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THE EFFECT OF WEATHER ON PERITONEAL DIALYSIS (PD) PRESCRIPTION: SEASONAL VARIATION IN PD DIALYSATE UTILIZATION

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♦ ***Background:*** **There have been no reports on peritoneal dialysis (PD) solution utilization since this treatment was developed in the 1920s. The aim of the present investigation was to investigate if weather affects PD prescription.**

♦ ***Study Design and Methods:*** **This 10-year observational study used the Taiwan National Health Insurance Research Database. Setting and Participants: Claims for different concentrate PD dialysate were analyzed monthly. 2.5% and 4.25% PD solutes were defined as hypertonic solutions. Predictor: Monthly outdoor mean temperature. Outcome and Measurement: The relationship between monthly mean of PD dialysate utilization and monthly outdoor temperature was analyzed by linear regression. Monthly mean PD dialysate utilization amount in 4 quarters was analyzed by ANOVA.**

♦ ***Results:*** **During the 10-year study period, a clear seasonal variation in PD dialysate was observed. This seasonal variation was present regardless of age, gender, and the presence of hypertension, diabetes, and dyslipidemia. Monthly mean temperature was positively correlated to 1.5% dialysate utilization amount ($r = 0.559$, $p < 0.001$) and negatively correlated to 2.5% ($r = -0.533$, $p < 0.001$) and 4.25% ($r = -0.410$, $p < 0.001$) dialysate utilization amount. In longitudinal follow-up, hypertonic PD fluid utilization was higher in diabetic patients than in nondiabetic patients from the beginning of treatment. Thereafter, it increased rapidly and reached a plateau within 1 year. Limitations: Analysis of ultrafiltration amount, blood pressure, and body weight was unfeasible due to the nature of the database.**

♦ ***Conclusion:*** **The utilization of differential strengths of PD solutions has a seasonal cyclic pattern, with more hypertonic PD solution utilized in winter and more hypotonic PD solution in summer.**

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KEY WORDS: Seasonal variation; ultrafiltration; Taiwan National Health Insurance Research Database.

Peritoneal dialysis (PD) is a widely used modality of renal replacement therapy for patients with end-stage renal failure. More than 150 000 patients around the world are currently receiving PD. For this lifesaving treatment, ultrafiltration volume has been documented to be positively correlated to survival benefit (1,2). It has also been used as a primary end point in many studies (3–5). Because dextrose concentration of PD solution directly influences ultrafiltration volume, the utilization of different strength PD fluids should be a major issue in this modality of dialysis. For decades it has been believed it is nephrologists' privilege to prescribed different concentration PD solutions to keep patients at their dry weight; however, there have been no large-scale reports of PD dialysate utilization patterns since this treatment was developed in the 1920s. Recently, seasonal variation in ultrafiltration volume, with higher values in the winter and lower values in the summer, has been found in hemodialysis (HD) (6–8). The same phenomenon was also documented in PD: daily ultrafiltration volume difference of 200 mL (9). The mechanism of this variation has not been well explained; however, our previous study speculated it is related to perspiration and different patterns of PD dialysate utilization for cold and warm seasons (9).

In Taiwan, the National Health Insurance (NHI) program — a compulsory social insurance program with up to 99% of the whole nation population enrolled — was established and has been in operation since 1995. Using a 10-year population-based dataset that comprises records

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of catastrophic illness in patients from 1997 to 2006, the current study conducted a nationwide survey in order to establish a pattern of PD dialysate utilization.

METHODS

DATA SOURCES

A universal health insurance program has been in place in Taiwan since 1995 (10) and covers 99% of the Taiwanese population of 23 million people. In 1999, the Bureau of NHI began to release all data in electronic form under the NHI Research Database project (11). Various extracted datasets are available to researchers. In this study, we excerpted data from patients in the registry of catastrophic illness, covering the period January 1997 to December 2006. Peritoneal dialysis patients are defined as those with catastrophic illness registration cards for end-stage renal disease (ESRD) and claiming for PD dialysate. In Taiwan, patients with ESRD in need of long-term renal replacement therapy can apply for catastrophic illness registration cards from the Bureau of NHI. They then do not need to make co-payments when seeking health care for renal disease.

STUDY DESIGN

We obtained data of patients receiving PD treatment from the 59 hospitals participating in the NHI PD program. The monthly utilization of different concentrate PD dialysates was analyzed. Both 2.5% and 4.25% PD solutions were defined as hypertonic solutions. Individuals were categorized by gender, geographic distribution, and presence of diabetes, hypertension, and dyslipidemia for subgroup analysis. Individuals were defined as diabetic if they claimed for insulin and/or oral hypoglycemic agent more than 3 months per year, hypertensive if they claimed for antihypertensive agents more than 3 months per year, and hyperlipidemic if they claimed for statins and/or fibrates more than 3 months per year.

The PD dialysates produced by Baxter Healthcare (Chicago, IL, USA) and Fresenius Medical Care (Homburg, Germany) were analyzed together according to the concentration of dextrose. Monthly mean temperatures over the study period were obtained from the Taiwan Central Weather Bureau.

DATA PROCESSING AND STATISTICAL ANALYSIS

Monthly mean PD dialysate utilization was calculated by dividing monthly total PD dialysate amount by monthly patient number. Monthly mean PD dialysate utilization amount in four quarters was analyzed by ANOVA. The relationship between monthly outdoor temperature and monthly mean PD dialysate utilization was analyzed by linear regression. The seasonality of the data was evaluated with the autoregressive integrated moving average method (ARIMA), which describes a univariate time series as a function of its past values and has been used in many studies to test for the presence of seasonality (12,13).

RESULTS

A total of 8748 adult patients with 265 542 outpatient months of treatment with PD were recorded from 1 January 1997 to 31 December 2006. These visits were identified from the database with a diagnosis of uremia (The International Classification of Disease, Ninth Revision, Clinical Modification ICD-9-CM codes, 585) and with claims for PD dialysate. After excluding patients with PD duration less than 1 year, 6033 patients with 250 788 outpatient months were enrolled in this study cohort. The PD population is predominantly female in Taiwan. Mean age was 46.3 years in 1997 and this population has become larger and older over the past 10 years. With PD patient number increasing from 1234 in 1997 to 3233 in 2006, the total dialysate utilization amount increased from 3 267 459 L to 9 307 444 L. The demographic data are listed in Table 1. Utilization of PD dialysate has been steadily increasing with PD patient numbers but with a cyclic increasing trend, with more hypertonic PD solution consumption in winter and more hypotonic PD solution consumption in summer (Figure 1). In analysis of personal utilization of different strength PD solution by season, the monthly mean of 1.5% concentrate PD solution utilization was 147.55 ± 4.65 L/month/patient in the first quarter, 153.46 ± 3.93 L/month/patient in the second quarter, 159.15 ± 3.94 L/month/patient in the third quarter, and 155.54 ± 5.14 L/month/patient in the fourth quarter ($p < 0.0001$). The monthly mean of 2.5% concentrate PD solution utilization was 104.86 ± 4.05 L/month/patient in the first quarter, 100.78 ± 3.06 L/month/patient in the second quarter, 97.48 ± 4.18 L/month/patient in the third quarter, and 100.40 ± 3.77 L/month/patient in the fourth quarter ($p = 0.0029$). Patients with diabetes used more hypertonic PD solution than nondiabetics in all seasons ($p < 0.0001$). Although utilization of 2.5% and 4.25% dextrose PD fluid showed no significant seasonal difference in diabetic patients when analyzed separately, the differences became statistically significant when

TABLE 1
Demographic Characteristics of Study Cohort

Year	Patients (*n*)	Mean age (years)	Male (%)	HTN (%)	DM (%)	1.5% (×10^4 L)	2.5% (×10^4 L)	4.25% (×10^4 L)	ICO (×10^4 L)	1.5%	2.5%	4.25%	ICO
1997	1234	46.3	43.7	29.7	17.59	100.9	50.4	6.6		64%	32%	4%	0%
1998	1542	47.0	42.6	29.6	19.00	111.5	67.2	7.1		60%	36%	4%	0%
1999	1768	47.8	41.7	30.8	20.98	120.3	78.7	7.3		58%	38%	4%	0%
2000	2027	47.9	41.3	32.7	21.81	133.3	89.3	7.7		58%	39%	3%	0%
2001	2390	48.2	40.1	33.1	21.97	166.8	103.1	8.8		60%	37%	3%	0%
2002	2704	48.9	39.6	34.0	22.71	194.2	127.2	9.9		59%	38%	3%	0%
2003	3016	49.1	39.1	33.4	22.58	213.0	137.5	9.6		59%	38%	3%	0%
2004	3343	49.9	38.8	32.7	22.38	235.0	147.0	9.7	0.03	60%	38%	2%	0%
2005	3639	50.2	39.3	31.2	22.29	254.8	156.7	9.6	8.0	59%	37%	2%	2%
2006	3233	50.7	39.0	30.9	21.31	236.2	155.0	11.7	18.5	56%	37%	3%	4%

HTN = hypertension; DM = diabetes mellitus; ICO = icodextrin.

they were put together and analyzed as hypertonic PD solution ($p = 0.009$). In the linear regression model, monthly outdoor mean temperature was positively correlated to 1.5% dialysate utilization amount ($r = 0.559$, $p < 0.001$) and negatively correlated to 2.5% ($r = -0.533$, $p < 0.001$) and 4.25% ($r = -0.410$, $p < 0.001$) dialysate utilization amount. In the ARIMA analysis, both 1.5% ($p = 0.0029$) and 2.5% ($p = 0.0002$) dextrose PD fluid utilization demonstrated significant seasonality. Detailed data are listed in Table 2 and Figure 2. In subgroup analyses, this seasonal variation was exhibited regardless of age, gender, hypertension, and dyslipidemia.

Longitudinal dialysate utilization in each patient was obtained from the beginning of his/her PD treatment. Because the patients started treatment in different calendar months, the seasonal variation pattern disappeared in this longitudinal analysis. In nondiabetic patients, hypertonic PD solution consumption, especially 2.5% dextrose solution, increased with treatment duration, which fits the consensus that residual renal function declines and solute transfer increases with time on PD (14). This trend was more obvious in diabetic individuals. Utilization of 2.5% dextrose PD solution was higher in diabetic than in nondiabetic patients from the beginning of treatment. Thereafter, it increased rapidly, reaching a plateau within the first year [Figure 3(a)]. In the subgroup analysis for hypertension, hypertensive patients tended to utilize more 2.5% dextrose PD solution than non-hypertensive subjects. This trend persisted with treatment duration [Figure 3(b)]. There was no difference in PD fluid utilization pattern between patients with and patients without dyslipidemia [Figure 3(c)].

DISCUSSION

Without normal kidney function to maintain homeostasis, patients with ESRD treated with HD were reported to have seasonal variations in blood pressure (15) and laboratory values (7). Seasonal changes in ultrafiltration volume were also found in HD patients (7,8,16). The cause of this ultrafiltration variation is not clear. The most reasonable explanation is the difference in fluid intake and perspiration during hot and cold seasons. During winter, people usually eat more but perspire less and that is why HD patients have more interdialytic weight gain and subsequent ultrafiltration volume. Peritoneal dialysis is another widely used modality of renal replacement therapy; due to its continuous nature, less abrupt changes in serum composition are presumed by most nephrologists. However, our previous study of 44 patients demonstrated that PD patients also have higher ultrafiltration volume in winter by means of more hypertonic PD solution utilization (9). The limited study subject number does not allow application of the result to all PD patients.

In the current nationwide study, patterns of PD dialysate utilization were analyzed for all PD patients during a 10-year period in Taiwan. A clear seasonal cycle, with more hypertonic PD dialysate utilized in winter, was demonstrated. This seasonal variation exhibits in subgroup analyses for gender and the presence of diabetes mellitus (DM), hypertension, and dyslipidemia. In the present study, we illustrated that PD patients consume more hypertonic PD solution in winter. Accordingly, hypertonic PD solution utilization in winter results in more ultrafiltration volume. This phenomenon exhibited

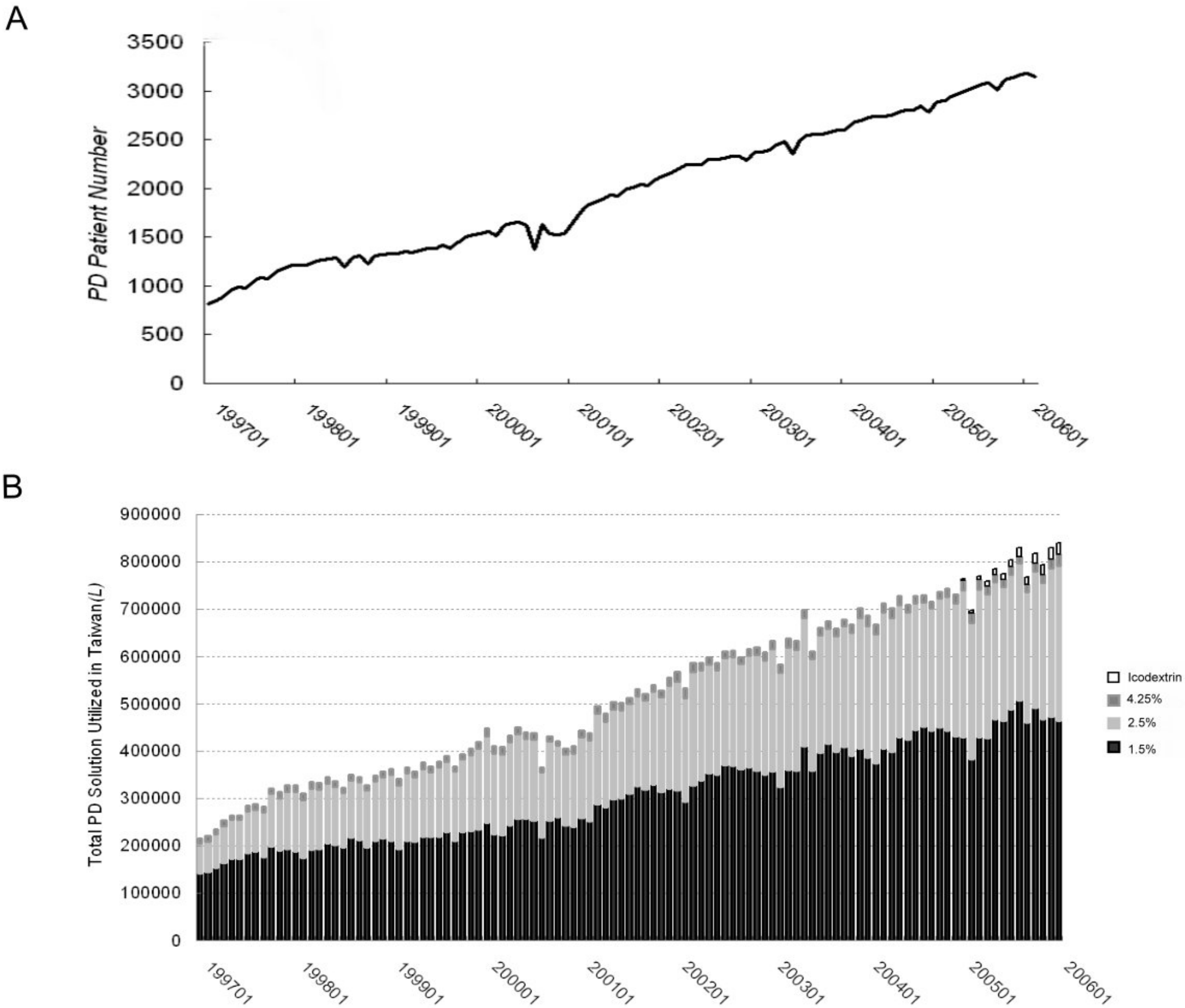

Figure 1 — Prevalent peritoneal dialysis (PD) patient numbers and dialysate utilization amounts from 1997 to 2006 are shown. The PD population increased steadily during the study period (panel A). The utilization of different strength PD solutions is illustrated in panel B. A cyclic increasing pattern for 1.5% dextrose PD solution is shown.

in non-hypertensive subjects excludes the hypothesis that more hypertonic PD solution utilization in winter is for blood pressure control only. In addition, Cheng *et al.* also demonstrated apparent seasonal changes in blood pressure without extracellular fluid volume variability in stable PD patients (17). Although annual intake/output records for such a large PD population would be almost impossible, we believe this seasonal difference in PD dialysate utilization is for fluid balance and dry weight control. Patients on PD use more hypertonic PD solution to compensate for less perspiration and to maintain dry weight during winter. We also believe this originated from patients' self-awareness because most nephrologists do not have this perception.

Another novel finding in our study is that diabetic patients tend to utilize more hypertonic solutions. One may speculate this is because diabetics lose residual renal function faster than nondiabetics, but our study demonstrated this trend starts from the beginning of PD treatments, the moment at which all patients should have similar residual renal function. A reasonable explanation is that diabetic PD patients tend to have faster solute transport than nondiabetics. Many studies have demonstrated that a high peritoneal membrane solute transport rate is associated with increased risk of mortality (18–20). Although the authors used mathematical approaches to diminish the effect of DM, the presence of more DM patients in high transporter groups could still

TABLE 2
Monthly Mean of Different Strength Peritoneal Dialysis Solution (PDS) Utilization

	1st quarter (Jan–Mar)	2nd quarter (Apr–Jun)	3rd quarter (Jul–Sep)	4th quarter (Oct–Dec)	Total (Jan–Dec)	*p* Value
Outdoor temperature (°C)	17.18±0.80	25.52±0.77	29.48±0.68	21.97±0.95	23.54±4.66	<0.0001[a]
1.5% PDS (L/month/patient)	147.55±4.65	153.46±3.93	159.15±3.94	155.54±5.14	153.92±6.02	<0.0001[a]
2.5% PDS (L/month/patient)	104.86±4.05	100.78±3.06	97.48±4.18	100.40±3.77	100.88±4.50	0.0029[a]
4.25% PDS (L/month/patient)	8.74±1.57	7.67±1.50	6.81±1.24	7.31±1.08	7.63±1.49	0.0345[a]
Icodextrin (L/month/patient)	1.14±2.87	1.53±3.40	1.81±3.87	2.12±4.41	1.65±3.54	0.9494
1.5% PDS in non-DM (L/month/patient)	154.31±3.56	160.12±3.34	165.72±3.75	162.53±4.66	160.67±5.62	<0.0001[a]
2.5% PDS in non-DM (L/month/patient)	99.43±3.44	95.57±2.78	92.52±3.78	95.27±3.27	95.70±4.05	0.0014[a]
4.25% PDS in non-DM (L/month/patient)	8.07±1.29	7.15±1.44	6.32±1.17	6.79±0.96	7.08±1.34	0.0335[a]
Icodextrin in non-DM (L/month/patient)	0.89±2.28	1.22±2.74	1.49±3.22	1.77±3.72	1.34±2.92	0.9362
1.5% PDS in DM (L/month/patient)	121.19±7.91	127.41±6.52	133.55±6.71	128.33±7.27	127.62±8.14	0.0091[a]
2.5% PDS in DM (L/month/patient)	126.31±7.69	121.48±6.56	117.10±7.64	120.54±6.94	121.63±7.67	0.0781
4.25% PDS in DM (L/month/patient)	11.46±3.09	9.72±2.07	8.77±1.73	9.35±1.78	9.83±2.37	0.0843
Icodextrin in DM (L/month/patient)	2.05±5.06	2.70±5.90	3.03±6.35	3.48±7.12	2.81±5.91	0.9669

DM = diabetes mellitus.
[a] Statistically significant.

be a confounding factor (21,22). In small sized studies, some authors suggested there is an association between DM and high peritoneal membrane permeability (23,24). However, one national survey from Australia and New Zealand disclosed that their high transporter group did not have more DM patients (19). Without including DM as a covariate in multivariate model analysis, the author concluded high transporter status is an independent risk factor for death and technique failure. In the current study, we approached this issue by analyzing PD dialysate utilization, which provides indirect evidence that Asian PD patients with DM are prone to be high transporters. In fact, some previous studies hinting that high transporter status has worse outcome also did not take diabetes as a covariate in their analysis (20,22,25). If DM is taken as a covariate in Cox proportional hazard modeling, high transporter status is no longer an independent risk factor (21). There was a major difference between our PD population and the other nationwide PD study: in our PD population, the prevalence of DM is 22%, compared to 38% in Australia (19). The proportion of prevalent diabetic ESRD patients in Taiwan and Australia are comparable. The low prevalence of DM in the Taiwan PD population is due to more ESRD patients in Taiwan choosing HD rather than PD as their renal replacement therapy. In Taiwan Nephrology Society annual reports, the proportion of diabetic patients is much higher in HD than in PD (26).

Icodextrin solution uses a novel osmotic agent, a polymer of glucose, to remove greater amounts of fluid over the long dwell period compared to standard 1.5% and 2.5% dextrose solutions. The availability of an icodextrin-based dialysis solution has been a major advance in fluid management for PD patients. Many studies have compared the effectiveness of icodextrin with 4.25% PD solution (27,28). Most nephrologists prescribe icodextrin to replace 4.25% dextrose solution in clinical practice for patients with DM or ultrafiltration failure. However, we have observed that 4.25% dextrose solution utilization amount decreased only 1% after icodextrin was introduced into Taiwan in 2003. On the contrary, while icodextrin utilization increased rapidly, the low concentrate PD solution utilization amount declined. This observation points to an important issue. The introduction of icodextrin has not decreased the utilization of high dextrose PD solution and subsequent total glucose exposure for PD patients in Taiwan as much as dialysate manufacturers and nephrologists expected. Icodextrin, with its high efficacy for ultrafiltration, offers PD patients a more flexible fluid intake restriction and better quality of life.

Most studies defined stable PD patients as those that received PD longer than 3 months. In the current study, to illustrate the seasonal change, we excluded those patients that had been on PD therapy less than 1 year. Only data for PD fluid claimed for outpatient visits were analyzed because inpatient PD fluid utilization would be influenced by peritonitis and other acute comorbidities.

There are some limitations in the current study due to the nature of the database. We do not have

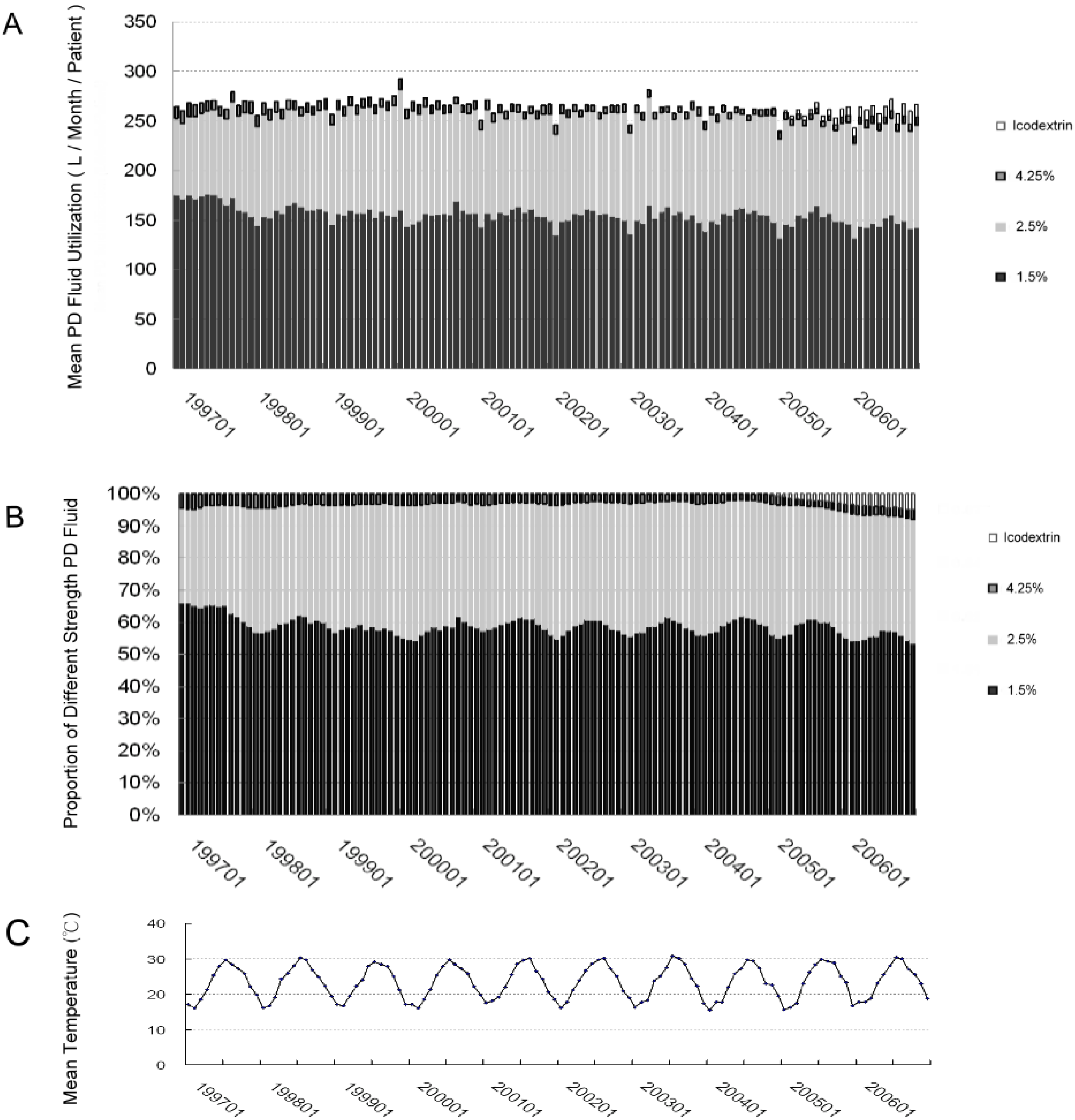

Figure 2 — Pattern of monthly mean utilization of different strength peritoneal dialysis (PD) solutions and mean temperatures are shown. The pattern of monthly mean of different PD solution utilization over 10 years is expressed in liters (panel A) and proportions (panel B). A clear seasonal variation is illustrated in 1.5% and 2.5% dextrose concentration PD solutions. The monthly mean of outdoor temperatures is shown in panel C.

peritoneal equilibration test (PET) results in this database. Ultrafiltration volume is determined by PET and glucose concentration of PD solution. Theoretically, we should consider the PET in the interpretation of seasonal variations in PD fluid utilization but it is difficult to believe that outdoor temperature would influence the permeability of peritoneum, which is maintained at constant body temperature. Another weak point is that we do not have records of water intake and urine amount, which are almost impossible to maintain in this large study population. It is possible that more hypertonic PD solution utilization in winter is due to more oral intake

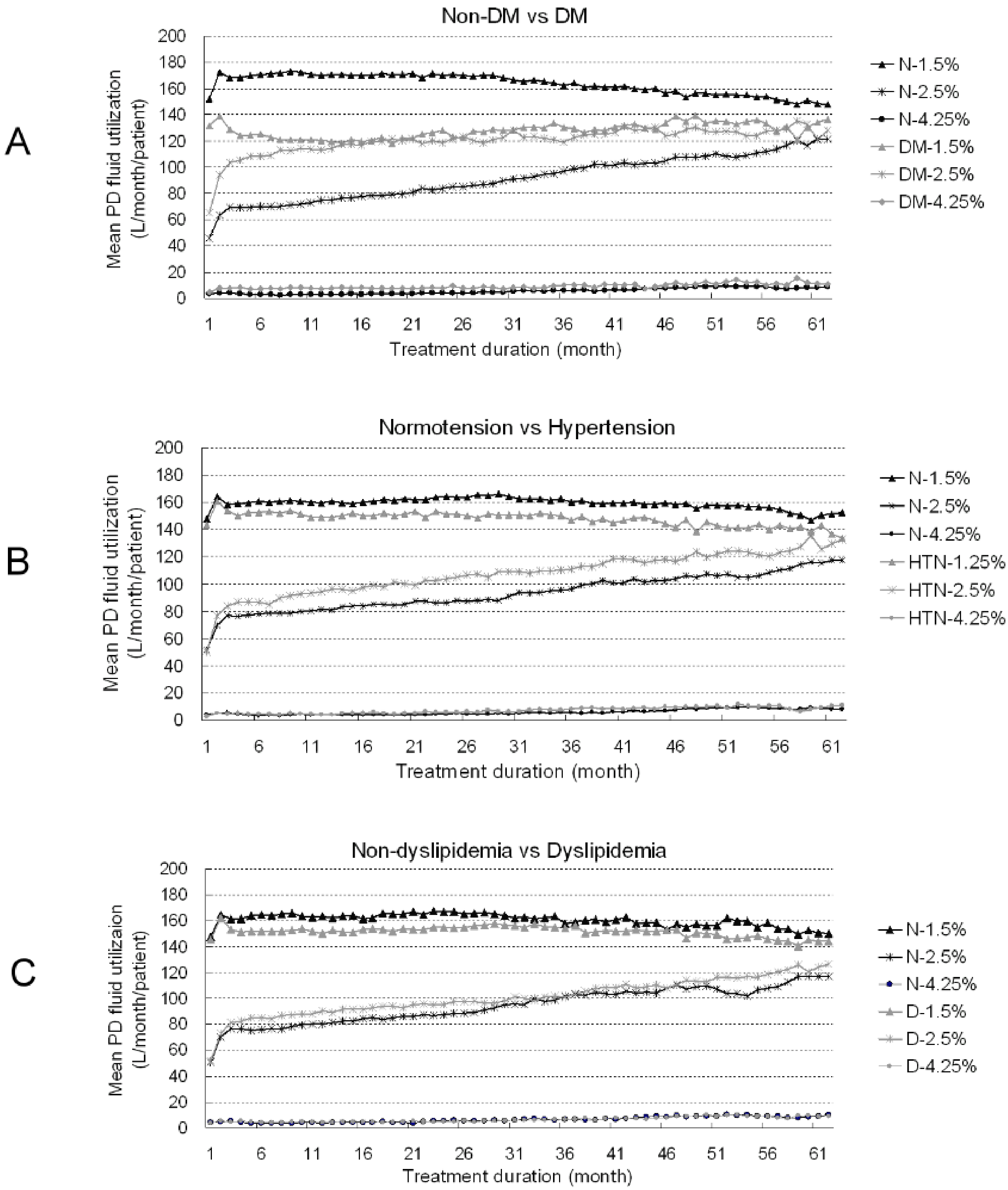

Figure 3 — Longitudinal peritoneal dialysis (PD) fluid utilization pattern and comorbidities are shown. Monthly mean of dialysate amount is illustrated from the beginning of PD treatment. 2.5% dextrose utilization amount increased with treatment duration, which indicates peritoneal membrane transport increases with treatment duration. The subjects with diabetes mellitus (DM) consumed more hypertonic PD solution and rapidly became higher transporters than nondiabetics (N). The trend reached a plateau within 1 year (panel A). Patients with hypertension (HTN) used more 2.5% dextrose dialysate than normotensive (N) subjects (panel B). The presence of dyslipidemia (D) did not influence the PD fluid utilization pattern (panel C); N = no dyslipidemia. Because patients start PD treatment in different calendar months, the seasonal variation is not apparent in this figure.

and less perspiration in cold months, but we cannot answer that question in this study.

To the best of our knowledge, this is the first nationwide study to investigate PD dialysate utilization. In addition to doctors' 1-month prescriptions, PD patients actually fine-tune their treatment to achieve well-being by themselves. To adapt to the greater physiologic insensible losses in the hotter months and therefore the requirement of less dialysis-induced ultrafiltration, the utilization of different strength PD solutions has a seasonal cyclic pattern, with more hypertonic PD solution utilized in winter and more hypotonic PD solution in summer. This quantitative analysis provides useful information for investigators to avoid bias in interpretation of ultrafiltration volume in their clinical trials, for nephrologists to prescribe different strength PD solution seasonally, and for PD solution manufacturers to decide the amount of stock. Although the clinical significance of the current study seems modest in Taiwan, an island with small temperature ranges, the same differences might be more marked in other countries with broader temperature variations.

DISCLOSURES

No financial conflict of interest exists.

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