for interdisciplinary collaboration."[33]

Sleep apnea

The Sleep Apnea Syndrome is characterized by repetitive cessation of respiration during sleep either from airway collapse as it occurs in obstructive sleep apnea (OSA), or from cessation of the respiratory effort as it occurs in central sleep apnea (CSA) or by a combination of OSA and CSA, named mixed sleep apnea (MSA). Five apneic event per hour are pathological and result in oxygen desaturation and arousal and abrupt changes in cardiac loading due to negative intra-thoracic pressure.[34] Obstructive sleep apnea syndrome (OSAS) affects 4% of middle-aged men and 2% of middle-aged woman.[35] It is associated with morbidity and mortality, mainly from cardiovascular disease, especially resistant hypertension,[35] left ventricular concentric hypertrophy and diastolic dysfunction. It contributes to the risk of fatal and non-fatal cardiovascular events. The risk of cardiovascular events is several times higher in patients with PaO_2<95%. OSA also predisposes to traffic accidents.

Studies in ESRD were started by Mitra *et al.* and by Millman *et al.*[36, 37] However a paper of Kimmel *et al.*[38] opened a new era in the studies of sleep disorders since it used polysomnography both in patients on hemodialysis and on conservative management and found a prevalence of Sleep Apnea Syndrome in 73% of symptomatic patients. We now that patients with end stage renal disease may develop central SAS, but usually OSA is the most frequently encountered. and its prevalence is in the range 30-80% [9, 16, 39-47] and does not discriminate for gender.

OSA exacerbate fatigue, sleep loss, excessive sleepiness and impaired cognition, hypertension and mortality and enhanced chemo-responsiveness [48] during both hypoxic and hyperoxic conditions which destabilise respiratory control. This gives support to the interesting findings of Zoccali *et al.* demonstrating a strong link of SAS and nocturnal hypoxemia in ESRD.[49, 50]

Tang *et al.*[51] have studied patients undergoing Nocturnal Peritoneal Dialysis (NPD) and on CAPD and found an intriguing prevalence of SAS of 91% in CAPD and of 52% on NPD. Converting NPD patients to CAPD induced a worsening of SAS and was accompanied by increased prevalence of SAS, prolongation of duration of hypoxia and more frequent arousal during sleep. The benefits of NPD did not depend on metabolic acidosis and hypoxia, but to better fluid control. However, it might be appropriate to ponder on the study of Merlino *et al.* who disclosed a prevalence of OSA of 23.6% and a prevalence of excessive daytime sleepiness 11.8%.[20]

PATHOGENESIS OF SAS

In some patients BUN, creatinine, Body Mass Index have predicted OSA, whereas PaO_2, $PaCO_2$ and cardiothoracic ratio have predicted central SAS.[52] The pathogenesis of SAS in patients with ESRD is well defined at present times. Probab1ly it has nothing to do with modality of dialysis, biochemistries, body mass index, and history of snoring, as thoroughly discussed by Parker.[33, 53] Fluid overload, anemia, hormonal imbalance and cytokine may have a pathogenetic role.[54-57] Clinical presentation including loud snoring witnesses apnea during sleep, daytime sleepiness in an overweight male patients. There are caveats since patients with ESRD may have either central or mixed respiratory events and daytime sleepiness may be not characteristic since there may be other causes.

Regular hemodialysis does not improve SAS, daily dialysis improves the syndrome, transplantation may improve but does not cure. Continuous positive airway pressure (CPAP) is a cost effective alternative [58] for hypopnoea and apnoea. It also improves daytime somnolence, performance, and neuropsychiatric state,[59] as well as QoL. In addition it reduces blood pressure.[60] However there is a need for further studies [34] in order to prevent the development of sympathetic

hyperactivity and left ventricular hypertrophy , as pointed out by Zoccali [40, 50, 56] since SAS affects quality of life in ESRD.[34]

Perhaps one can learn more from nondialyzed CKD patients.[61] A prevalence of SDB of 54.3% was reported in 35 patients with an estimated GFR of 26.8±9.2 mL/min. The prevalence was higher than in the general population for middle aged adults. SDB was of the obstructive type and unrelated to gender, hemoglobin, the diabetic status, and symptoms of daytime sleepiness, and moderately associated with renal function, but no difference was seen when patients were divided in two groups divided by in according to eGFR greater or lower than 15 ml/min.

Restless legs syndrome

The restless legs syndrome (RLS) is a common neurological disorder that is characterized by an urge to move the legs (rarely also the arms) and peculiar, unpleasant sensation of paresthesias, deep in the legs.[62]

Sensation appears during period of rest or inactivity, particularly in the evening and at night and is typically relieved by movement. Paresthesias are be exceedingly unpleasant and give rise to severe sleep disturbances. That unpleasant creeping or crawling sensation deep is felt within the lower legs, most commonly between the knees and the ankles. It has been defined as creeping, crawling, tingling, aching, burning, pulling, itching, and cramping sensation, and may be experienced also in the thighs and sometimes in the feet. That disagreeable long-lasting sensation is usually felt prior to sleep onset and causes an almost irresistible urge to move legs and causes disrupted sleep and excessive daytime sleepiness. RLS may be unilateral but commonly is bilateral and symmetrical. Patients walk to get relief (Night-walker's syndrome). Loss of sleep is a consequence.

RLS occurs at any age between 8 and 80 years. In the general population the prevalence is 5-20%. In dialysis population is greater the variability is in the range 6.6% to 80%.[62] Diagnosis is made by means of the Criteria of the International RLS Study Group as modified recently.[62, 63] Recently however the Athens chronic insomnia scale has also gained popularity in epidemiological studies because of its simplicity and easiness to administer.[63]

In 50% of the patients there is a positive family history. Physical examination is normal. Symptoms may be generated in brain by local iron deficiency. Coffee, cigarette smoking may have a predictive role.

As pointed in Table I RLS is very common in ESRD. Recent data (Table IV) point to a prevalence of 12-15% whereas in the past a prevalence of 6.5-83% [8, 15, 18, 20, 24, 33, 61, 63-80] was reported, which was associated with diminished QoL and increased mortality. However in the very recent study of Al Jadhali *et al.*[62] the prevalence in hemodialysis patients was 50.2%: there were more women, more diabetic, more chronic insomnia, more EDS, and more cases of OSAs.

The list of potential predictors of RLS includes anemia, ferritin, iron, calcium, phosphorus, creatinine, and urea Kt/V, but recently doubts have been cast on these relationships. Patients with RLS are at high risk of chronic insomnia and disturbed sleep, daily time sleepiness,[8, 15, 62, 67, 80, 81] poor QoL and mortality. QoL depends both on sleep related and sleep independent factors.[67] In nondialyzed patients a prevalence of 37.1% was reported by Markou *et al.*[61] RLS is difficult to manage, transplantation may ameliorate it but RLS deteriorates again with falling GFR.[73] In the study of Molnar *et al.*[82] the prevalence of RLS after transplantation was 4.8% close to the prevalence in the general population, but also in those patients predicted mortality. However Sabbatini et al reported a prevalence of 37% in 301 patients receiving a kidney graft.[83]

In 80% of the cases patients with RLS have also PLMD, that is periodic limb movement disease. However it is a distinct entity positively associated with age. As pointed out by the American Sleep Disorder Association, 34% of the cases occur in patients older than 60 years. The prevalence of PLMD may be as high as 70% [83] and as important as RLS in terms of sleep disorder.[33, 74]

Excessive daytime sleepiness

Sabbatini *et al.* found a prevalence of EDS in 53% of poor sleeping hemodialysis patients.[15] In a study by Gigli *et al.* a prevalence of 16.3 % in poor sleepers with RLS and of 3.4 in those without RLS, was found, and patients with RLS had a more daytime sonnolence.[81] Merlino *et al.* found a prevalence of 11.8%.[20] In the latter study EDF was not associated to the use of benzodiazepines and of clonidine and with type and timing of dialysis.

Parker *et al.* using the Multiple Sleep Latency Test (MSLT)and the Epworth Sleepiness Scale (ESS) disclosed a 32.6 % prevalence of abnormal sleepiness.[84]

Narcolepsy

In the previously quotet paper of Parker *et al.*[84] hemodialyzed patients had a MSLT <5 minutes, which is an index to diagnose narcolepsy. Merlino et al reported a prevalence of narcolepsy of 1.4%, significantly higher than in general population (0.03-0.05%) and advanced the hypothesis of a disorder related to a damage of the hyposecretin level which was disclosed in uremic rats and humans.[81]

Bodily pain and poor sleep

This problem, although known to the community of kidney disease specialists since 1982 has attracted little interest, and is an underappreciated problem.[85-91] The importance of pain and its prevalence in dialysis patients was highlighted by Binik *et al.* who reported that half of the patients had pain [85] which correlated with dialysis vintage. In addition in a study of Shayamsunder et *al.*[88, 89] in 128 black, stable, hemodialysis patients, the majority referred pain at the time of the needle insertion (which however did not correlate with QoL) as well as on non-dialysis days (which correlated with QoL).

In a cross-sectional study of 205 Canadian patients on hemodialysis Davison and Jhangri [90] reported a 50.2% prevalence of chronic pain and a prevalence of 41.4% of moderate to severe pain. The higher degree of pain was associated with a significantly higher prevalence of depression (37.1% *vs.* 18.3%, P<0.001), a significantly higher prevalence of I (74.7% *vs.* 53%, P<0.02), and a significantly higher prevalence of patients desiring to withdraw (46% *vs.* 16.7%, P<0.001).

Hui *et al.*[25] studied 179 PD patients in Hong Kong and showed that bone pain and personality traits were significantly associated with self reported sleep disorders. Furthermore in a study by Yang et al on 190 Chinese PD patients, disclosing a prevalence of 85.6% of sleep disorders,[26] PSQI correlated negatively with bodily pain.

Pain is common in CKD patients. In a group of 92 CKD patients, studied by Cohen *et al.*[91] in Washington, 69% experienced pain, 55.2% had disordered sleep. Pain was associated with indicators of QoL including depression, burden of illness and life satisfaction. Disordered sleep correlated with depression, illness burden, social support and pain frequency. There were no differences in perception of pain or sleep disturbances between CKD patients and general medical patients. The study points that in early CKD patients pain is common and correlates with sleep a disordered sleep.

Parathyroid hormone and sleep disorders

PTH, although considered a pivotal uremic toxin,[92] has been rarely related to sleep disorders in patients with end-stage renal disease. However Parker [33] attributed a role to PTH in sleeping disorders since elevated PTH concentrations have a neurotoxic effect,[93] and have also been associated with increasing waking electroenecephalograms, slow wave activity in uremic animals [94] and in stable patients.[95]

In a recent study performed in Taiwan Chou *et al.*[96] reported a prevalence of sleep disorder of 97% in patients with insuppressible secondary hyperparthyroidism requiring parathyroidectomy. iPTH. declined after surgery and the sleep quality and quantity improved within 3 months (Table V). These studies were confirmed (Table V) in two reports from our laboratory [13, 14] in hemodialysis patients with mean iPTH con-

TABLE IV.—*Studies on RLS.*

Study No.	Authors	Year	Country	Prevalence
1	Walker *et al.*[8]	1995	USA	33
2	Winkelman *et al.*[75]	1996	USA	20
3	Collado-Seidel *et al.*[72]	1998	Germany	23
4	Huiqui *et al.*[78]	2000	Stizerlamd	34
5	Hui *et al.*[25]	2000	China	62
6	Thorp *et al.*[79]	2001	USA	42
7	Kutner *et al.*[71]	2002	USA	48-68
8	Sabbatini *et al.*[83]	2002	Italy	52
9	Hui *et al.*[25]	2002	China	34
10.	Takaki *et al.*[66]	2003	Japan	12
11	Bhownik [65]	2003	India	6.6
12	Goffredo Filho *et al.*[77]	2003	Brazil	14.8
13	Mucsi *et al.*[18]	2004	Hungary	15
14	Unruh *et al.*[22]	2004	USA	15
15	Mucsi *et al.*[67]	2005	Hungary	14
17	Siddiqui *et al.*[76]	2006	Japan	23
17	Merlino *et al.*[20]	2006	Italy	18.4
18	Markou *et al.*[61]	2006	Greece	37.1
19	Bastos *et al.*[24]	2007	Brazil	48
20.	Hsu *et al.*[107]	2008	Taiwan	22,7
21	Holhl-Radke *et al.*[100]	2008	Germany	30.5
22	Al-Jadhali *et al.*[101]	2009	Saudi	50.2

TABLE V.—*Sleep disorders in patients with severe hyperparathyroidism before and 1 year after parathyroidectomy*

				Insomniacs (%)	
Authors	Reference	Patients	Year	Before	After
Chou *et al.*	96	30*/31	2005	97.0	22.6
De Santo *et al.*	13	21*/22	2008	97.5	50%
Esposito *et al.*	14	16*/16	2008	100	Not done

*Patients with insomnia

centration of 1 434±400 pg/mL, who in comparison with patients not needing parathyroidectomy had significantly higher prevalence of sleep disorder and higher Charlson Comorbidity index, systolic and diastolic blood pressure, calcium and phosphate concentration, and pain. The prevalence of sleep disorder was 94.55%. After the operation an improvement of disordered sleep occurred. Plasma calcium might have a causative role, since occasional or constant insomnia was associated with hypercalcemia.[97-99]

Taken together available data attribute a role to PTH in the genesis of sleep disorders in secondary hyperparathyroidism in hemodialyzed patients. The fact that nearly all patients with high concentration of PTH unsuppressed by medical therapy have a disrupted sleep warrants further studies both in experimental and clinical settings in end stage renal disease.

Dialysis shift and disordered sleep

Vega et al were the first in disclosing a causative shift effect on sleep disorders of patients treated with maintenance hemodialysis.[100] Their study showed that patients dialyzed in the morning sleep less. A good finding subsequently confirmed by us and by others, which opened a field although published in a journal with a small impact factor.

TABLE VI.—*Characterization in the weekly schedule of treatment in patients dialyzed on Monday-Wednesday-Friday.*[101]

Night	Dialytic treatment	Night	Characteristics
Monday	Yes	A	After dialysis
Tuesdays	No	B	Before dialysis
Wednesday	Yes	A	After dialysis
Thursday	No	B	Before dialysis
Friday	Yes	A	After dialysis
Saturday	No	C	Not before or after dialysis
Sunday	No	D	Night of the longest dialytic interval

TABLE VII.—*Characterization in the weekly schedule of treatment in patients dialyzed on Tuesday-Thursday-Saturday.*[101]

Night	Dialytic treatment	Night	Characteristics
Monday	No	D	Longest interval
Tuesdays	Yes	A	After dialysis
Wednesday	No	B	Before dialysis
Thursday	Yes	A	After dialysis
Friday	No	B	Before dialysis
Saturday	Yes	A	After dialysis
Sunday	No	C	Not before not after dialysis

Prompted from that study we carried a generalized analysis of sleep disorders seven days a week,[101] in relation to the weekly dialysis schedule, in patients dialyzed thrice a week (Monday-Wednesday-Friday or Tuesday-Thursday-Saturday) either in morning or in the afternoon, as indicated in Tables VI,VII.

Tables VI,VII show that within the weekly schedule of treatment we may isolate 4 typical nights (A,B,C,D). A indicates the nights after dialysis, B indicates the nights before dialysis, C indicates the night nor preceded and nor followed by dialysis, and D indicates the night of the longest inter-dialytic interval.

For patients dialyzing on Monday-Wednesday-Friday, night A (after dialysis) corresponds to the nights of Monday-Wednesday-Friday, night B corresponds Tuesday-Thursday, night C corresponds to Saturday, night D is that of Sunday or the night with the longest interdialytic interval.

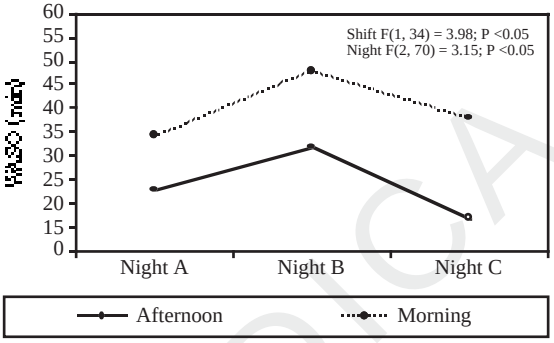

Figure 1.—Wake after sleep onset (WASO) according to shift and to night in 37 patients on maintenance hemodialysis. Night A immediately follows dialysis. Night B immediately preceding dialysis. Night C neither preceded nor followed by dialysis. Night D is the night of the longest interdialytic interval (72 hours). Differences according to shift. From reference no. 101.

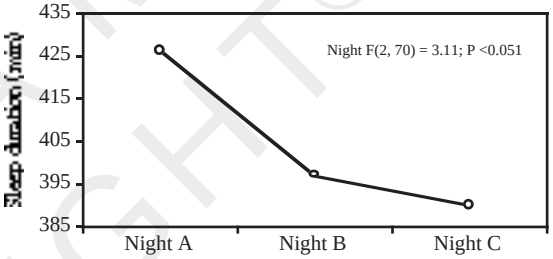

Figure 2.—Total sleep time in 37 patients on maintenance hemodialysis. Night A immediately following dialysis. Night B immediately preceding dialysis. Night C neither preceded nor followed by dialysis. Differences according to shift. From reference no. 101.

For patients dialyzed on Tuesday-Thursday-Saturday, night A corresponds to the nights of Tuesday, Thursday and Saturday, night B corresponds to the nights of Wednesday and Friday, night C is the Sunday night which does not precede or follow a dialysis treatment, night D is on Monday since it corresponds to the night of the longest interdialytic interval.

Sleep was studied by means of the Sleep Diary of Violani *et al.*[102] which is filled by patients for 14 consecutive days in the morning, immediately after waking-up, and evaluated daily naps, fatigue, sleep induced refreshment, sleep latency, number of nocturnal awakenings, wakefulness after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE).

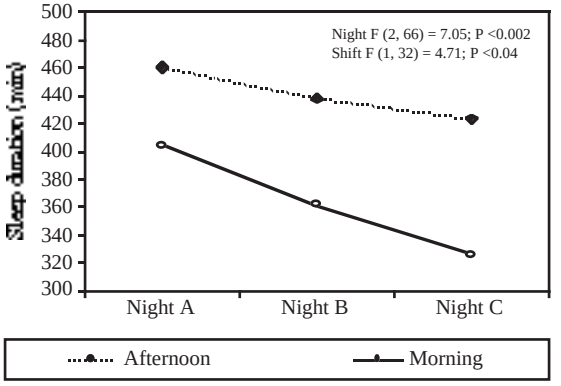

Figure 3.—Total sleep time according to shift. Night A immediately following dialysis. Night B immediately preceding dialysis. Night C neither preceded nor followed by dialysis. Differences according to shift. From reference no. 101.

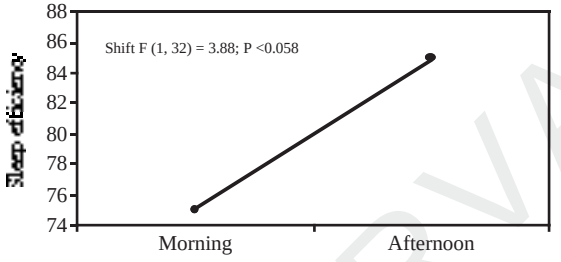

Figure 4.—Sleep efficiency according to shift (Night A, Night B, Night C).From reference no. 101.

No difference was found for daily naps, fatigue, subjective sleep induced refreshment, sleep latency. WASO was significantly higher for patients dialyzed in the morning shift, and was maximal on night B (the night before dialysis),as indicated in Figure 1. There was a significant reduction in TTS from night A to night C, not considering the shift (Figure 2). There was a significant reduction of Total Sleep Time from Night A to B and Night D. Those dialyzed in the morning slept 60-100 minutes less, and the difference was statistically significant (Figure 3). Also SE was significantly better in patients dialyzed in the afternoon when Nights A, B and C are compared (Figure 4). Sleep efficiency is significantly higher in patients dialysed in the afternoon when Nights A,B and D are compared (Figure 5).

All together, the data,[103-106] show that patients dialyzed in the morning, in comparison with those dialyzed in the afternoon,

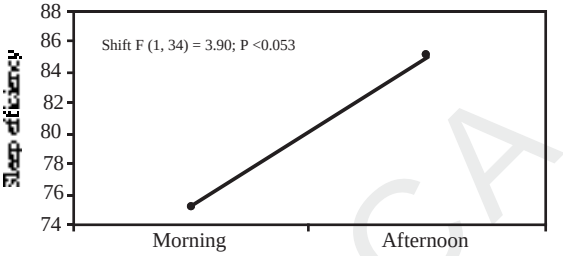

Figure 5.—Sleep efficiency according to shift (Night A, B, D).From reference no.101.

sleep less efficiently and have higher total wakefulness after sleep onset. The difference is statistically significant. Total sleep time is significantly reduced from night A to B and C, and the time and the reduction is greater in patients dialyzed in the morning. Total sleep time is also significantly reduced from night A to B and D and is the reduction is greater in those treated in the morning shift.

In 2005 we have further reported on the problem of sleep disorders in 88 hemodialysis patients and showed by multivariate analysis that is associated with and morning shift, age, comorbidities, and antihypertensive drugs.[12]

Sabbatini *et al.*[15] studied the prevalence of sleep disorders in 694 hemodialysis patients and found a prevalence of I of 45%. Chronical insomnia correlated significantly with morning shift, plasma urea and creatinine, higher PTH levels and pain.

Also in the study by Merlino *et al.*[16] in 2006, insomnia was associated with morning shift as well as older age, alcohol intake, cigarette smoking, diabetes, polyneuropathy. In both cases the prevalence of disturbed sleep in the morning shift was ascribed to psychological problems.

Bastos *et al.*[24] in 2007 reported on 1) 23 patients receiving dialysis very early in the morning (6.30 AM) defined morning treatment; 2) 41 patients undergoing hemodialysis between 11 AM and 3.00 PM defined as afternoon shift; and 3) 36 patients receiving hemodialysis from 4.00 to 8.00 PM. In our opinion the definition of morning, afternoon and evening shift were not appropriate. Poor quality of sleep was found in 75% of the cases, RLS in 48%, EDS in 28% and snoring in 41%.

Disturbed sleep, RLS, and EDS were not dependent on dialysis shift. Poor sleep was significantly associated with snoring, RLS and EDS.

Recently Hsu *et al.*[107] have studied sleep disorders in 150 hemodialysis patients and showed a 58% prevalence of snoring, a 38% of chronical insomnia, and a 22.7% prevalence of RLS, and a 14.7% prevalence of PLMD and daytime sleepiness. Patients dialyzed in the evening were the best sleepers (as indicated by total sleep time, sleep efficiency, and less use of sleep medications).

It is interesting to note that being dialyzed in the morning reduced the mortality risk in the paper of Bliwise *et al.*[108] where survival was associated the male sex, black race, BMI >23, absence of cardiovascular disease and hours/week on dialysis.

Sleep and hypertension

We were the first to report in 2001 [12] on the association of systolic blood pressure with sleep disturbance in an a large cohort of patients achieving target levels of hemoglobin concentration by erythropoietin treatment. In that study, 85% of the patients complained sleep disorders. Systolic blood pressure was associated with age and disordered sleep. This may be easily understood by taking into account data in hypertensive patients and on blood pressure in population based studies, and on the prevalence of hypertension in CKD. We were able to show [12] that the risk of a disordered sleep is increased by 39% by 1 unit increase in the Charlson Comorbidity Index, it is increased by 51 % by 10 years of age, and by 400 % by the morning shift and by 440% by use of antihypertensive drugs (yes or no). Also in our studies in patients on secondary hyperparathyroidism needing parathyroidectomy blood pressure was higher that in control patients.[13, 14]

Sleep disorders in CKD

There is presently a contrast between the huge number of studies on sleep disorders on hemodialysis patients and the few studies available on sleep disorders in patients with CKD.

Iliescu *et al.*[16] studied patients with a mean creatinine clearance of 20.96±10.93 mL/min. A disordered sleep was found in 53% of the persons. Sleep efficiency correlated significantly with blood urea, serum creatinine, serum albumin and hemoglobin. Depression was the only significant predictor of poor sleep. The comorbidity index did not discriminate poor sleepers from good sleepers. The study for the first time demonstrate the occurrence of sleep disorders in patients non needing dialysis.

Kurella *et al.*[19] studied patients with a mean eGFR of 25.5 mL/min and a Charlson Comorbidity Index of 4.8±2.1 by the Kidney Disease Quality of Life (KDQOL) 4 item sleep subscale and found a KDQOL score of 69 inversely correlated with plasma creatinine concentration, systolic and diastolic blood pressure. Unfortunately no data were available about use of antihypertensive drugs. When patients were divided into 2 groups, those with eGFR above or below 25 mL/min, those with lower GFR, had a 27% prevalence of sleep maintenance disturbance which was only 14% in patients with higher eGFR. The difference was statistically significant.

Parker *et al.*[109] studied by somnography a small group of patients with CKD grade 4-5 and a mean eGFR of 14.5±7.2 mL/min. CKD patients showed shorter Total Sleep Time and lower Sleep Efficiency than controls. The study suggests that psychological and functional factors might trigger sleep disorders in early CKD, whereas intrinsic sleep disruption occurs in hemodialysis patients.

Markou *et al.*[61] Studied patients with a creatinine clearance of 26.8±9.2 mL/min and found a prevalence of sleep-disordered breathing (SDS) of 54.3% (almost exclusively obstructive events), a prevalence much higher than that reported for the general middle-aged population. The prevalence of RLS was 37.1%, which was also higher than in the general population. The study lacks of data on blood pressure which may be a problem for 80-90% of the CKD people.

Four studies were completed in the years 2005-2007 in 349 patients with early CKD consecutively recruited from the outpatients clinic of the First Division of Nephrology at the Second University of Naples.[110-115]

Study 1 [110, 111] enrolled 52 patients with a

mean plasma creatinine of 1.9±0.8 mg/dLl. They were enrolled for the study within 2 months after the CKD diagnosis was made. Patients had a Charlson Comorbidity Index<6, plasma concentrations of albumin, phosphate and PTH was normal. Hemoglobin concentration averaged 11.7±2.3 g/dL. The prevalence of sleep disorder was 80.7%. Patients with sleep disorders complained increased sleep latency (42.6%), frequent awakenings (62.9%9, early awakenings (57.4%), no refreshing sleep (50%), snoring (12.9%), snoring + sleep apnea (7.4%), nightmares (29.6%), and somnambulism (7.4%).

Study 2 [112, 113] enrolled patients with a mean eGFR of 44.6±27.7 mL/min. The prevalence of sleep disorders was greater than 82%, a prevalence typical of patients treated with dialysis..

Study 3 [114] enrolled 124 patients studied within 4 weeks following the first diagnosis of CKD. Mean eGFR was 58.6±34.7, some 85.5% of the patients needed antihypertensive drugs, 87% were anemic (Hb 11.8±1.6 g/dL) but did not receive erythropoiethin. For this study two groups of age/sex matched chronic non-renal patients were also studied: 1) 50 patients with chronic HCV hepatitis before treatment with interpheron and/or ribavirin; and 2) 64 patients with heart failure (Grade I and II NYHA). Studies in chronic non-renal persons disclosed a 30% prevalence of sleep disorders in chronic HCV hepatitis and 25% in heart failure.

Study 4 [115] reported on a group of 100 CKD patients, equally divided by sex, with a mean eGFR of 59.1±26.7. They were studied at the time of their first admission to the ambulatory kidney care unit. A total of 89% had a disordered sleep and slept less hours. At the time of the study the Charlson Comorbidity Index averaged 3.8±2.1. The prevalence of anemia was 69% (no patient had received erythopoiethin), 84% received antihypertesive drugs.

Based on a cumulative experience on 349 patients with early CKD, the studies allow to speculate that at the time patients became aware of their kidney dysfunction they began to experience a disrupted sleep. The prevalence of poor sleepers is very high and is not different from that observed in dialyzed patients. It is interesting to note that hypertension was a problem even in early CKD and was treated vigorously. This links CKD patients to patients on hemodialysis who may frequently need antihypertensive drugs.

As detailed earlier we were the first to address the relevance of systolic blood pressure in explaining sleep disorders in uremic patients on hemodialysis,[12, 13] and of course we now advance its importance also for CKD, a condition in which hypertension is a marker of vascular disease [116, 117] and affects up to 86% of them.[118]

Hypertension is a strong link between dialyzed patients and CKD as well with non-CKD hypertensive persons. One may speculate that immediately after the diagnosis of CKD, patients face the difficulty of coping with a long lasting disease leading very probably to a dialysis treatment or at the best to a renal transplantation. The data point to disease intrusiveness into the genesis of sleep disorders in early CKD and call for early intervention.

In a 2007 study of Kimmel's group in Washington a 55.2% prevalence of sleep disorders was ascertained in 92 patients with a mean eGFR of 33.4±12.5 ml/min and a mean Hb concentration of 11.9±1.7.[89] In a group of general medical outpatients having normal haemoglobin and eGFR the prevalence of sleep disorder was not different from that in the CKD group. However the study did not analyze blood pressure and the use of antihypertensive drugs and did not measure comorbidities.

Murtagh *et al.* studied a group of patients with a mean age of 82±6.6 years and the lowest GFR in patients not treated with dialysis;[119] 41% had sleep disturbances, 48% restless legs syndrome, and 58% pain.

Sabbatini *et al.*[120] enrolled 154 CKD patients, in good metabolic control, with a mean estimated GFR of 35.9±24.3 mL/min, treated with 1.36 hypotensive drugs for keeping their mean arterial blood pressure at 99.8±11.7 mmHg. The prevalence of poor sleeper was 50.4%. The study supported the lack of correlation between level of renal function and prevalence of sleep disorders. Three years later the Pittsburgh Index for

TABLE VIII.—*Characterization of studies on early CKD.*[16, 19, 61, 109-115, 119-120]

Study No.	Year	Patients	Cr*, CrCl** or eGFR***	% with sleep disorders
Iliescu *et al.*	2004	117	20.96±10.93 ml/min	53
Kurella M *et al.*	2005	78	25,5 mL/min	
		36	<25 mL/min	27
		42	>25 mL/min/	14
Parker KP *et al.*	2005	8	14.5±7.2 mL/min	100+
Markou N *et al.*	2006	35	26.8±9.2	54.3++
De Santo RM *et al.*	2006	52	1.9±0.8 mg/dL	80.7
De Santo RM *et al.*	2006	73	44.6±27.7 mL/min	82.2
Murtagh FE *et al.*	2007	66	11.2±2.8 mL/min	66.0
Cohen SD *et al.*	2007	92	33.4±12.5	55
De Santo RM *et al.*	2008	124	58.6±34.7	89.5
De Santo RM *et al.*	2008	100	59.1±27.6 mL/min	89
Sabatini M *et al.*	2008	154	35.9±24.3 mL/min	50.4

Cr: plasma creatinine concentration (mg/DL), CrCl = measured creatinine clearance, eGFR is estimated GFR; + reduced total sleep time and sleep efficiency; ++54.3% SDB and 37.1 % RLS.

sleep disorders increased from 6.19 to 10.2, whereas eGFR declined by 13.2 mL/min, and the mean arterial pressure increased from 95.2 to 103.7 mmHg (+ 8.5 mmHg) notwithstanding an increase of antihypertensive pills from 1.36±1.05 to 1.78±1.10.

Sleep disorder after kidney transplantation

A few paper have addressed the problem of sleep quality in renal transplant patients.[121] Two case reports [122, 123] one with obstructive SAS and the other with central SAS published in 1993 and 1997 brought the novelty of remarkable improvement of sleep apnoea after renal transplantation. This might have given origin to the erroneous concept that renal transplantation healed sleep disorders which was reinforced when it became evident that also the RLS recovered after renal transplantation and reappeared when kidney function deteriorated.[74] However the concept was weakened recently by a cross sectional analysis of sleep disorders in 301 patients who had undergone renal transplantation showing that 52.5% of them were poor sleepers.[82] The study also disclosed the occurrence of stop-breathing episodes in 52 patients (18%), 69% of them being poor sleepers. Finally a restless-legs syndrome was present in 114 persons(37%), 38% being poor sleepers. The study showed for the first time that sleep quality is poor after successful renal transplantation and preserved kidney function. Sleep disorders correlated only with age but not with time on dialysis, C.-reactive protein, calculated creatinine clearance, blood levels of cyclosporin, steroids, and tacrolimus.

This has generated new interest in the field. In a large group of patients enrolled to study health related QoL, sleep quality and depression in hemodialysis patients waiting for transplantation (N=183) and in transplant recipients (N=884) chronical insomnia affected 15% of the persons on dialysis and only 8% of those undergoing renal transplantation which was associated with declining kidney function.[124]

Erylmaz *et al.*[125] studied a group of 100 kidney recipients using the Pittsburgh Index and showed that one third of them, being younger, less educated and more depressed were poor sleepers and had impaired QoL.

Concerning sleep apnea it was possible to confirm that only a minority (27.3%) of patients were cured by kidney transplantation in 11 patients studied with polysomnography. The study because of the limited number of participants did not solve the problem of identifying responder and non-responders. The persistent of obstructive SAS following transplantation may be a cause for cardiovascular disease in this condition as well as to the persistence of disordered sleep.[126]

Also in the TransQoL-HU study the prevalence of sleep apnea-hypopnea syndrome

TABLE IX.—*Factors potentially contributing to sleep disorders in CKD, ESRD, and transplanted patients. Modified from reference 33.*

1. Demographic factors
— aging
— male sex (?)
— white race

2. Lifestyle factors
- coffee intake
— alcohol intake
— cigarette smoking
— poor sleep hygiene
— sedentary life
— obesity

3. Disease-related factors
— general health status
— declining GFR
— comorbidities
— anemia
— symptoms of uremia
— metabolic changes
blood urea
creatinine
PTH
calcium concentration
altered neurotransmitter production
altered circadian rhythms
— hypertension and antihypertensive drugs

4. Psychological factors
— anxiety
— depression
— stress
— worries
— alexithymia

5. Treatment related factors
— interleukins, chemokines, other immune products
— C-reactive protein
— albumin concentration
— rapid changes in fluid-electrolyte balance
— rapid changes in acid-base balance
— abnormalities in melatonin
— hyperparathyroidism resistant to medical therapy
— alteration in thermoregulatory
— changes to light exposure
— premature discontinuation of dialysis
— dialysis in the morning
— the dialysis team
— day of the weekly dialytic cycle
night before dialysis
night of the longest intradialytic interval
night following dialysis
— inadequate dialysis
— water for dialysis
— dialysate temperature
— a machine-dependent life
— losses and dependencies linked to treatment

6. social factors
— lower education
— life in urban environments
— economic conditions
— living alone
— hyper-independent patients

was 27% and was independently predicted by the male gender, age, lower education, consumption of hypnotic drugs and the comorbidity index and declining renal function [127] and of worse QoL.[128]

The study also showed a 4.8% prevalence of the RLS,[81] which predicted mortality.[129] Furthermore 29% of patients with the syndrome had insomnia, whereas only 9% were insomniac in the group without RLS.[130] By contrast in a recent report Periodic Limb Movements in Sleep were reduced after renal transplantation.[46]

Factors contributing to sleep disturbance in CKD

Dialysis patients have a disturbed sleep characterized by a) changes in sleep architecture, b) sleep apnea syndrome, c) restless leg syndrome, d) periodic limb movement disorder, e) excessive daytime sleepiness, f) nightmares, g) sleepwalking, h) narcolepsy. Also patients on CKD have a disordered sleep. Even renal transplantation is ineffective in restoring a refreshing sleep.

Parker [33] has identified 1) demographic factors; 2) lifestyle factors; 3) disease-related factors; 4) psychological factors; and 5) treatment related factors. Since also early and late CKD patients have a disordered sleep we may unify all categories of patients with renal disease and by taking into consideration our original findings on a) sleep and the weekly schedule and the morning shift, b) sleep disorders and blood pressure, c). the role of PTH, d) the presence of a disordered sleep at the time of early diagnosis of chronic kid-

ney disease, and e) the role of comorbidities, we modify Parker hypotheses for patients on dialysis by including socioeconomic factors. The result is given in Table IX.

Among the various factors depression is crucial. Depression is associated with sleep disorders in the general population, but in end-stage renal disease 90% of the patients with depression complain about sleep quality and quantity [16, 29, 131-133] and is prevalent in women and carries a mortality risk. In the paper of Drayer *et al.*[133] was associated with a risk of death (adjusted hazard ratio=4.1-95% CI 1.5-32). Kimmel *et al.* have extensively studied depression in association with pain and sleep complaints.[89, 134-139] They showed not only the importance of illness burden and the mortality risk and stressed the need to evaluate and treat symptoms and improve sleep disorders alleviate pain as an effective measure to improve QoL.

Circadian rhythm are disturbed in CKD.[33,110] This has stimulated interest in melatonin metabolism.[140] In hemodialyzed patients no rise in nocturnal melatonin concentration was found,[141-142] thus confirming the suspicion of melatonin involvement in sleep disorders of hemodialyzed patients. Recent studies have also disclosed [143] an impaired rise of nocturnal melatonin concentration in CKD in patients with eGFR of 57±20 mL/min. eGFR correlated to melatonin amplitude and total melatonin production. Patients with eGFR>80 mL/min had the highest nocturnal melatonin peak concentration, those with eGFR<30 mL/min had the lowest peak concentration. No correlation was found between the rhythm of core body temperature, melatonin and cortisol. These data further support the existence of correlation between nocturnal melatonin rise and declining GFR and suggest to study the effects of exogenous melatonin administration in CKD patients and disturbed sleep.

Finally one cannot neglect that circadian rhythms are disrupted in CKD/ESRD and can be influenced by exposure to light, by dialysate temperature. A reduction in dialysate temperature may ameliorates sleep after dialysis treatment.[144] Finally insomnia correlates with interleukins, chemokines, immunological products, plasma albumin and C-reactive protein.[31]

Riassunto

Disordini del sonno nella nefropatia

I disordini del sonno sono frequenti nei pazienti affetti da nefropatia in fase terminale in terapia emodialitica o in dialisi peritoneale. Tuttavia, anche un trapianto di rene ben funzionante non risolve i problemi relativi al sonno, che sono presenti anche nell'insufficienza renale cronica in fase iniziale. Quando i pazienti vengono a conoscenza per la prima volta di essere affetti da una patologia come la malattia renale cronica, che può portare alla dialisi o nelle migliori delle ipotesi al trapianto di rene, iniziano a riferire un sonno disturbato. I disordini del sonno includono l'insonnia (I), l'apnea (SAS), la sindrome delle gambe senza riposo (RLS), il movimento periodico degli arti (PLMD), l'eccessiva sonnolenza diurna (EDS), il sonnambulismo, gli incubi, e la narcolessia. Il sonno disturbato non ha incontrato l'interesse clinico e scientifico che merita, inoltre non è disponibile una soluzione ben definita dei disturbi legati al sonno. Tuttavia, la conoscenza del fatto che il sonno di scarsa qualità è associato ad una scarsa qualità di vita e che comporta un aumento del rischio di mortalità ha recentemente stimolato l'interesse in questo ambito. Vi sono numerose cause putative dei disordini del sonno nell'insufficienza renale cronica e nella nefropatia in fase terminale. Per un'ipotesi unificatrice, fattori demografici, stili di vita, fattori correlati alla patologia, fattori psicologici, fattori correlati ai trattamenti medici e fattori sociali devono essere tenuti in considerazione.

Parole chiave: Malattia renale cronica - Disturbi del sonno - Sindrome delle gambe senza riposo - Sonnanbulismo - Dialisi - Trapianti - Ipertensione arteriosa.

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