Sleep Behavior Disorders in a Large Cohort of Chinese (Taiwanese) Patients Maintained by Long-Term Hemodialysis

Wen-Ching Chen, MD, Paik-Seong Lim, MD, PhD, Wen-Chieh Wu, MD, Hsien-Chang Chiu, MD, Chih-Hsuan Chen, MD, Ho-Yen Kuo, MD, Tsung-Wei Tsai, MD, Po-I Chien, MD, Yue-Jane Su, MD, Yu-Liang Su, Sze-Hung Hung, MD, and H. Feidhlim Woods, MB, MRCP(UK)

• ***Background:*** **Disorders of sleep behavior and sleep-related breathing disorders are common in hemodialysis patients. Most such evidence is based on studies involving small numbers of patients.** ***Methods:*** **We undertook a large multicenter analysis of sleep behavior in more than 700 Taiwanese patients on maintenance hemodialysis therapy for 6 months to 20-plus years by using self-administered questionnaires: the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and Berlin Questionnaire for risk for sleep apnea, validated for the general population. Patients also completed a questionnaire to assess symptoms related to restless legs and periodic limb movements (PLMs). Sleep behavior was analyzed in relation to demographic and dialysis-related parameters provided by the participating dialysis centers.** ***Results:*** **Sleep disturbance was very common in this cohort, with problems of insomnia (66.6%) exceeding those related to daytime sleepiness (17.8%). Sleep disturbances were associated with restless legs syndrome (RLS)/PLM and a high risk for sleep apnea, determined by using the Berlin Questionnaire. Older age increased the odds of daytime sleepiness, but not insomnia. Lower dialysis dose (single-pool Kt/V) increased the likelihood of daytime sleepiness and was associated with greater rates for RLS/PLM and risk for sleep apnea. Use of antihypertensive medications (a probable surrogate for more severe hypertension) was associated strongly with high risk for sleep apnea. Smoking was associated with RLS/PLM and risk for sleep apnea, whereas consumption of stimulant beverages (coffee and tea) had contrary effects on RLS/PLM and risk for sleep apnea and were not implicated in measures of insomnia or daytime sleepiness. A greater likelihood of insomnia for greater hemoglobin levels and greater likelihood of daytime sleepiness for patients administered vitamin D analogues were not explained by the available data.** ***Conclusion:*** **Sleep disorders and sleep-related breathing disorders are common in hemodialysis patients. Greater attention in the care of dialysis patients needs to be directed to the diagnosis and management of sleep disorders.** ***Am J Kidney Dis*** **48:277-284.**

INDEX WORDS: Hemodialysis (HD); sleep behavior; sleep apnea.

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SLEEP DISORDERS (dyssomnias) are common in hemodialysis (HD) patients, occurring in up to 80% of patients,[1-5] and recently were reviewed by Wadhwa and Akhtar.[6] Despite the numerous reports in the literature, neither the Kidney Dialysis Outcomes Quality Initiative nor the European Best Practice Guidelines for Dialysis specifically refer to management of sleep problems. Commonly reported sleep disturbances include insomnia (difficulty initiating sleep and/or frequent nocturnal waking) and daytime sleepiness. Dyssomnia in HD patients commonly is associated with restless legs syndrome (RLS) and/or periodic limb movement (PLM).[7] Dyssomnia also is associated with sleep-related breathing disorder (sleep apnea [SA]), which is more common in patients with chronic kidney disease and dialysis patients.[8,9] Impairment of health-related quality of life in HD patients is associated with sleep disorders[10,11] and sleep-related breathing disorders.[12] More worrying is the association of SA or hypopnea with adverse effects on blood pressure control and left ventricular remodeling and the association of SA with risk for cardiovascular events.[13] In addition, sleep

From An Hsin Chia-Yi Clinic; Department of Food & Nutrition, Tung's Taichung Metro Harbor Hospital and Providence University; Shin Loong Clinic; An Hsin Chushan Clinic; Ever New Hospital; Min Sheng Lung-Tan Hospital; Lee Fooh Clinic; Tai Shin Hospital; Su's Clinic; Tseng Han Chi Hospital, Taiwan; and NephroCare Asiapacific, Hong Kong.

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Address reprint requests to H. Feidhlim Woods, MB, MRCP(UK), Medical Director, NephroCare Asiapacific, 5101 Sun Hung Gai Bldg, 30 Harbour Rd, Hong Kong (SAR). E-mail: feidhlim.woods@fmc-asia.com

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deficit has been related to immune suppression.[14] Thus, sleep disorders possibly are associated with the 2 most common causes of morbidity and mortality in dialysis patients: cardiovascular disease and infection.

Causes of sleep disturbance in dialysis patients are unknown and likely to be multifactorial. Dyssomnia and its associations are evident in patients with advanced chronic kidney disease, appear to worsen as chronic kidney disease progresses, and are ameliorated only partially by dialysis treatment.[1-3] Although nocturnal quotidian HD was reported to improve sleep patterns, only modest effects of this intense modality of HD were seen for RLS and PLM, whereas significant improvement was reported for SA.[15] We are aware of only 1 other large cohort observational study that assessed self-reported sleep disturbances in HD patients.[5] In that study, the investigators devised their own instrument for assessing sleep disorders, whereas we choose to use assessment instruments validated in the general population. Complete analysis of sleep disorders that might direct specific therapy are complex and time consuming (eg, polysomnography in sleep laboratories). To identify patients who might benefit most from such studies, it is first required to undertake screening studies with validated instruments. We have undertaken such a cohort study in more than 700 HD patients treated in 10 dialysis centers affiliated with Nephrocare Asia Pacific, Taiwan (a business unit of Fresenius Medical Care). Our findings generally support those of smaller studies and additionally provide possible new insights into the understanding of dyssomnias in HD patients.

METHODS

The study was conducted between September 1, 2004, and December 31, 2004. Of the 12 Nephrocare centers then operating in Taiwan, 10 centers agreed to recruit study subjects. A total of 1,024 patients were approached to participate in a self-assessment of sleep health, and 806 patients (78.7%) agreed. Of these, 736 patients completed the provided self-assessment questionnaires. The centers provided additional demographic data and data related to dialysis and laboratory parameters for each patient. The study was approved by the Medical Advisory Committee of Nephrocare Asia Pacific, Taiwan, following good practice guidelines for the conduct of clinical studies.

Sleep Health Assessment

Three validated questionnaires (translated into Chinese) were self-administered by the patients, assisted as required by dialysis center staff: the Pittsburgh Sleep Quality Index (PSQI),[16] the Epworth Sleepiness Score (ESS),[17] and the Berlin Questionnaire[18] for identification of risk for SA. Although not specifically validated for a Chinese-speaking population, we found no components of the questionnaires that might make them inapplicable for this population. In addition, patients completed a questionnaire with their physicians to assess the presence of RLS and PLM of sleep. Patients documented their consumption of alcohol, coffee, and tea and their use of hypnotic agents.

Other Data

Participating dialysis centers provided relevant and coincident data for dialysis prescription (frequency, dialysis time, filter flux, and blood flow rate); use of erythropoietin, vitamin D analogues, and antihypertensive medications; and results of laboratory tests, including calculated single-pool Kt/V (spKt/V). For laboratory results, reliance was placed on the routine monthly blood testing of patients according to procedures in place in each center.

Statistical Analysis

All data initially were entered in an Excel database (Microsoft Corp, Seattle, WA) and subsequently uploaded to an SPSS data file (SPSS, version 13; SSPS Inc, Chicago, IL) for analysis. As appropriate, data are summarized as mean $\pm$ SD or median and range or interquartile range. Significance for associations was tested by using Spearman correlation and Kruskal-Wallis tests, as appropriate. To assess the possible influence of demographic and other variables on measures of sleep health, univariate logistic regression models were established for the odds of PSQI score higher than 5 (insomnia) or ESS score higher than 10 (daytime sleepiness), risk for SA (Berlin Questionnaire: high risk, 1; no risk, 0), and reporting of RLS/PLM (yes/no). For logistic regression analyses, variables were entered by using the forward conditional method, with statistical significance determined for $\alpha = 0.05$.

RESULTS

Of 736 completed questionnaires, 26 were rejected for incompleteness of data. Principal demographic and clinical characteristics of respondents are listed in Table 1. Mean age was 57.7 $\pm$ 13.4 (SD) years, and median time on dialysis therapy was 58 months (range, 6 to 287 months). Twenty-four percent of patients had diabetes. Ninety percent were administered erythropoietin; 38%, antihypertensive medications; and 25%, vitamin D analogues. Alcohol consumption was extremely low (<2% of patients), and less than 10% of patients smoked cigarettes (20% in males). Less than 5% regularly drank

Table 1. General Characteristics

Women	375 (52.8)
Men	335 (47.2)
Diabetes	167 (23.5)
Age (y)	57.6 ± 13.38
Vintage (mo)	58 (6–287)
Antihypertensives	266 (37.5)
Erythropoietin	639 (90.0)
Vitamin D analogues	176 (24.8)
Drink alcohol	13 (1.8)
Smoke cigarettes	70 (9.9)
Drink coffee	29 (4.1)
Drink tea	134 (18.9)
Drink coffee or tea	153 (21.5)
Require hypnotics for sleep	252 (35.5)
Dialysis	
Morning	307 (43.2)
Afternoon	296 (41.7)
Evening	107 (15.1)
Dialyzer	
High flux	271 (38.2)
Low flux	439 (61.8)
Blood flow (mL/min)	269 ± 35
Dialysis time (h)	4.01 ± 0.23
Predialysis blood urea nitrogen (mg/dL)	61.7 ± 16.21
spKt/V	1.47 ± 0.29
Hemoglobin (g/dL)	10.2 ± 1.44
Albumin (g/dL)	3.91 ± 0.40
Creatinine (mg/dL)	12.0 ± 4.18
Sodium (mEq/L)	138.8 ± 3.42
Potassium (mEq/L)	4.53 ± 0.77
Chloride (mEq/L)	100. ± 4.26
Calcium (mg/dL)	9.64 ± 0.91
Phosphate (mg/dL)	4.66 ± 1.43
Calcium-phosphate product	44.8 ± 14.15
iPTH (pg/mL)	203.5 ± 304.2

NOTE. To convert blood urea nitrogen in mg/dL to mmol/L, multiply by 0.357; hemoglobin and albumin in g/dL to g/L, multiply by 10; creatinine in mg/dL to μmol/L, multiply by 88.4; sodium, potassium, and chloride in mEq/L to mmol/L, multiply by 1; calcium in mg/dL to mmol/L, multiply by 0.2495; phosphates in mg/dL to mmol/L, multiply by 0.323; iPTH in pg/mL to pmol/mL, multiply by 0.9.

coffee, whereas 19% regularly consumed tea. More than 35% of patients stated that they regularly used hypnotics to aid sleep. Fifteen percent of patients dialyzed in the evening, and the remainder were divided equally between morning and afternoon shifts. All patients dialyzed against bicarbonate-buffered dialysate and with dialysis machines with volumetrically controlled ultrafiltration. Thirty-eight percent of patients regularly dialyzed with a high-flux membrane. Average dialysis session duration was 4 hours, with little spread. Average blood flow rate was 269 ± 35 mL/min, and average achieved spKt/V was 1.47 ± 0.29: women had a higher spKt/V than men (1.56 ± 0.29 versus 1.37 ± 0.25; $P <$ 0.0001). Patients generally were well nourished (serum albumin, 3.9 ± 0.4 g/dL), and mean values for calcium, phosphate, calcium-phosphate product, and intact parathyroid hormone (iPTH) were within acceptable ranges (Table 1).

Median values and percentile distributions and frequencies for relevant sleep health indices are shown in Table 2 and Fig 1. We were unable to identify a significant impact of patient sex for any of the measured indices (ESS and PSQI) and therefore report these results for men and women together. Values for the PSQI were normally distributed, whereas those for the ESS were highly skewed (Fig 1). Daytime sleepiness (ESS score $>$ 10) was reported by 16.8% of patients, whereas problems with nocturnal sleeping were present in 66.6% of patients. Men and women had similar scores for the PSQI and ESS. RLS and/or PLM were reported by 23% of patients. According to results of the Berlin Questionnaire, 20% of patients were at risk for SA. Men had significantly greater rates for both conditions compared with women (risk for SA, $P < 0.0001$; RLS/PLM, $P = 0.007$).

Significant associations (Kruskal-Wallis) for RLS/PLM were identified for a high PSQI score ($P = 0.04$), but not for a high ESS score ($P =$ 0.07). RLS/PLM was associated with a high risk for SA ($P = 0.013$), lower spKt/V ($P = 0.006$), smoking ($P = 0.038$), and consumption of coffee ($P = 0.001$), but not consumption of tea ($P =$ 0.233). No significant associations for RLS/PLM were identified for age, dialysis vintage, diabetes, use of antihypertensives, or blood hemoglobin, serum albumin, calcium, phosphate, or iPTH levels.

For risk for SA, significant associations were seen for use of antihypertensives ($P < 0.0001$), smoking ($P = 0.005$), consumption of tea ($P =$ 0.009), but not coffee ($P = 0.58$), and lower spKt/V ($P = 0.003$). Risk for SA also was associated with high PSQI ($P = 0.003$) and high ESS scores ($P < 0.0001$). No significant associations for risk for SA were identified for age, vintage, diabetes, or blood hemoglobin, serum albumin, calcium, phosphate, or iPTH levels. Body mass index for patients at high risk for SA (22.62 ± 3.95 kg/m^2) was not significantly differ-

Table 2. Quality of Sleep

	Minimum	25th Percentile	Median	75th Percentile	Maximum
ESS	0	2	5	8	24
PSQI	0	4	7.5	11	20
Patients with:	All	Men	Women		
PSQI > 5 (%)	66.62	65.37	67.73		
ESS > 10 (%)	16.76	16.12	17.33		
RLS (%)	12.96	14.63	11.47		
PLM (%)	12.96	16.12	10.13		
RLS and/or PLM (%)	22.96	27.46	18.93		
High risk for SA*	20.14	25.97	14.93		

*Berlin Questionnaire.

ent from that of patients without this risk (22.25 ± 3.56 kg/m^2), and only 9 of 144 patients with high Berlin Questionnaire scores had a body mass index greater than 30 kg/m^2. Use of hypnotics was associated with RLS/PLM ($P = 0.005$), but not risk for SA ($P = 0.22$).

Four logistic regression models were calculated for each PSQI score higher than 5, ESS score higher than 10, reported RLS/PLM, and high risk for SA by Berlin Questionnaire. Variables entered in the models included patient sex; age; diabetes; dialysis vintage; type of dialyzer (low or high flux); dialysis shift (morning, afternoon, evening); categorical variables for consumption of tea and coffee; cigarette smoking; use of antihypertensives, vitamin D analogues, and hypnotics; and laboratory variables, including hemoglobin, albumin, creatinine, calcium-phosphate product, iPTH, and calculated spKt/V. For each model, sleep indices other than the dependent variable were included as either scalar (PSQI and ESS) or categorical variables (risk for SA, RLS/PLM). Results of the final iterations for each model are listed in Table 3.

The likelihood of a high PSQI score was increased by a higher ESS score (10% for each unit) and for greater hemoglobin level (17% for each 1 g/dL [10 g/L]). High PSQI score was much more likely for patients reporting regular use of hypnotic agents, but this almost certainly represents reverse causality.

The likelihood of a high ESS score was increased by patient age (3% for each additional year), but marginally decreased for longer time on dialysis treatment (0.6% for each additional month). Use of vitamin D analogues increased the odds of a high ESS score, as did a high PSQI score (8% for each additional score unit). Daytime sleepiness was less likely in patients reporting regular use of hypnotics, and high ESS score was less likely for greater serum albumin levels. Daytime sleepiness was almost 4 times more likely to occur in patients with a high risk for SA by Berlin Questionnaire.

Patients with diabetes were 60% more likely to report RLS/PLM, and this symptom also was more likely for patients with higher scores for the PSQI and ESS (10% and 6% per unit score, respectively). The odds of RLS/PLM increased for greater serum creatinine level (7% per 1 g/dL [88 μmol/L]) and were lower in patients treated by using low-flux dialyzers. Regular coffee consumption greatly increased the likelihood of reporting RLS/PLM.

High risk for SA was less likely in women than men. Higher PSQI and ESS scores increased the likelihood of a high score on the Berlin Questionnaire (5% and 14% per unit score, respectively), and risk for SA was greater for those regularly consuming tea. Use of antihypertensives greatly increased the likelihood of risk for SA.

DISCUSSION

To our knowledge, this is the largest survey of sleep behavior in Asian HD patients. We confirm that sleep disorders and such associated problems as RLS, PLM, and risk for SA are common in this HD population. Our results differ from others in that daytime sleepiness affected a minority of patients. We found significant correlations between various patterns of sleep disturbance and certain behaviors (eg, cigarette smoking, consumption of stimulant beverages). Higher scores for the PSQI and ESS independently predicted self-report of RLS and/or PLM, and, not surprisingly, daytime sleepiness was 4-fold more

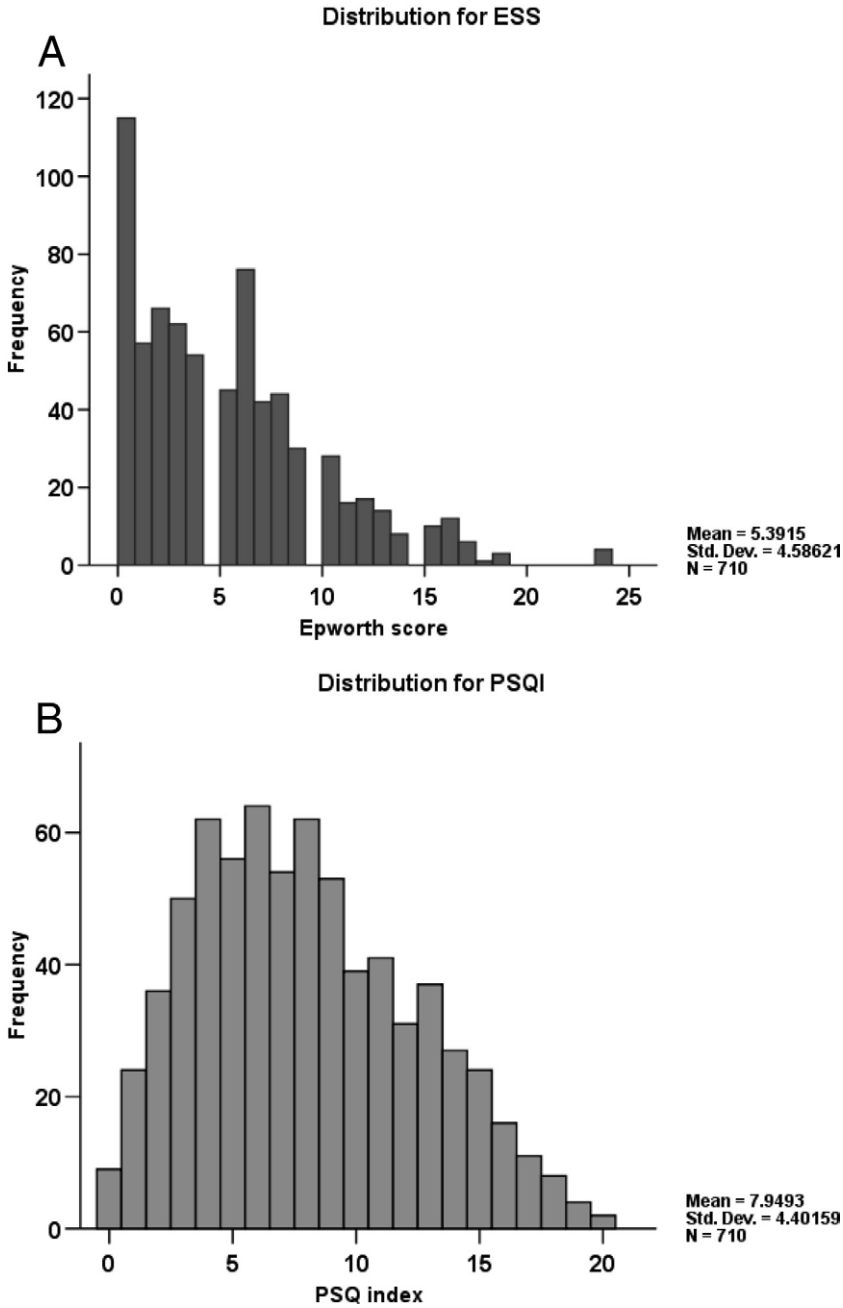

Fig 1. Histograms show distribution for (A) ESS and (B) PSQI scores. For the ESS, a score higher than 10 indicates excess daytime sleepiness. For the PSQI, a score higher than 5 indicates insomnia.

likely in patients identified as high risk for SA. We interpret the increased likelihood of SA for use of antihypertensives as an example of reverse causality, which probably also explains the high likelihood of insomnia for patients regularly using hypnotic agents.

Hui et al[19] reported that sleep disorders, RLS, and SA were common in Chinese (Hong Kong) patients treated with continuous ambulatory peritoneal dialysis, and their results are not greatly dissimilar to our findings. Sabbatini et al[5] analyzed insomnia patterns in a large multicentric cohort of Italian HD patients. Eighty-six percent of 694 Italian HD patients had some degree of insomnia, and the investigators classified 45% as severely insomniac. Comparisons across these 2 large studies are hampered by the use of different assessment instruments, but the investigators re-

Table 3. Logistic Regression Models for Sleep Disorders

			95% CI	
	P	Odds	Lower	Upper
Logistic regression PSQI > 5				
Use hypnotics (yes *v* no)	<0.0001	15.356	8.754	26.937
Hemoglobin (g/dL)	0.027	1.168	1.018	1.336
ESS (unit)	<0.0001	1.102	1.056	1.150
Logistic regression ESS > 10				
Age (y)	0.009	1.026	1.006	1.046
Vintage (mo)	0.009	0.994	0.989	0.998
Use hypnotics (yes *v* no)	0.049	0.592	0.352	0.997
Use vitamin D analogue (yes *v* no)	0.039	1.675	1.026	2.735
Risk for SA (yes *v* no)	<0.0001	3.915	2.470	6.206
Albumin (g/dL)	0.040	0.541	0.300	0.973
PSQI (unit)	0.008	1.079	1.020	1.141
Logistic regression RLS/PLM				
Diabetes (yes *v* no)	0.032	1.603	1.043	2.465
Consumes coffee (yes *v* no)	0.001	3.742	1.666	8.404
Low-flux dialyzer (*v* high flux)	0.033	0.660	0.450	0.966
Creatinine (mg/dL)	0.001	1.071	1.027	1.117
PSQI (unit)	<0.0001	1.102	1.056	1.150
ESS (unit)	0.005	1.058	1.017	1.100
Logistic regression risk for SA				
Sex (female *v* male)	0.005	0.547	0.360	0.831
Use antihypertensives (yes *v* no)	<0.0001	2.220	1.479	3.331
Consumes tea (yes *v* no)	0.011	1.860	1.150	3.006
PSQI (unit)	0.029	1.054	1.005	1.104
ESS (unit)	<0.0001	1.144	1.097	1.194

NOTE. See text for full description of regression models. Risk for SA according to Berlin Questionnaire.

ported greater rates for daytime sleepiness (41%) and RLS/PLM (37%) in the Italian cohort than we found in Taiwanese patients. In contrast to other reports, our patients showed more problems with insomnia (PSQI score > 5) than daytime somnolence (ESS score > 10), although both indices of dyssomnia correlated. Men and women scored equally on the PSQI and ESS, but men were more likely to be at risk for SA. The likelihood of daytime sleepiness, but not insomnia, was associated with older age. We could not identify an additional risk for sleep disturbance comparing patients with and without diabetes, which is consistent with the Italian study,[5] but diabetes increased the likelihood of RLS/PLM. Current smoking was associated with RLS/PLM and risk for SA (Kruskall Wallis), but was not an independent predictor of either in logistic regression. Consumption of stimulant beverages (coffee and tea) also did not significantly impact on the odds of high PSQI and ESS scores and had contrary effects on RLS/PLM (coffee increased) and risk for SA (tea increased). We probably also should have enquired about other beverages, such as colas.

Use of antihypertensive medications was associated strongly with risk for SA. Assuming that use of antihypertensive medications identifies patients with more severe hypertension, this association may be cause and effect. Obstructive SA (the form more likely to be associated with dialysis therapy) is associated with hypertension. Blood pressure increases during and immediately after apneic episodes, and this finding was confirmed in dialysis patients.[20] This increase in blood pressure reflects a surge of sympathetic activity about the time of apneic episodes, but other and complex cardiodynamic responses are likely. In at least 1 well-controlled study, continuous positive airway pressure decreased nocturnal blood pressure and had a modest effect on daytime blood pressure.[21] In the longer term, SA and the consequent hypoxemia are associated with left ventricular hypertrophy[22] and predict adverse cardiovascular outcomes in dialysis patients.[13] Zocalli et al[22] also provided evidence

that SA may contribute to autonomic neuropathy in HD patients. Combined, effects of SA on left ventricular remodeling and autonomic neuropathy therefore might contribute to such intradialytic symptoms as hypotension. As far as we are aware, such an association has not been researched. In our population, 20% of patients had a high risk for SA, determined by using the Berlin Questionnaire. These patients are candidates for more detailed sleep studies, including polysomnography and oximetry. Appropriate management of SA possibly would aid in management of hypertension, decrease the risk for cardiovascular disease, and ameliorate intradialytic symptomatic hypotension. Our data also suggest that management of SA would improve daytime sleepiness.

Dialysis shift had no independent effect on any of the recorded sleep patterns, whereas Sabbatini et al[5] identified greater odds of insomnia for patients dialyzing in the morning. However, in our patients, risk for SA was significantly less in patients dialyzing on the morning shift ($P = 0.031$, Mann-Whitney U test) compared with afternoon and evening shifts. This finding may reflect confounding for male patients, who were more likely to dialyze in the evenings. We could not identify an effect of dialyzer membrane flux on dyssomnia. Lower dose of dialysis (spKt/V) was associated with RLS/PLM and risk for SA, but dialysis dose was not an independent predictor of any sleep disorder, and the association of low spKt/V and RLS/PLM and risk for SA may be confounded by male sex (lower spKt/V than women).

Somnolence is a recognized symptom of advanced renal failure, and patients report greater alertness after initiation of dialysis therapy. This suggests retention of uremic toxin(s) with soporific properties, but also may reflect a complex derangement of multiple neurotransmitter systems that is only partially amenable to dialysis treatment. Yoshioka et al[23] reported actual worsening of sleep behavior after initiation of dialysis treatment, and the finding that sleep disturbance is similar on dialysis and nondialysis days is not consistent with a dialyzable soporific toxin(s) exerting an acutely reversible effect on sleep behavior.[3,24] We are not aware of studies that specifically examined the relationship between dialysis dose or type (diffusive versus convective) and sleep disorders, although as reported, long nocturnal quotidian dialysis may improve some features of disordered sleep.[15]

The increased odds of high PSQI score for greater hemoglobin level and for high ESS score for use of vitamin D analogues were unexpected results for which we cannot speculate about the cause or association and that may simply be spurious findings arising from statistical analysis. Although dyssomnias and sleep-related breathing disorders in dialysis patients are common in the medical literature, the absence of reference to these disorders in the index of available textbooks about dialysis might suggest that sleep disorder is not a cause for concern. We confirm a high prevalence of sleep disorders in this large population of Taiwanese HD patients and believe it is a cause for concern and appropriate management. Lifestyle and dietary habits in this population may differ from those in other cultures and races, so we cannot confidently state that our findings are representative, but they generally are consistent with those of the Italian patients of Sabbatini et al[5] and results of smaller studies. We are especially alarmed at the high prevalence of risk for SA, 10-fold greater than reported in the general adult population,[25] because of its known association with risk for cardiovascular disease and possible contribution to hypertension.[13,20,22] For those patients, it is planned to pursue further diagnostics and, as appropriate, implement specific treatment. However, other less life-threatening forms of dyssomnia in dialysis patients are likely to impair functioning and quality of life,[9,10] and remedial measures should be actively pursued. In the absence of specific guidelines, dialysis patients should receive the benefit of sleep hygiene remedial measures effective in the general population.[26] As with adequate nutrition, adequate sleep is a necessity of normal living. Unlike the attention given to adequate nutrition in dialysis patients, little or no attention is given to ensuring adequate sleep. This is a deficit that requires redressing.

Since submitting this report, we have become aware of another large (883 Italian patients) cohort screening study of sleep disorders in dialysis patients. Their results are very similar to ours in that insomnia was present in 69.1% and daytime sleepiness was present in 11.8% of patients. RLS

was reported in 18.4% and high risk for SA was reported in 23.6%. Taken together and from 2 diverse ethnicities, the report from Merlino et al[27] and our own clearly identify disordered sleep in dialysis patients as a problem requiring more intensive management.

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