Seasonal Variations in Clinical and Laboratory Variables among Chronic Hemodialysis Patients

ALFRED K. CHEUNG, GUOFEN YAN, TOM GREENE, JOHN T. DAUGIRDAS, JOHANNA T. DWYER, NATHAN W. LEVIN, DANIEL B. ORNT, GERALD SCHULMAN, GARABED EKNOYAN, and the Hemodialysis Study Group

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.

Abstract. Seasonal variations in BP among chronic hemodialysis patients have been reported. It was hypothesized that other characteristics of these patients might also vary with the seasons. Twenty-one clinical and laboratory variables were examined for seasonal variations among 1445 patients enrolled in the Hemodialysis Study, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. Mixed-effects models were applied to longitudinal changes (up to 45 mo) for individual patients for 19 of the 21 variables, which were measured at least twice each year, to determine the seasonal component of each variable. Seasonal variations in the other two variables, i.e., protein and energy intakes determined from annual dietary records, were assessed in cross-sectional comparisons of intakes of patients entering the study at different time points. Thirteen of the 21 variables examined demonstrated statistically significant ($P < 0.01$) seasonal components in their longitudinal variations. Predialysis blood urea nitrogen concentrations peaked in March, which coincided approximately with the peak protein catabolic rates, as well as protein and energy intakes (determined by dietary recall). Predialysis systolic and diastolic BP values were highest in winter and lowest in summer, corroborating previous reports. In addition, the lower predialysis BP values in summer were associated with higher outdoor temperatures and less interdialytic fluid gain. The mean predialysis hematocrit values were highest in July, which could not be attributed solely to the estimated changes in plasma volume. Seasonal variations in clinical and laboratory variables occur commonly among chronic hemodialysis patients. The reasons for most of these variations are not apparent and require further investigation. Nonetheless, failure to consider these variations might lead to biases in the interpretation of clinical studies. In addition, awareness of these variations might facilitate the interpretation of laboratory results and the clinical treatment of these patients.

Normal cell physiologic processes (1), body composition (2,3), organ function (4–8), clinical laboratory test results (9–14), and disease processes (15–17) have all been demonstrated to be subject to seasonal variations in the general population. In particular, BP undergoes cyclic changes that are inversely correlated with outdoor temperatures, with peak levels in winter and the nadir in summer (2,4–7). Seasonal variations in predialysis BP were recently observed among chronic hemodialysis patients on three different continents, encompassing both hemispheres, i.e., Europe, South America, and Asia (18–21). The magnitudes of the reported seasonal changes were as great as 12 mmHg for systolic pressure and 7 mmHg for diastolic pressure in one study (18). Similar to findings for the general population, BP values for the dialysis patients in three of those studies (18,19,21) were inversely correlated with outdoor temperatures, with the highest mean BP occurring in the winter. In addition, BP was positively correlated with outdoor humidity in two studies (18,21).

In addition to variations in BP, it is conceivable that seasonal changes might affect other bodily functions among dialysis patients, as observed for the general population. These physiologic changes would be expected to affect, in turn, the results of clinical and laboratory evaluations of the dialysis patients. This study was performed with a large cohort of chronic hemodialysis patients, to examine whether seasonal variations in 21 selected clinical and laboratory variables could be observed.

Materials and Methods

Hemodialysis Study Design

The Hemodialysis (HEMO) Study is a multicenter trial sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases of the United States National Institutes of Health. The basic design of the study has been reported (22). Patients were randomized to either a standard (i.e., 1.05) or high (i.e., 1.45) equilibrated urea Kt/V (eKt/V) goal and to dialysis with either a low-flux or high-flux dialyzer, with a $2 \times 2$ factorial design. Among other inclusion criteria, enrolled subjects were required to exhibit residual renal urea clearance of $<1.5$ ml/min per 35 L of urea distribution volume. Included in the analyses presented here were all subjects who were enrolled in the follow-up phase of the HEMO Study from the beginning of the study (February 1995) to March 1999. A total of 1445 patients were recruited from 15 clinical centers in various parts of the United States.
The geographic locations of these centers and the number of study patients in each center are presented in Figure 1.

**Dialysis Sessions and Standards of Medical Care**

Dialysis procedures and the standards of general medical care potentially have effects on the outcome variables examined in this study. All patients were scheduled to undergo dialysis three times/wk throughout the HEMO Study. The duration of the dialysis sessions varied, depending on the target eKt/V and the fluid volume targeted for removal; the minimal duration was 150 min. The composition of the dialysate was individualized to the needs of each patient, with bicarbonate as the primary buffer. The target dry weight for each patient was determined by his or her primary nephrologist. Standards for general medical care were established in the HEMO Study protocol. These standards included dietary fluid, protein, energy, electrolyte, and vitamin intakes, dry weight evaluations, predialysis and postdialysis BP limits, serum chemistry (bicarbonate, calcium, phosphorus, and albumin) limits, and hematocrit limits. Although adherence to these standards of care is being monitored throughout the trial, they are not as strictly enforced as are the main interventions of the study, i.e., eKt/V and membrane flux.

**Data Collection**

Twenty-one variables being regularly monitored in the HEMO Study were examined for seasonal variations. The frequency and total number of measurements and the number of patients used in the analysis of each variable are presented in Table 1. Some variables, such as BP, were determined more frequently as part of routine clinical practice; they were reported to the Data Coordinating Center at regular but less frequent intervals. At least two measurements/patient per yr were required for all variables that were analyzed longitudinally. The mean number of measurements per patient during the study ranged from >20 for weight and BP to 2.03 for protein and energy intakes (calculated from Table 1). Because the frequency of measurements for different variables varied according to the HEMO Study protocol, the number of patients examined for each variable varied between 1172 and 1445.

Twelve of these variables were measured at monthly urea kinetic modeling sessions, with a median number of measurements per patient of 19.0 to 20.0 and a follow-up duration of 19.9 ± 13.1 mo (maximum, 45 mo). The first measurements used in the analysis for these 12 variables were the first measurements obtained during the follow-up phase (generally approximately 1 mo after randomization). BP was measured in the sitting position and was recorded once immediately before dialysis and after dialysis. Pre- and postdialysis weights were measured by using a scale. Blood samples for blood urea nitrogen (BUN) assessments were collected immediately before dialysis and 20 s after dialysis, after the dialyzer blood flow rate had been reduced to <80 ml/min.

Seven laboratory variables (serum creatinine, sodium, potassium, bicarbonate, and phosphorus levels, hematocrit, and leukocyte counts) were recorded monthly as part of routine care and were reported to the Data Coordinating Center every 6 mo. The median number of measurements was 4.0 to 5.0/patient and the mean follow-up period was 22.8 ± 11.3 mo (maximum, 45 mo) for these variables. For these seven variables, the first measurements in the analysis were the baseline (prerandomization) values.

The other two variables, namely dietary protein and energy intakes, were estimated from 2-d (one dialysis day and one nondialysis day), diary-assisted, dietary recalls conducted annually. The median number of measurements was 2.0/patient and the mean follow-up period was 14.4 ± 13.5 mo (maximum, 40 mo) for these variables. For these two variables, the first measurements in the analysis were the baseline (prerandomization) values.

**Assays and Calculations**

Blood samples were immediately centrifuged, and all serum samples were assayed for BUN and albumin levels at a central laboratory (LifeChem, Rockleigh, NJ). BUN levels were measured with an autoanalyzer (Hitachi 747-200; Boehringer Mannheim, Indianapolis, IN), using a kinetic urease method. Albumin levels were measured with a nephelometer (Array360; Beckman, Fullerton, CA), using reagents obtained from Beckman. Determination of hematocrit values, leukocyte counts, and serum creatinine, sodium, potassium, bicarbonate, and phosphorus levels was performed in the clinical laboratories associated with individual clinical centers.

The total ultrafiltration volume was estimated as the difference between the predialysis and postdialysis weights. The ultrafiltration rate was calculated as the total ultrafiltration volume divided by the duration of the dialysis session. The equilibrated normalized protein catabolic rate (enPCR) (23) and the distribution volume of urea (24) were determined by urea kinetic modeling, using predialysis and postdialysis BUN concentrations. Protein, energy, sodium, and potassium intakes were calculated from the dietary recalls by using the Nutritionist IV nutrient analysis program (First DataBank Inc., San Bruno, CA).

**Climatic Data**

Daily outdoor temperatures at individual clinical centers were obtained from the National Oceanic and Atmospheric Administration. The average of the highest and lowest temperatures for each day was used in subsequent analyses.

**Statistical Analyses**

The longitudinal variation of each of the 19 clinical and laboratory variables measured at least twice each year was investigated by analyzing the changes in the serial measurements from the initial values for each patient, using mixed-effects models to account for serially correlated data (25). First, the overall pattern of variation of a variable with calendar time was described by plotting the mean changes in the serial measurements estimated by using mixed-effects models, which also accounted for the day of the week of the measurements, the time from randomization, and the interactions with the Kt/V and flux treatment groups. Next, for evaluation of the seasonal variation of a variable, the changes in the serial
Table 1. Seasonal variations in 21 outcome variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency of Samples (mo)</th>
<th>No. of Patients/Observations</th>
<th>Mean(^b)</th>
<th>Amplitude of Seasonal Effect(^c)</th>
<th>SEM of Seasonal Effect(^d)</th>
<th>(t) for Seasonal Effect (e)</th>
<th>(P) for Seasonal Effect</th>
<th>Amplitude/Mean ((\times100))(^f)</th>
<th>Peak month (from July 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>protein intake (g/kg per d)</td>
<td>12</td>
<td>1445/2988</td>
<td>0.94</td>
<td>0.051</td>
<td>0.021</td>
<td>2.4</td>
<td>0.015</td>
<td>5.5</td>
<td>9.1 (April)</td>
</tr>
<tr>
<td>energy intake (kcal/kg per d)</td>
<td>12</td>
<td>1445/2988</td>
<td>22.94</td>
<td>1.11</td>
<td>0.50</td>
<td>2.2</td>
<td>0.027</td>
<td>4.8</td>
<td>9.3 (April)</td>
</tr>
<tr>
<td>pre sys BP (mmHg)</td>
<td>1</td>
<td>1416/28,843</td>
<td>152.15</td>
<td>2.99</td>
<td>0.41</td>
<td>7.2</td>
<td>&lt;0.001</td>
<td>2.0</td>
<td>5.9 (December)</td>
</tr>
<tr>
<td>pre dias BP (mmHg)</td>
<td>1</td>
<td>1398/28,426</td>
<td>81.62</td>
<td>1.65</td>
<td>0.24</td>
<td>6.8</td>
<td>&lt;0.001</td>
<td>2.0</td>
<td>6.2 (January)</td>
</tr>
<tr>
<td>post sys BP (mmHg)</td>
<td>1</td>
<td>1414/28,823</td>
<td>137.10</td>
<td>0.48</td>
<td>0.39</td>
<td>1.2</td>
<td>0.223</td>
<td>0.3</td>
<td>3.0 (October)</td>
</tr>
<tr>
<td>post dias BP (mmHg)</td>
<td>1</td>
<td>1397/28,336</td>
<td>74.41</td>
<td>0.11</td>
<td>0.22</td>
<td>0.5</td>
<td>0.629</td>
<td>0.1</td>
<td>3.4 (October)</td>
</tr>
<tr>
<td>UFR (ml/min)</td>
<td>1</td>
<td>1416/28,875</td>
<td>14.57</td>
<td>0.38</td>
<td>0.09</td>
<td>4.0</td>
<td>&lt;0.001</td>
<td>2.6</td>
<td>5.7 (December)</td>
</tr>
<tr>
<td>UF vol (ml)</td>
<td>1</td>
<td>1416/28,875</td>
<td>2929</td>
<td>73</td>
<td>19</td>
<td>3.9</td>
<td>&lt;0.001</td>
<td>2.5</td>
<td>5.5 (December)</td>
</tr>
<tr>
<td>pre wt (kg)</td>
<td>1</td>
<td>1416/28,875</td>
<td>71.90</td>
<td>0.17</td>
<td>0.05</td>
<td>3.0</td>
<td>0.002</td>
<td>0.2</td>
<td>6.7 (January)</td>
</tr>
<tr>
<td>post wt (kg)</td>
<td>1</td>
<td>1416/28,875</td>
<td>68.97</td>
<td>0.12</td>
<td>0.05</td>
<td>2.3</td>
<td>0.022</td>
<td>0.2</td>
<td>7.4 (February)</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre BUN (mg/dl)</td>
<td>1</td>
<td>1416/28,875</td>
<td>59.99</td>
<td>2.41</td>
<td>0.26</td>
<td>9.3</td>
<td>&lt;0.001</td>
<td>4.0</td>
<td>8.0 (March)</td>
</tr>
<tr>
<td>post BUN (mg/dl)</td>
<td>1</td>
<td>1416/28,875</td>
<td>17.74</td>
<td>0.97</td>
<td>0.10</td>
<td>10.0</td>
<td>&lt;0.001</td>
<td>5.5</td>
<td>8.4 (March)</td>
</tr>
<tr>
<td>enPCR (g/kg per d)</td>
<td>1</td>
<td>1415/28,846</td>
<td>1.00</td>
<td>0.032</td>
<td>0.004</td>
<td>0.14</td>
<td>13.0</td>
<td>1.8</td>
<td>5.7 (February)</td>
</tr>
<tr>
<td>creatinine (mg/dl)</td>
<td>6</td>
<td>1186/5505</td>
<td>10.56</td>
<td>0.076</td>
<td>0.058</td>
<td>1.3</td>
<td>0.187</td>
<td>0.7</td>
<td>0.1 (July)</td>
</tr>
<tr>
<td>sodium (mEq/L)</td>
<td>6</td>
<td>1172/5357</td>
<td>138.13</td>
<td>0.89</td>
<td>0.14</td>
<td>6.3</td>
<td>&lt;0.001</td>
<td>0.6</td>
<td>5.9 (December)</td>
</tr>
<tr>
<td>potassium (mEq/L)</td>
<td>6</td>
<td>1184/5485</td>
<td>4.82</td>
<td>0.074</td>
<td>0.027</td>
<td>2.7</td>
<td>0.007</td>
<td>1.5</td>
<td>7.8 (February)</td>
</tr>
<tr>
<td>bicarbonate (mEq/L)</td>
<td>6</td>
<td>1181/5463</td>
<td>21.45</td>
<td>0.58</td>
<td>0.12</td>
<td>5.0</td>
<td>&lt;0.001</td>
<td>2.7</td>
<td>5.8 (December)</td>
</tr>
<tr>
<td>phosphorus (mg/dl)</td>
<td>6</td>
<td>1184/5489</td>
<td>5.74</td>
<td>0.11</td>
<td>0.06</td>
<td>1.8</td>
<td>0.072</td>
<td>1.9</td>
<td>7.9 (February)</td>
</tr>
<tr>
<td>albumin (g/dl)</td>
<td>1</td>
<td>1410/28,509</td>
<td>3.63</td>
<td>0.048</td>
<td>0.006</td>
<td>8.3</td>
<td>&lt;0.001</td>
<td>1.3</td>
<td>3.8 (October)</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>6</td>
<td>1186/5609</td>
<td>32.85</td>
<td>0.62</td>
<td>0.15</td>
<td>4.2</td>
<td>&lt;0.001</td>
<td>1.9</td>
<td>0.6 (July)</td>
</tr>
<tr>
<td>leukocyte ((\times10^6/L))</td>
<td>6</td>
<td>1179/5430</td>
<td>6.83</td>
<td>0.14</td>
<td>0.06</td>
<td>2.1</td>
<td>0.036</td>
<td>2.0</td>
<td>6.9 (January)</td>
</tr>
</tbody>
</table>

\(^a\) protein intake, protein intake determined by dietary recall; energy intake, energy intake determined by dietary recall; pre sys BP, predialysis systolic BP; pre dias BP, predialysis diastolic BP; post sys BP, postdialysis systolic BP; post dias BP, postdialysis diastolic BP; UFR, ultrafiltration rate during hemodialysis; UF vol, total ultrafiltration volume during a dialysis session; pre wt, predialysis body weight; post wt, postdialysis body weight; pre BUN, predialysis blood urea nitrogen concentration; post BUN, postdialysis blood urea nitrogen concentration; enPCR, equilibrated normalized protein catabolic rate determined by urea kinetic modeling. Serum creatinine, sodium, potassium, bicarbonate, phosphate, and albumin concentrations, blood hematocrit (Hct) values, and total leukocyte counts were determined in predialysis samples.

\(^b\) Initial mean value of the variable.

\(^c\) Difference between the maximal and minimal values in the sine/cosine function (seasonal variation).

\(^d\) SEM of the amplitude of the seasonal effect.

\(^e\) \(t\) value (amplitude of seasonal variation/SEM ratio) for the seasonal effect (i.e., statistical significance of the longitudinal values conforming to the sine/cosine function).

\(^f\) Amplitude of the seasonal variation divided by the initial mean value of the variable \(\times 100\%\).
measurements were related to sine and cosine functions with periods of 12 calendar months, again controlling for the day of the week, the time from randomization, and the interactions with the treatment group. Standard trigonometric identities used in Fourier analyses were used to convert the coefficients of the sine and cosine functions, for estimation of the amplitude and phase of the seasonal variation for each outcome variable (26). The amplitude indicates the average difference between the peak and trough values, whereas the phase indicates the calendar time of the peak. This approach was feasible even for variables that were measured only twice-yearly for each patient, because the patients were enrolled in the HEMO Study at different times of the calendar year and measurements of each variable throughout the year were therefore available. Because the periodicity was set at 12 mo for the sine and cosine functions, the trough value of the seasonal component of each variable was always estimated, in this assessment of seasonal variation, to occur 6 mo after the peak value. To evaluate the possibility that some variables demonstrated systematic variations with time that deviated from this annual seasonal pattern, nonparametric curves relating each variable to calendar time were constructed by fitting cubic splines (27) to the residuals of the initial mixed-effects analyses that remained after removal of the seasonal effect.

For dietary protein and energy intakes, which were measured annually for each patient, it was not possible to evaluate seasonal variations on the basis of longitudinal changes with time, because the assessments were performed at the same time of the year for each patient. Therefore, for these two variables, the overall, seasonal, and nonseasonal variations were evaluated by using mixed-effects models, which compared the measurements for different patients who entered the study at different calendar times.

For each variable, the results are presented as the mean value at baseline, the amplitude and SEM of the seasonal effect, the r value (amplitude/SEM ratio) and P value for the seasonal effect, the amplitude/mean ratio (×100%), and the month in which the peak value of the variable was observed (counting from July 1). The amplitude of the seasonal effect is expressed as the difference between the maximal and minimal values of the sine/cosine curve for the seasonal effect. Because the sample sizes are large (2988 to 28,875 observations), the P values are mostly small. Therefore, the r values are presented to provide better indications of the statistical significance of the seasonal effect. P values of <0.01 were considered to be statistically significant. The amplitude/mean ratio provides an indication of the potential biologic or clinical significance. For indirect examination of the association between fluid accumulation and BP, similar mixed-effects analyses were used to relate the longitudinal changes in predialysis systolic or diastolic BP to the longitudinal changes in predialysis weight during the same time intervals.

In sensitivity analyses, similar results were obtained if the longitudinal changes were assessed relative to each patient’s mean value instead of the baseline value for each variable. Similar results were also obtained if more complex models, which incorporated the month of the initial measurements in the analysis, were used. Therefore, only results obtained by using changes relative to baseline values and the models described above are presented.

To examine the potential effects of outdoor temperatures on outcome variables, two separate analyses were performed. For these analyses, temperature was treated as a continuous variable. In the first analysis, the outcome measurements were related to the temperatures recorded at the designated weather station for each patient’s clinical center on the day of the day of the outcome measurements, controlling for the day of the week, the time from randomization, and the interactions with the Kt/V and flux groups. As in the analyses described above, mixed-effects models were used to control for serially correlated data. This first analysis assessed the direct association of temperature with each variable, irrespective of seasonal effects. In the second analysis, sine and cosine terms for the seasonal variation were added to the aforementioned models for the effects of temperature. This analysis estimated the amplitudes of the seasonal effects for each variable that were not related to seasonal variations in temperature during the same time intervals.

For certain subanalyses, as described below, the 15 clinical centers in the HEMO Study were arbitrarily categorized into three geographic regions. Centers in New York City (New York), Boston (Massachusetts) (two centers), Philadelphia (Pennsylvania), Chicago (Illinois), Rochester (New York), and St. Louis (Missouri) were grouped as the Northeast/Midwest group. Centers in Durham (North Carolina), Atlanta (Georgia), Birmingham (Alabama), Dallas (Texas), Nashville (Tennessee), and Winston-Salem (North Carolina) were grouped as the South group. Sacramento (California) and Salt Lake City (Utah) were grouped as the West group. The exact locations of these cities are depicted in Figure 1. For some other subanalyses, individual clinical centers were compared with each other.

Results

Patient Characteristics

Of the 1416 patients included in the analyses of monthly data, 44.3% were male. The mean age was 57.6 ± 14.1 yr (range, 18.0 to 80.5 yr). The mean duration of end-stage renal disease at the time of enrollment was 4.0 ± 4.4 yr (range, 0.19 to 31.3 yr). African-American subjects represented 64.5% of the study population. The causes of end-stage renal disease were diabetic nephropathy (36.4%), nephrosclerosis (33.4%), miscellaneous glomerulonephritides (14.5%), polycystic kidney disease (3.4%), and other causes (12.2%).

Overview of Seasonal Variations

Three variables were selected for graphic display in Figures 2 to 4, to illustrate the seasonal component, nonseasonal component, and overall variation. Statistically significant (P < 0.01) seasonal effects were observed for 13 of the 21 variables (Table 1). Ten variables were associated with particularly large seasonal effects (t > 4.0, P < 0.001), i.e., predialysis and postdialysis BUN levels, enPCR, predialysis systolic and diastolic BP, ultrafiltration rate, serum sodium, bicarbonate, and albumin concentrations, and hematocrit values. These variables are presented in greater detail below.

Variations in BUN Levels and Protein Metabolism

Both predialysis BUN levels (t = 9.3, P < 0.001) and postdialysis BUN levels (t = 10.0, P < 0.001) exhibited strong seasonal patterns, with the peak values for both parameters occurring in March. The fluctuations were 4.0 and 5.5%, respectively. Dietary protein intake (t = 2.4, P = 0.015) and enPCR (t = 8.2, P < 0.001) also seemed to vary with seasons and peaked within approximately 1 mo (February to April) of the peak predialysis and postdialysis BUN levels (March) (Figure 2), although the statistical significance of dietary protein intake conforming to a regular seasonal pattern was only marginal.
Variations in BP, Ultrafiltration Volume, and Body Weight

The seasonal variations for predialysis systolic (t = 7.2, P < 0.001) and diastolic (t = 6.8, P < 0.001) BP were statistically strong (Figure 3), with the highest values being observed within 9-d periods in December and January, respectively. In contrast, neither postdialysis systolic BP nor postdialysis diastolic BP varied with the seasons. Of potential relevance to changes in BP, the intradialytic ultrafiltration rate (t = 4.0, P < 0.001) and total ultrafiltration volume (t = 3.9, P < 0.001) also varied with the seasons and attained their highest levels in December. Predialysis weight (t = 3.1, P = 0.002) varied with the seasons and peaked in January (Table 1). To examine the relationship between BP and volume, we related the changes in predialysis BP to the changes in predialysis weight from the initial baseline measurements for a given patient. Each 1-kg increase in predialysis body weight was associated with increases in predialysis systolic and diastolic BP of 0.67 ± 0.07 mmHg and 0.30 ± 0.04 mmHg, respectively (P < 0.0001 for both).

Variations in Other Laboratory Variables

Predialysis serum sodium (t = 6.3, P < 0.001) and bicarbonate (t = 5.0, P < 0.001) levels both attained peak values in December; the magnitude of the seasonal variation was greater for bicarbonate (2.7%) than for sodium (0.6%). Predialysis serum albumin levels (t = 8.3, P < 0.001) attained peak values in October. Hematocrit values varied with the seasons (t = 4.2, P < 0.001) and attained a peak in July (Figure 4).

Associations of Temperature with Outcome Variables

Because temperature changes with the calendar months might contribute to the seasonal variations in outcome variables, associations between outdoor temperatures and outcomes were examined. When the daily outdoor temperatures in all geographic regions were combined, the expected seasonal
pattern was evident. The lowest mean temperatures were consistently observed in either December or January, which coincided with the highest predialysis BP (Figure 2).

The univariate associations between temperature and outcome variables are presented in Table 2. The outdoor temperature was inversely associated with predialysis systolic and diastolic BP, ultrafiltration rate and volume, predialysis weight, predialysis and postdialysis BUN levels, enPCR, and serum sodium and bicarbonate concentrations. The outdoor temperature was also positively associated with hematocrit values. With controlling for temperature, some outcome variables (\( P < 0.01 \) for predialysis and postdialysis BUN levels, serum sodium levels, serum albumin levels, and hematocrit values; \( P = 0.011 \) for enPCR) retained their seasonal variations. In contrast, predialysis and postdialysis BP, ultrafiltration rate and volume, predialysis weight, serum potassium levels, and serum bicarbonate levels exhibited seasonal variations without controlling for temperature (Table 1) but lost their seasonal patterns (\( P > 0.05 \)) with controlling for temperature.

### Subgroup Analyses for Seasonal Variations

The seasonal variations in the different variables were examined for consistency in subgroup analyses. For predialysis systolic and diastolic BP, predialysis and postdialysis BUN levels, and enPCR, statistically significant seasonal variations were observed for the African-American and non-African-American subgroups, the male and female subgroups, the <55-yr and >55-yr age groups, and each of the three arbitrarily designated geographic regions (Northeast/Midwest, South, and West). When each of the 15 clinical centers was analyzed separately, there were no statistically significant differences in the amplitudes of the seasonal effects on predialysis systolic and diastolic BP, predialysis and postdialysis BUN levels, and enPCR among the centers.

### Discussion

#### Seasonal Variations in Parameters for the General Population

In the general population, seasonal variations in certain cellular and bodily functions have been well established and have a sound physiologic basis. In addition to the well known seasonal variations in plasma vitamin D levels and allergic rhinitis rates, variations in BP (2,4,5), physical activity and energy expenditure levels (8), rates of mental depression (16), rates of Helicobacter pylori associated with peptic ulcer disease (17), and rates of death resulting from chronic heart failure (15) have been reported to be seasonal.

---

**Table 2. Association of temperature with outcome parameters**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Association with Temperature (per 10°F)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( m )</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>pre sys BP (mmHg)</td>
<td>-0.67</td>
</tr>
<tr>
<td>pre dias BP (mmHg)</td>
<td>-0.41</td>
</tr>
<tr>
<td>UFR (ml/min)</td>
<td>-0.08</td>
</tr>
<tr>
<td>UF vol (ml)</td>
<td>-13.9</td>
</tr>
<tr>
<td>pre wt (kg)</td>
<td>-0.04</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
</tr>
<tr>
<td>pre BUN (mg/dl)</td>
<td>-0.45</td>
</tr>
<tr>
<td>post BUN (mg/dl)</td>
<td>-0.15</td>
</tr>
<tr>
<td>enPCR (g/kg per d)</td>
<td>-0.01</td>
</tr>
<tr>
<td>sodium (mEq/L)</td>
<td>-0.20</td>
</tr>
<tr>
<td>potassium (mEq/L)</td>
<td>-0.01</td>
</tr>
<tr>
<td>bicarbonate (mEq/L)</td>
<td>-0.13</td>
</tr>
<tr>
<td>albumin (g/dl)</td>
<td>-0.00</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Only outcome variables that were noted to have statistically significant (\( P < 0.01 \)) seasonal variations (Table 1) are included.

Abbreviations are as in Table 1. \( m \), regression coefficient; SEM, SEM of the regression coefficient.
Variations in BUN Levels and Protein Metabolism

A novel major finding of this study was the seasonal variation in predialysis BUN levels (Table 1). The mean fluctuation was 4% (i.e., 2.41 mg/dL). Variations in predialysis BUN levels could theoretically be attributable to variations in urea removal, protein catabolism, or protein intake. Differences in urea removal were unlikely to be the explanation, because the urea reduction ratio did not fluctuate accordingly (as calculated from the data presented in Table 1). An analysis of eKt/V values demonstrated that they did not exhibit a seasonal pattern. The consistency in eKt/V values was expected, because this variable was part of the HEMO Study intervention and was tightly controlled throughout the trial.

A second potential explanation for the variations in predialysis BUN levels involves variations in protein catabolism. Variations in enPCR, with the peak occurring at a similar time point (Table 1), are consistent with this possibility. An increase in enPCR does not distinguish, however, between an increase in dietary protein intake and excessive protein catabolism, which might occur without changes in protein intake. The seasonal variations (albeit at only marginally significant levels) in protein and energy intakes (as assessed by dietary recall), with peak values occurring at similar time points (Table 1), provide support for the former mechanism.

Seasonal variations in BUN levels and enPCR do not necessarily indicate that these variations are attributable to climatic changes. The fact that the seasonal variations persisted with controlling for contemporaneously measured outdoor temperatures argues against the dependence of BUN levels and enPCR on temperature.

The highest predialysis weights for the dialysis patients in this study were observed in December, similar to findings observed during the holidays (mid-November to mid-January) for the general population (3). Higher predialysis weights, however, do not distinguish between fluid weight and lean body mass. The highest protein and energy intakes occurred in April and the highest BUN levels were observed in March, i.e., 3 to 4 mo after the peak predialysis weights. In contrast, changes in predialysis weight were associated with changes in predialysis BP, suggesting that the highest body weights in the winter were likely attributable to extra fluid accumulation, rather than increases in fat or muscle mass. Direct assessments of lean body mass, using methods such as dual energy x-ray absorptiometry, were not performed in the HEMO Study.

Variations in BP

In the general population, both systolic and diastolic BP are highest in the winter (2.4-7). Similar findings for predialysis BP were noted in studies of 16 patients in Brazil (19), 102 patients in Uruguay (20), 53 patients in France (18), 144 patients in Japan (21), and the 1416 patients in studies of 16 patients in Brazil (19), 102 patients in Uruguay (20), 53 patients in France (18), 144 patients in Japan (21), and the 1416 patients in the winter (2.4-7). The highest predialysis weights for the dialysis patients in this study were observed in December, similar to findings observed during the holidays (mid-November to mid-January) for the general population (3). Higher predialysis weights, however, do not distinguish between fluid weight and lean body mass. The highest protein and energy intakes occurred in April and the highest BUN levels were observed in March, i.e., 3 to 4 mo after the peak predialysis weights. In contrast, changes in predialysis weight were associated with changes in predialysis BP, suggesting that the highest body weights in the winter were likely attributable to extra fluid accumulation, rather than increases in fat or muscle mass. Direct assessments of lean body mass, using methods such as dual energy x-ray absorptiometry, were not performed in the HEMO Study.

Variations in Hematocrit

In this study, hematocrit values also varied with the seasons (Figure 4). The reasons for this seasonal variation are not apparent. Estimation of the effect of ultrafiltration volume (reflecting interdialytic weight gain) on predialysis hematocrit values, even with the assumption that all of the shifts in body fluid were derived exclusively from the extracellular compartment, demonstrates that hemoconcentration per se seems to be insufficient to explain the observed changes in hematocrit values. Detailed data on erythropoietin dosages and blood loss are not available in the HEMO Study.

Caveats

A limitation of this study, and potentially other studies, is the fact that the data were not obtained in a manner that could definitively exclude the possibility of factors other than actual biologic seasonal variations in the variables that could affect the measurements. For example, it is possible that certain blood chemistry values might be affected by conditions during shipment of the blood samples or assays at the laboratory. The risk of the latter is particularly great for serum albumin concentrations determined with the nephelometry assay, which were measured in a single central laboratory and exhibited highly significant nonseasonal variations (P < 0.001). The hypothesis of seasonal variations in data collection, sample shipment, or laboratory assay procedures, however, would need to invoke changes in the instruments or human error on a regular seasonal basis. A further caution regarding the interpretation of these data, which is applicable to many epidemiologic studies, is that the data indicate only associations and not cause-and-effect relationships.
Seasonal variations in clinical and laboratory variables seem to be common among chronic hemodialysis patients. Seasonal variations in predialysis BUN levels were prominent and were likely caused by variations in dietary protein intake. The variations in predialysis BP confirm earlier reports. In addition to vasodilation, however, this study provides data suggesting that lower interdialytic fluid gain in the summer might be a mechanism for the cyclic decreases in BP. Regardless of the causes, these seasonal variations might lead to biases in the interpretation of results in clinical studies in which measurement schedules vary during the year. Although the magnitude of seasonal variations in the mean values of the various variables was modest, seasonal changes could be substantial for individual patients. An awareness of these variations might facilitate the interpretation of laboratory results and the treatment of chronic hemodialysis patients.

Acknowledgments

Part of this work was presented at the 32nd Annual Meeting of the American Society of Nephrology and was published in abstract form (Cheung et al.: J Am Soc Nephrol 10: 236A, 1999).

References

10. Outila TA, Karkkainen MU, Seppanen RH, Lamberg-Allardt CJ: Dietary intake of vitamin D in premenopausal, healthy vegans was insufficient to maintain concentrations of serum 25-hydroxyvitamin D and intact parathyroid hormone within normal ranges during the winter in Finland. J Am Diet Assoc 100: 434–441, 2000