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Nonadherence in hemodialysis: Associations with mortality, hospitalization, and practice patterns in the DOPPS

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Nonadherence in hemodialysis: Associations with mortality, hospitalization, and practice patterns in the DOPPS.

Background. Nonadherence among hemodialysis patients compromises dialysis delivery, which could influence patient morbidity and mortality. The Dialysis Outcomes and Practice Patterns Study (DOPPS) provides a unique opportunity to review this problem and its determinants on a global level.

Methods. Nonadherence was studied using data from the DOPPS, an international, observational, prospective hemodialysis study. Patients were considered nonadherent if they skipped one or more sessions per month, shortened one or more sessions by more than 10 minutes per month, had a serum potassium level of >6.0 mEq/L, a serum phosphate level of >7.5 mg/dL (>2.4 mmol/L), or interdialytic weight gain (IDWG) >5.7% of body weight. Predictors of nonadherence were identified using logistic regression. Survival analysis used the Cox proportional hazards model adjusting for case-mix.

Results. Skipping treatment was associated with increased mortality [relative risk (RR) = 1.30, $P = 0.01$], as were excessive IDWG (RR = 1.12, $P = 0.047$) and high phosphate levels (RR = 1.17, $P = 0.001$). Skipping also was associated with increased hospitalization (RR = 1.13, $P = 0.04$), as were high phosphate levels (RR = 1.07, $P = 0.05$). Larger facility size (per 10 patients) was associated with higher odds ratios (OR) of skipping (OR = 1.03, $P = 0.06$), shortening (OR = 1.03, $P = 0.05$), and IDWG (OR = 1.02, $P = 0.07$). An increased percentage of highly trained staff hours was associated with lower OR of skipping (OR = 0.84 per 10%, $P = 0.02$); presence of a dietitian was associated with lower OR of excessive IDWG (OR = 0.75, $P = 0.08$).

Conclusion. Nonadherence was associated with increased mortality risk (skipping treatment, excessive IDWG, and high phosphate) and with hospitalization risk (skipping, high phosphate). Certain patient/facility characteristics also were associated with nonadherence.

Key words: nonadherence, noncompliance, DOPPS, outcomes, hemodialysis, skipping treatments.

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Hemodialysis is a lifesaving but complex therapy. It makes enormous demands on patients with end-stage renal disease (ESRD), thereby affecting their quality of life [1]. Adherence to complicated treatment regimens associated with hemodialysis is vital. The definition of nonadherence and its assessment have both proven controversial [2, 3]. However, by compromising the delivery of dialysis, nonadherence can affect both patient morbidity and mortality, a finding that is well recognized [4].

It has been known for some time that survival of ESRD patients is better in Europe and Japan in comparison with the United States after adjustments for age, gender, and diabetes mellitus [5]. Reasons for these differences are unclear. Differences in practice patterns may provide one explanation. A detailed examination of practice patterns has been undertaken in the Dialysis Outcomes and Practice Patterns Study (DOPPS), an international, observational, prospective hemodialysis study initiated between 1996 and 1999 [6]. In addition to practice patterns, patient behavior and adherence to prescribed treatment may be other determinants of outcomes. A few studies have looked at the effect of nonadherence on outcomes, but these have been based mainly on patients from the United States, used a limited set of variables, utilized relatively small sample sizes, and have not always measured the long-term consequences of nonadherence. Two studies have shown that nonadherence to the hemodialysis regimen is associated with an increased risk of death [7, 8]. One study has addressed international comparisons of nonadherence in hemodialysis with a descriptive approach [9], based on questionnaires mailed to health professionals caring for hemodialysis patients in different countries; associations with patient outcomes were not examined.

The present study was based on the hypothesis that facilities with lower nonadherence rates are likely to

manifest lower mortality and fewer hospitalizations. It was designed to provide an international perspective on the magnitude, distribution, and predictors of nonadherence (both at patient and facility level).

METHODS

Data source

The patient sample was drawn from the DOPPS database, which includes information about hemodialysis patients in Japan, the United States, and five European countries (France, Germany, Italy, Spain, and the United Kingdom, collectively referred to as Euro-DOPPS). A nationally representative sample of dialysis facilities was enrolled in each country, followed by selection of a random sample of hemodialysis patients at each participating center. The study design and data collection instruments were uniform across nations. Data on nonadherence were collected at each dialysis facility by a center-based research coordinator. Details of study design, facility sampling, patient sampling, and data collection have been published previously [10].

A data validation study was carried out in all five European countries by the contracting research organization (CRO) in Europe. The CRO extracted data from a sample of dialysis facilities, which was compared with the data extracted by the staff at those facilities. While a formal data validation has not been conducted for the United States facilities, the values for age, diabetes mellitus as a primary cause of ESRD, and proportion of female and African American patients in the United States-DOPPS sample are very similar to the values reported for the 1997 United States population of in-center hemodialysis patients by the United States Renal Data System (USRDS) [11], suggesting that the United States-DOPPS data are indeed representative of the United States ESRD population.

The current study reflects data obtained from the United States (145 facilities, 3359 patients), Euro-DOPPS (101 facilities, 2337 patients), and Japan (65 facilities, 1980 patients). An average of 30 adult chronic hemodialysis patients (age >17 years) participated from each facility. Study patients who departed from a facility were periodically replaced with patients who started hemodialysis treatment at the facility. Data collection began in the United States in June 1996, in Europe in May 1998, and in Japan in February 1999. For the mortality analyses, patients were followed until January 2002 in the United States, November 2000 in Europe, and October 2001 in Japan. Data were collected using a standardized chart abstraction procedure performed by a facility-based coordinator at each dialysis center. Data included demographic characteristics and comorbid conditions. For this analysis, data from an initial cross section of patients (i.e., prevalent patients) were used. Follow-up information was obtained approximately every 4 months, including dates, diagnoses, and procedures associated with each hospitalization.

Measures of nonadherence

The patient measures of nonadherence used in this study are skipping one or more dialysis sessions in 1 month, shortening one or more dialysis sessions by more than 10 minutes in 1 month, serum potassium concentration of >6.0 mEq/L, phosphate level of >7.5 mg/dL, or interdialytic weight gain (IDWG) >5.7% of body weight (the last cut-off was based on a >4 kg IDWG in a 70 kg patient). IDWG was obtained using the intradialytic weight loss, with the assumption that all the weight gained in the interdialytic interval was lost during the dialysis session. These definitions are identical to those used in a prior publication from a USRDS special study [8]. A session missed because of hospitalization was not considered nonadherence. IDWG was estimated using the amount of weight removed during a hemodialysis session and was expressed as the percentage of body weight removed. The prevalence of each adherence measure was calculated for the initial round of patients at time of entry into the study. Skipping and shortening status were evaluated for the 30 days prior to enrollment into the DOPPS. IDWG was calculated from the most recent hemodialysis treatment before enrollment, and potassium and phosphorus measurements were those obtained on or before the enrollment date.

Practice pattern and mortality models included all patients enrolled and used data at the time of their entry into the study.

Statistical analysis

The prevalence of each nonadherence measure was calculated in each participating continent for the initial cross section of prevalent patients entering the study. To avoid the influence of residual renal function on urine output and, hence, IDWG, patients who had been on dialysis for less than 90 days were removed from the prevalence calculations, and adjustments were made in all models for patients who had been on hemodialysis for less than 1 year. Linear mixed models were used to compare the prevalence of each nonadherence measure among the continents, taking into account facility clustering. The nonadherence measures of IDWG, potassium, and phosphate were adjusted for the day of the week of the blood draw. All patients were adjusted to a Wednesday blood draw value to ensure comparability.

Predictors of nonadherence were identified using logistic regression. Model specification included age, race, ethnicity, gender, diabetic ESRD, depression (presence or absence of a diagnosis of depression in the past 12 months was obtained from the DOPPS Medical Ques-

tionnaire), facility size, years on dialysis, smoking, education, living status, marital status, employment, and prior failed transplantation. These models also took into account facility clustering. The results were expressed as adjusted odds ratios.

Cox proportional hazards models were used to express the strength of the relationship between each measure of nonadherence and both mortality and hospitalization. Mortality models examined time to death, while hospitalization models examined time to first hospitalization after enrollment into the study. Adjustments were made for the same variables used in the logistic regression analysis and were supplemented with 15 summary comorbid conditions (diabetes, coronary heart disease, congestive heart failure, other cardiovascular diseases, hypertension, cerebrovascular disease, peripheral vascular disease, lung disease, cancer, HIV/AIDS, gastrointestinal bleed, neurologic disease, psychiatric disorder, cellulitis/gangrene, and dyspnea) and facility clustering effects. Cox models were stratified by continent. Facility clustering effects were addressed using robust standard estimates based on the sandwich estimator [12]. A separate model was determined for each measure of nonadherence, as was a model that included all five nonadherence measures. For measuring the association between hyperphosphatemia and mortality, intact parathyroid hormone (PTH) levels were included in the model, as phosphate levels could, in part, reflect underlying hyperparathyroidism. The median follow-up time in each continent was as follows: Euro-DOPPS = 1.8 years, Japan = 2.0 years, and the United States = 2.9 years.

Logistic regression also was employed to investigate the relationship between facility practice patterns and patient nonadherence. Practice patterns investigated included facility size, percentage of highly trained staff hours in relation to direct patient care staff hours, percentage of highly trained staff (defined as having 2 or more years of formal nursing training), presence of a dietitian in the unit, and physician/patient contact time (minutes/month). These models were adjusted for the list of comorbid conditions previously described, as well as for the predictors of nonadherence variables and continent of residence. Models took into account facility clustering. All analyses were carried out using SAS version 8.2 [13]. A P value of <0.05 was considered to indicate statistical significance.

RESULTS

Patient demographics

There were 14,930 patients available for analysis (8396 United States, 4075 Euro-DOPPS, and 2459 Japanese hemodialysis patients). The patient numbers for the initial cross section sampled were Euro-DOPPS = 2337, Japan = 1980, and the United States = 3359, for a total of 7676 patients used in the predictors of nonadherence analysis; the full sample was used for the mortality and practice pattern analyses. The demographic profile of the initial cross section of patients is given in Table 1. The proportion of African Americans was higher in the United States (33.5%) compared with Euro-DOPPS (1.6%) and Japan (0%). While the age groups were quite similar across nations, all comorbid conditions, except smoking and other cardiac conditions, were more prevalent in the United States. Employment status for those 18 to 60 years old was highest for Japan (51.1%) and lowest for the United States (13.7%); disability rates were lowest for Japan (4.9%) and higher for the United States (25.5%) and Euro-DOPPS (20.3%). The proportion of nursing home residents was highest for the United States (8.1%), and equivalent for Euro-DOPPS (2.3%) and Japan (2.6%). The percentage of married patients was highest for Japan (70.7%) versus 63.5% for Euro-DOPPS and 47.5% for the United States. Time on ESRD was longest for Japan (6.9 ± 6.5 years).

Distribution of nonadherence measures

Table 2 shows the prevalence of each parameter of nonadherence studied. In the United States, 7.9% of patients skipped one or more hemodialysis sessions/month compared with only 0.6% in Euro-DOPPS and 0.6% in Japan. Similarly, more United States patients shortened a hemodialysis session by 10 minutes or more in a month (19.6%) compared with 9.8% in Euro-DOPPS and 5.7% in Japan. For patients with excessive IDWG, the distribution was highest in Japan (34.5%) compared with 16.8% in the United States and 11.0% in Euro-DOPPS. Hyperphosphatemia ≥7.5g/dL was present among 15.4% of patients in the United States, 12.8% in Euro-DOPPS, and 12.1% in Japan. Finally, hyperkalemia of >6.0 mEq/L was seen more commonly in Euro-DOPPS (20.0%) than in Japan (7.6%) or the United States (6.3%).

Patient level predictors of nonadherence

Table 3 shows the results from logistic regression analyses of possible predictors of the presence of nonadherence among the hemodialysis populations studied. Analyses adjusted for all factors in this table, as well as for those in Table 1, including Kt/V and comorbidities. Predictors of higher odds of nonadherence included younger age (for skipping, shortening, excessive IDWG, and hyperphosphatemia), female gender (for IDWG), African American race (for skipping and shortening), employed status (hyperphosphatemia), living alone (hyperphosphatemia), smoking status (skipping and IDWG), depression (skipping and shortening), marital status (hyperphosphatemia), and time on ESRD (shortening, IDWG, and hyperkalemia). In addition, there exists a high degree of correlation among different measurements of

Table 1. Patient characteristics

Characteristic	Euro-DOPPS	Japan	United States	Overall
Demographics				
Age *years* (mean, SD)	60.1 (15.2)	58.9 (12.5)	60.8 (15.8)	60.3 (15.2)
Male %	59.7	62.4	55.1	57.5
African American %	1.6	0.0	33.5	19.8
Hispanic %	0.0	0.0	9.4	5.4
Comorbidities %				
Coronary heart disease	29.3	20.5	49.1	39.4
Congestive heart failure	25.1	8.8	45.9	34.6
Other cardiac conditions	34.2	24.6	32.1	31.5
Hypertension	76.4	57.0	82.8	77.0
Peripheral vascular disease	21.7	12.1	25.9	22.6
Cardiovascular disease	12.6	13.0	18.9	16.3
Diabetes[a]	22.6	27.9	49.1	38.8
Lung disease	10.0	1.5	13.9	10.9
Cancer (other than skin)	10.3	5.9	10.7	9.8
HIV/AIDS	0.1	0.0	1.3	0.8
Gastrointestinal bleeding	5.9	4.1	8.5	7.1
Neurologic disease	5.9	5.0	10.8	8.6
Psychiatric disorder	22.8	2.9	25.6	21.3
Recurrent cellulitis	5.5	2.5	9.8	7.5
Dyspnea	21.0	4.0	34.1	26.0
Smoking	19.6	26.5	21.1	21.6
Employment status[b] %				
Employed	27.7	51.1	13.7	24.1
Disabled	20.3	4.9	25.5	20.4
Education %				
Less than 12 years	52.7	20.1	26.8	32.6
Some college	10.8	9.9	19.6	15.7
Living status %				
Alone	14.7	9.6	15.7	14.5
Friends/family	83.0	87.5	75.8	79.5
Nursing home	2.3	2.6	8.1	5.7
Homeless/prisoner	0.0	0.3	0.4	0.3
Married %	63.5	70.7	47.5	55.4
Prior kidney transplant %	11.1	1.4	4.9	6.0
Time on ESRD *years* (mean, SD)	3.84 (5.4)	6.86 (6.5)	1.9 (3.3)	3.2 (4.9)
Average Kt/V single pool (mean, SD)	1.29 (0.31)	1.32 (0.28)	1.31 (0.30)	1.31 (0.30)

ESRD is end-stage renal disease.
[a] Primary or contributing
[b] Age <60 years

Table 2. Distribution of nonadherence measures by continent

	Patients %			
Nonadherence measure	Euro-DOPPS	Japan	United States	Overall
Skipped ≥ 1 hemodialysis session/month[a]	0.6	0.6	7.9	3.8
Shortened session by ≥ 10 minutes[b]	9.8	5.7	19.6	13.0
IDWG > 5.7% of dry weight	11.0	34.5	16.8	19.6
PO_4 > 7.5 g/dL	12.8	12.1	15.4	13.7
K > 6 mEq/L	20.0	7.6	6.3	10.8

IDWG is interdialytic weight gain.
[a] One session skipped (N = 136) (46.6%); two sessions skipped (N = 67) (23.0%); and three or more sessions skipped (N = 89) (30.4%)
[b] One session shortened (N = 370) (37.0%); two sessions shortened (N = 231) (23.1%); and three or more sessions shortened (N = 399) (39.9%)

nonadherence (Table 4). For any given measure of nonadherence, the odds of any other measure of nonadherence were greater than 1.0 and the majority of these odds ratios (OR) were statistically significant. The highest correlation was seen between shortening and skipping hemodialysis sessions (OR = 4.91; $P < 0.05$).

Correlates of nonadherence with mortality

Table 5 shows the relative risk (RR) of mortality for each of the five measures of nonadherence for all DOPPS countries. Skipping one or more dialysis sessions a month (versus not skipping) was associated with a relative mortality risk of 1.30 ($P = 0.01$). The relative mortality risks

Table 3. Factors associated with nonadherence[a]

Characteristic	Odds ratios (OR) by nonadherence measure				
	Skip	Shorten	IDWG	PO_4	K
Demographics					
Age (per 10 years)	0.87[b]	0.93[b]	0.85[b]	0.75[b]	0.99
Male (vs. female)	1.00	0.96	0.82[b]	0.99	1.03
African American (vs. non-African American)	2.11[b]	1.31[b]	0.89	0.76[b]	0.78[b]
Hispanic (vs. non-Hispanic)	1.26	1.21	1.12	1.08	1.03
Employment status					
Employed	1.16	0.95	0.92	1.21[b]	1.05
Disabled	1.00	1.00	1.00	1.00	1.00
Unemployed and not disabled (reference)	1.00	1.31[b]	1.31[b]	1.04	1.12
Education					
Less than 12 years	1.31	1.13	1.02	1.07	1.09
12 years (reference)	1.00	1.00	1.00	1.00	1.00
Some college	0.98	0.99	1.01	0.93	0.87
Living status					
Alone	1.09	1.07	1.01	1.22[b]	0.95
Friends/family (reference)	1.00	1.00	1.00	1.00	1.00
Nursing home	0.53[b]	1.15	1.18	0.79	1.14
Homeless/prisoner	1.36	0.82	0.80	1.32	—
Smoker (yes vs. no)	1.53[b]	1.14	1.43[b]	1.10	0.96
Depressed (yes vs. no)	1.62[b]	1.22[b]	0.96	0.99	0.98
Married (yes vs. no)	0.90	0.93	0.92	1.21[b]	1.03
Prior kidney transplant (yes vs. no)	0.79	0.82	0.86	0.91	1.08
Time on ESRD (per year)	1.02	1.05[b]	1.07[b]	0.99	1.03[b]

ESRD is end-stage renal disease; IDWG is interdialytic weight gain.
[a] Adjusted for continent of residence and all factors listed here and in Table 4
[b] $P < 0.05$

Table 4. Associations of nonadherence[a]

Characteristic	Odds ratios (OR) by nonadherence measure				
	Skip	Shorten	IDWG	PO_4	K
Skipped ≥ 1 hemodialysis session/month	—	4.36[b]	1.40[b]	1.37[b]	1.14
Shortened session by ≥ 10 minutes	4.91[b]	—	1.56[b]	1.59[b]	1.16
IDWG > 5.7% of dry weight	1.33	1.53[b]	—	1.36[b]	2.31[b]
PO_4 > 7.5 mg/dL	1.36[b]	1.51[b]	1.35[b]	—	2.14[b]
K > 6 mEq/L	1.21	1.11	2.30[b]	2.12[b]	—

IDWG is interdialytic weight gain.
[a] Adjusted for continent of residence and all factors listed here and in Table 3. This table does not represent a correlation matrix but instead presents the results from five different logistic regression models.
[b] $P < 0.05$

Table 5. The relative risk (RR) of mortality and first hospitalization by nonadherence measures

Nonadherence measure	RR of mortality (95% CI)		RR of hospitalization (95% CI)	
	Univariate adjusted[a]	Multivariate adjusted[b]	Univariate adjusted[a]	Multivariate adjusted[b]
Skipped ≥ 1 hemodialysis session/month	1.33 (1.09–1.63)	1.30 (1.06–1.59)	1.16 (1.02–1.32)	1.13 (1.01–1.28)
Shortened session by ≥ 10 minutes	1.14 (0.99–1.30)	1.11 (0.97–1.27)	1.10 (1.00–1.21)	1.09 (0.99–1.19)
IDWG > 5.7% of dry weight	1.14 (1.01–1.28)	1.12 (1.00–1.26)	1.00 (0.92–1.08)	1.00 (0.92–1.08)
PO_4 > 7.5 g/dL	1.19 (1.09–1.30)	1.17 (1.07–1.28)	1.07 (1.00–1.14)	1.07 (1.00–1.14)
K > 6 mEq/L	1.12 (1.00–1.26)	1.09 (0.97–1.22)	0.96 (0.88–1.05)	0.96 (0.88–1.05)

IDWG is interdialytic weight gain.
[a] Adjusted for factors listed in Table 1 and country (used as strata variable in the Cox model)
[b] Adjusted for factors listed in Table 1, other nonadherence measures, and country (used as strata variable in the Cox model)

for excessive IDWG and for phosphate levels >7.5 mg/dL were 1.12 ($P = 0.05$) and 1.17 ($P = 0.001$), respectively. The RR for the association between mortality and hyperphosphatemia increased to 1.27 ($P = 0.0001$) following adjustment for intact PTH levels. The RR associated with shortening dialysis treatments (RR = 1.11; $P = 0.14$) and hyperkalemia (RR = 1.09; $P = 0.14$) were not statistically significant. The measures of nonadherence were independently associated with higher mortality. The presence of comorbid conditions showed a significant increase in mortality, as did lower dialysis dose.

Table 6. Practice patterns associated with nonadherence measures[a]

Practice pattern (individual models)	Odds ratio		
	Skip	Short	IDWG
Facility size			
Per 10 patients	1.03[b]	1.03[c]	1.02[b]
Facility > 60 patients (vs. ≤ 60 patients)	1.77[c]	1.30	0.97
Facility > 75 patients (vs. ≤ 75 patients)	1.50[b]	1.57[c]	1.03
Facility > 125 patients (vs. ≤ 125 patients)	1.15	1.07	1.43[c]
% Highly trained staff hours (per 10%)	0.84[c]	0.94	1.04
% Highly trained staff (per 10%)	0.89[b]	1.00	1.04
Dietitian in unit (yes/no)	1.22	1.07	0.75[b]
Physician contact time (per 10 min/month)	0.97	0.99	1.01[c]

IDWG is interdialytic weight gain.
[a] Adjusted for variables in Table 1, country, and facility clustering
[b] $0.05 < P = 0.10$
[c] $P = 0.05$

Correlates of nonadherence with hospitalization

Table 5 also shows the RR for hospitalization (modeled as time to first hospitalization after entering the study) for each of the five measures of nonadherence for all DOPPS countries. Skipping one or more dialysis sessions a month (versus not skipping) was associated with a RR of 1.13 ($P = 0.04$) for hospitalization. For phosphate levels >7.5 mg/dL the RR was 1.07 ($P = 0.05$). The RR results for shortening dialysis treatments (RR = 1.09; $P = 0.09$), excessive IDWG (RR = 1.00; $P = 0.91$), and hyperkalemia (RR = 0.96; $P = 0.34$) were not statistically significant.

Correlates of nonadherence with facility practice patterns

Dialysis facility size and certain facility practice patterns were found to be significantly associated with nonadherence measures (Table 6). Larger facility size (per 10 more hemodialysis patients) was associated with an increased likelihood of skipping (OR = 1.03, $P = 0.06$), shortening (OR = 1.03, $P = 0.05$), and IDWG (OR = 1.02, $P = 0.07$). When looking for an optimum facility size, it was found that the risk of skipping significantly increased at a facility size of >60 patients (OR = 1.77, $P = 0.001$; reference group facility size <60 patients). The odds of shortening sessions increased significantly in facilities with more than 75 patients (OR = 1.57, $P = 0.006$; reference group facility size <75 patients), while the odds for excessive IDWG went up significantly at a facility size of 125 patients or more (OR = 1.45, $P = 0.03$; reference group facility size <125 patients). For a 10% increase in highly trained staff hours, there was a decrease in the likelihood of skipping (OR = 0.84, $P = 0.02$). Odds of skipping were 11% lower for every 10% increase in highly trained staff in the unit (OR = 0.89, $P = 0.06$). The presence of a dietitian in the facility was associated with a lower likelihood of nonadherence in terms of IDWG (OR = 0.75, $P = 0.08$), while a positive association was seen between IDWG and physician/patient contact time (OR = 1.01 per 10 minutes/month, $P = 0.05$).

DISCUSSION

Hemodialysis places multiple and unavoidable demands on a patient's lifestyle, related to the dialysis regimen, dietary and fluid restrictions, the requirement for multiple medications with potential side effects, as well as management of multiple comorbid conditions. Nonadherence with various aspects of management is not uncommon and is understandable from the patient's perspective. Quantification of the degree of nonadherence is clearly required to understand the impact of treatment on a patient's life. But solutions to this problem are difficult, and multiple aspects of therapy have to be addressed [4]. However, consensus does not exist as to what these ought to be. The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines pertaining to patient adherence rightly emphasize compliance with hemodialysis itself but do not address other aspects of patient nonadherence [14]. While no gold standard exists, the sensitivity and specificity of the cut-off values used in this study are not known and may have influenced the results.

No prior international comparisons of this magnitude and detail are available. A brief publication by Bleyer et al [9] reports a cross-sectional analysis based on a survey of 86 nurses and nephrologists from Japan ($N = 21$), Sweden ($N = 16$), and the United States ($N = 49$). They concluded that nonadherence (based on "missed dialysis" treatments as the main outcome measure) was much more common in the United States compared with Sweden and Japan and recommended further study to determine the significance of their results for patient survival.

In this study of representative samples of hemodialysis patients from seven countries, measurable indices of nonadherence that have been published previously [8] were related to patient outcomes. Behavioral compliance measures of skipping dialysis and shortening dialysis times were studied, as well as indirect measures of dietary and medication compliance such as IDWG, serum phosphate levels, and serum potassium levels. By adjusting for patients who had been on dialysis for less than 1 year, an attempt was made in this study to account for the confounding influence of residual renal function on IDWG. To account for the possibility of survival bias that could potentially influence results in an analysis of a cross section of prevalent patients, all analyses were adjusted for multiple covariates, including years on hemodialysis. It also was thought desirable to express IDWG as a percentage of body weight, because absolute values can have different implications for individuals of different weight. Furthermore, for the purposes of this

study, intradialytic weight loss served as a proxy for IDWG since data on weights determined for two consecutive sessions were not uniformly available. Phosphate levels above 7.5 mg/dL were more likely to reflect nonadherence with diet and/or medication than levels between 5.5 mg/dL and 6.5 mg/dL. These latter levels could exist despite a patient's attempt at adherence with diet and drugs [15, 16], the result of the relatively inefficient phosphate clearance achieved by conventional three times a week hemodialysis [17].

Analysis revealed significant correlations between different measures of nonadherence. Results in this regard are in agreement with the study by Leggat et al [8] but at variance with Kimmel et al [18]. In the latter study, at three urban hemodialysis centers in the United States with predominantly African American populations, no correlation was observed between skipping and shortening behavior. The authors reasoned that this possibly reflected different underlying behavioral causes for skipping versus shortening.

Multiple demographic characteristics were observed in this study to predict patient nonadherence (Table 3). Younger age, African American race, female gender, disabled status, living alone, smoking, depression, and time on ESRD were associated with higher odds of nonadherence with one or more of the measurements of nonadherence. Some college education and prior kidney transplant were associated with neutral odds of nonadherence in all the domains studied. Living in a nursing home was associated with 47% lower odds of skipping treatment, perhaps owing to staff supervision and predictable transportation arrangements to and from the dialysis unit. A number of patient comorbidities tested were not significantly associated with nonadherence.

Skipping and shortening hemodialysis treatments is much more common in the United States than in Euro-DOPPS or Japan. Excessive IDWG was more prevalent in Japan, followed by the United States and Euro-DOPPS. High phosphate was almost equally prevalent in each of the three geographic regions, and potassium levels of >6.0 mEq/L were more prevalent in Euro-DOPPS compared with Japan and the United States. Furthermore, while skipping one or more dialysis sessions in a month was associated with a 30% increased mortality risk compared with not skipping, shortening dialysis time was associated with an 11% higher RR of mortality than not shortening. Whereas the latter failed to reach statistical significance, the effect was in the expected direction and likely to be of clinical relevance, as shortening dialysis time represents a behavioral tendency to other measures of nonadherence in such patients. Skipping dialysis decreases the total delivered dose and may affect mortality by that mechanism. Dose of dialysis previously has been shown to have a relationship with RR of mortality in large observational studies [8, 19], although this remains a controversial subject [20]. The magnitude of mortality risk associated with skipping dialysis seems almost as large as that predicted from the dose effect alone (with Kt/V in the model, the RR for mortality was 1.28, $P = 0.05$). This suggests that the detrimental effect of skipping on mortality risk is independent of the delivered dialysis dose and that other detrimental factors or behaviors associated with skipping dialysis may contribute to the mortality risk. Hyperphosphatemia was significantly associated with a higher RR of mortality, confirming previous reports [21]. It is recognized that hyperphosphatemia may not simply reflect nonadherence with regard to diet. It may also be secondary to hyperparathyroidism, as well as underdialysis. When the mortality analyses were adjusted for intact PTH levels, the association between hyperphosphatemia and mortality seemed to strengthen. Hyperkalemia above 6.0 mEq/L failed to achieve statistical significance with respect to RR of mortality. The latter finding, however, should not lull practicing nephrologists into ignoring marked hyperkalemia as a risk factor for mortality in an individual patient and may indicate that the criterion of hyperkalemia is not always indicative of nonadherence and may be dependent upon variations in dietary pattern.

Few studies have looked at the effect of nonadherence on mortality. Held et al [7] reported a 14% higher risk of death from a single skipped session in one month. Ifudu, Henry, and Friedman [22], however, reported no increased risk. Leggat et al [8], based on a USRDS special study, reported definite mortality associations with nonadherence with respect to skipping or shortening sessions. Based on their analysis, one or more skipped hemodialysis session per month was associated with a 25% higher risk of death ($P < 0.01$). Shortening three or more sessions, excessive IDWG, and hyperphosphatemia also correlate with heightened mortality risk, as in this study. Greater IDWG is associated with better nutritional indices and lower mortality in a Japanese hemodialysis registry report [23], as well as in a single-center study by Testa and Beaud [24]. However, these results support the contention that, after adjustments for age, race, gender, ethnicity, time on ESRD, 15 summary comorbid conditions, depression, smoking status, education, employment, and living status, high IDWG is associated with a higher mortality risk. It is conceivable that the "J-shaped" relationship suggested in the literature [23, 24] is not seen because of adjustments made in this study for the variables that would possibly be correlated with low IDWG (e.g., age, nursing home residence, depression, and comorbidity). The high mortality risk is perhaps secondary to excessive cardiovascular burden related to expanded extracellular volume. It has been reasoned quite convincingly that excessive salt intake increases thirst, and patients should be counseled to restrict salt

intake in the first instance so as to significantly reduce their water intake [25].

The data pertaining to hospitalization as an outcome of nonadherence (Table 5) indicate that skipping dialysis is a significant risk factor for hospitalization (with a 16% higher risk of hospitalization in those who skipped one or more sessions of hemodialysis in a month versus those who did not skip). The risk of hospitalization was 7% higher in those with a phosphate level >7.5 mg/dL. These results are consistent with the mortality data. Previous studies have not looked at hospitalization as an outcome while evaluating nonadherence, despite its importance with regard to patient morbidity and its effect on cost of care.

Facility size was correlated by group to see if this was a consistent linear pattern. As shown in Table 6, smaller facilities (lowest quartile) were associated with the observation on skipping, while the larger facilities (highest quartile) were associated with IDWG. Thus, facilities with more than 60 patients had a significantly higher OR of skipping dialysis (1.77, $P = 0.001$) and those with more than 75 patients had a significantly higher OR of shortening dialysis (1.57, $P = 0.006$). It was only when facility size exceeded 125 patients that a significantly higher OR was detected for IDWG. This analysis, the authors believe, is the first to report a relationship between facility size and measures of patient nonadherence. A prior national study on facility size and intermediate patient outcomes did not have information on nonadherence in the hemodialysis patients studied and recommended further exploration in this area [26].

The results of the current study also point to the potential importance of the percentage of direct patient-care staff that is highly trained. Both the percentage of highly trained staff hours and of highly trained staff members in a facility seem to have an effect on patient nonadherence, as measured by skipping in a given facility. This result was statistically significant (OR = 0.84 for 10% more highly trained staff, $P = 0.02$; see Table 6) and points to the possible negative effect of hiring less than highly trained staff in dialysis units, a trend more commonly observed in the United States (Abstract; Mapes DL, et al, *J Am Soc Nephol* 12:337A, 2001). Dedicated nursing time spent counseling patients to reduce nonadherence is beneficial, based on a recent literature review [27]. Furthermore, the presence of a registered dietitian seemed to lower the odds of high IDWG ($P = 0.08$) in this study. Perhaps the time that a registered dietitian spends in counseling patients results in this trend. With respect to physician-patient contact time, the result is at odds with what would be expected, although the effect size is rather small (OR = 1.01; $P = 0.05$).

CONCLUSION

This is the first comprehensive international report on nonadherence in hemodialysis. Measures described include prevalence, patient and facility-level predictors, and hospitalization and mortality associations. Nonadherence, as measured by skipping and shortening hemodialysis treatments, was more prevalent in the United States than in Euro-DOPPS and Japan. Japan demonstrated the highest prevalence of IDWG per dry weight. After adjustments for multiple covariates, increased mortality risk was associated with skipping and shortening dialysis sessions, high IDWG, and hyperphosphatemia. Risk of hospitalization was significantly higher for those patients who skipped dialysis sessions and ran high phosphate levels, with implications for patient morbidity and thus cost to health care systems. Larger facilities were more likely to encounter a higher level of nonadherence, especially with respect to skipping and shortening dialysis. Highly trained staff may help to decrease nonadherence. The presence of a dietitian in the facility was found to lower the odds of excessive IDWG. Appropriate measures to minimize the nonadherence among patients (both at the patient and facility levels) are likely to reduce mortality and hospitalization risks in hemodialysis patients. Further research into effective ways to minimize nonadherence rates must continue in order to improve outcomes among hemodialysis patients.

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