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Vintage, nutritional status, and survival in hemodialysis patients

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Vintage, nutritional status, and survival in hemodialysis patients.

Background. The link between dialysis "vintage" (length of time on dialysis in months to years) and survival has been difficult to define, largely because of selection effects. End-stage renal disease (ESRD) is thought to be a wasting illness, but there are no published reports describing the associations between vintage and body composition in hemodialysis patients.

Methods. We explored the relationships among vintage, nutritional status, and survival in a 3009 patient cohort of prevalent hemodialysis patients. Body weight, total body water, body cell mass, and phase angle by bioelectrical impedance analysis were the body composition parameters of interest. We examined vintage as an explanatory variable in multiple linear regression analyses (adjusted for age, gender, race, and diabetes) using body composition parameters and biochemical indicators of nutritional status as dependent variables. Proportional hazards regression was used to evaluate the association of vintage and survival with and without adjustment for case mix and laboratory variables.

Results. Dialysis vintage was 3.8 ± 3.7 (median 2.6) years. Body composition parameters tended to be lower after dialysis year 2. Linear estimates per year of vintage beyond year 2 include −0.66 kg body wt ($P < 0.0001$), −0.17 kg total body water ($P = 0.0003$), −0.14 kg body cell mass ($P < 0.0001$), and −0.07 degrees phase angle ($P < 0.0001$). In unadjusted analyses, vintage was not associated with survival, either as a linear or higher order term. The adjustment for case mix yielded a vintage term associated with an increased relative risk (RR) of death (RR 1.04 (95% CI, 1.01 to 1.07 per year). A further adjustment for laboratory data yielded a RR of 1.06 (95% CI, 1.03 to 1.09 per year).

Conclusion. Dialysis vintage is related to nutritional status in hemodialysis patients, with vintage of more than years associated with a significant decline in all measured nutritional parameters. Cross-sectional analyses probably underestimate these effects. A year accrued on dialysis is associated with a 6% increase in the risk of death, all else equal. Longitudinal assessments of nutritional status, including body composition, are required to better understand the natural history of wasting with ESRD and its implications for long-term survival.

Key words: ESRD, bioelectrical impedance analysis, wasting, long-term dialysis survivors, phase angle.

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The link between dialysis "vintage" (length of time on dialysis in months to years) and survival of hemodialysis patients has been difficult to define, largely because of selection effects. Over time, patients leave the dialysis realm either because of transplantation or death, so that the steady-state (that is, prevalent) dialysis population differs considerably from the incident population. Accordingly, patients of long vintage might be expected to differ greatly from patients of short vintage. Several reports have described clinical characteristics of "long-term dialysis survivors." [1–3]. In general, long-term survivors tend to be younger in age at the time of dialysis initiation and African American rather than white. Primary renal diseases are more likely to be glomerulonephritis or polycystic kidney disease rather than diabetes mellitus, hypertensive nephrosclerosis, or other conditions.

Few investigators have explored the association of vintage with nutritional status in end-stage renal disease (ESRD). Avram et al compared long-term (>10 years) with "average" (<5 years) survivors on dialysis, and found that the serum albumin and creatinine concentrations at dialysis enrollment were higher in the 86 patients (58 hemodialysis and 28 peritoneal dialysis) of extended vintage (>10 years) [3]. Lowrie and Lew found an inverse relationship between vintage and death risk in prevalent hemodialysis patients during 1988 [4] and 1989 [5]. Bloembergen et al found no association between vintage and overall or cause-specific death risk during 1990 through 1993 [6]. Indeed, most attention on vintage has been focused on its relationship with various forms of renal osteodystrophy, including dialysis-related (β_2-microglobulin) amyloidosis [7–10].

We recently had the opportunity to perform bioelectrical impedance analysis (BIA) on a large cohort of hemodialysis patients and to estimate body composition from impedance values. There was a wide range of vintage (>27 years) in the cohort, including 218 patients whose vintage was more than 10 years. We aimed to describe the associations among vintage, nutritional status (with a focus on body composition), and survival. While such an analysis could not substitute for a longitudinal study of nutritional status in ESRD patients, we hoped that it would generate hypotheses for future testing. Specifically, we hypothesized that increasing vintage would be inversely related to most nutritional parameters, and increasing vintage would be associated with an increased relative risk (RR) of death.

METHODS

Study subjects

Study subjects were 3009 prevalent adult hemodialysis patients from 101 free-standing Fresenius Medical Care North America (FMCNA) dialysis units across the United States. Inclusion criteria included age ≥18 years and three-times weekly in-center hemodialysis for ≥3 months. Patients with an amputation above the transmetatarsal site were excluded from participation. BIA (BIA Quantum; RJL Systems, Inc., Clinton Twp., MI, USA) was performed before a midweek dialysis session during the first six months of 1995. Weight was obtained before dialysis. Details of the BIA examination are provided elsewhere [11]. Resistance and reactance in ohms were obtained directly from the BIA device. The phase angle was calculated in radians and multiplied by $180/\pi$ (approximately 3.14159265) to covert radians to degrees. Reactance, resistance, phase angle, and the derived estimates of total body water (TBW) and body cell mass (BCM) were merged with the Patient Statistical Profile, a database with selected demographic, historic, and laboratory information on patients cared for at FMCNA-affiliated dialysis facilities. Laboratory values were the means of the three months proceeding BIA testing. The duration of follow-up after BIA testing ranged from 2 days to 18 months (closing at the end of June 1996). Patients whose survival time was unknown or uninterpretable ($N = 19, 0.6\%$) were excluded from the analysis.

Statistical analysis

Vintage was evaluated as a continuous variable in the primary analyses. The associations among vintage and other patient characteristics were explored by categorizing vintage into six predefined categories (<1, 1 to 2, 2 to 3, 3 to 5, 5 to 10, and >10 years). For continuous variables, category means were compared with analysis of variance. Pair-wise comparisons were performed with the Student–Newman–Keuls procedure [12]. Discrete variables were analyzed using the χ^2 goodness-of-fit test and χ^2 test for trend.

Linear regression was used to evaluate the relationships among vintage, body composition, and biochemical indicators of nutritional status, with and without adjustment for case mix (age, gender, race, and diabetes). To estimate a linear decline in nutritional parameters over the long-term (estimated change per year vintage), we conducted companion analyses in which patients on dialysis for less than two years were excluded.

The relationship between vintage and survival was analyzed using proportional hazards ("Cox") regression, with vintage expressed as a continuous variable [13]. In this case, the RR represents the expected increase in risk per one-year increase in dialysis vintage. Companion analyses using vintage categories were performed, thereby avoiding the linearity assumption. Multivariable analyses were performed with adjustment for case mix, and case mix plus laboratory variables significantly associated with survival on univariate screening (that is, albumin, prealbumin, creatinine, cholesterol, hemoglobin, ferritin, and dialysis dose, expressed either as URR and URR^2 or Kt). Additional "saturated" multivariable models were tested to evaluate whether the relationship between vintage and survival could be extinguished by adjustment for body weight or composition. The stepwise procedure was used for all multivariable analyses, with entry and exit criteria set at the $P = 0.05$ level [9]. Plots of log [−log (survival rate)] against log (survival time) were performed to establish the validity of the proportionality assumption [14]. Multiplicative interaction terms were tested to explore interactions among vintage and other explanatory variables. Unadjusted and multivariable RRs and 95% confidence intervals (95% CI) were calculated based on model parameter coefficients and standard errors, respectively. Patients who underwent kidney transplantation ($N = 82, 2.7\%$), recovered renal function ($N = 18, 0.6\%$), transferred dialysis facilities ($N = 287, 9.7\%$), withdrew from dialysis ($N = 42, 1.3\%$), or were lost to follow-up for unknown reasons ($N = 8, 0.3\%$) were censored. Two-tailed P values < 0.05 were considered statistically significant. Statistical analyses were conducted using SAS 6.08 (SAS Institute, Cary, NC, USA).

RESULTS

The mean dialysis vintage was 3.8 ± 3.7 years (median 2.6 years, range < 1 to 27.3 years). The distribution of patient characteristics by vintage category is shown in Table 1. The mean age was 60.5 ± 15.5 years, 47.2% were women. 46.9% were African American, and 45.4% Caucasian, 6.5% Hispanic, and 1.2% other races or ethnicities. The mean urea reduction ratio (URR) was 65.6 ± 7.0%. The mean hemoglobin was 10.3 g/dL (10%, 90% limits 8.9 and 11.5 g/dL, respectively, and the mean

Table 1. Selected patient characteristics by vintage category

	<1	1 to 2	2 to 3	3 to 5	5 to 10	>10	
	years						*P* value
Age *years*	60.5[a]	61.9[a]	61.5[a]	60.8[a]	59.3[b]	55.3[c]	<0.0001
Gender % *female*	46.6	48.5	40.5	48.0	51.3	46.8	NS
Race/ethnicity %							<0.0001
White	52.5	50.6	45.9	42.8	37.0	40.8	
Black	39.6	43.3	46.5	48.3	55.2	50.5	
Hispanic	7.4	5.4	6.1	6.9	6.9	6.9	
Other	0.5	0.7	1.4	2.0	1.0	1.8	
Diabetes %	48.0	42.1	40.9	36.2	25.0	11.5	<0.0001
Height *cm*	167.7	167.0	167.3	167.1	166.2	165.8	NS
Weight *kg*	73.4[a,b]	74.7[a,b]	76.1[a]	75.3[a,b]	73.9[b]	68.8[c]	<0.0001
Total body water *L*	41.0[a,b]	40.5[b,c]	41.0[a]	41.3[a,b]	40.9[b,c]	39.6[c]	0.05
Body cell mass *kg*	26.1[b,c]	26.2[b,c]	26.4[a]	26.4[a,b]	25.8[b,c]	25.0[c]	<0.0001
Phase angle *degrees*	4.70[b,c]	4.90[b]	5.09[a]	4.93[a,b]	4.62[b]	4.22[c]	<0.0001
Albumin *g/dL*	3.69[c]	3.85[b]	3.91[a]	3.89[a,b]	3.88[a,b]	3.85[a,b]	<0.0001
Prealbumin *g/L*	26.4[a,b]	27.4[a]	26.9[a,b]	26.5[a,b]	26.8[a]	24.4[b]	0.0007
Cholesterol *mg/dL*	184[a]	181[a,b]	177[b,c]	174[b,c]	168[c,d]	168[d]	<0.0001

Overall sample sizes are $N = 444$, 718, 492, 594, 524, and 218 for categories <1, 1 to 2, 2 to 3, 3 to 5, 5 to 10, and >10 years, respectively.
NS indicates not statistically significant.
Continuous values compared with ANOVA, and simultaneously adjusted for age, gender, race, and diabetes. *P*-values refer to the overall ANOVA. Category means not accompanied by the same letter symbol are significantly different from each other (Student–Newman–Keuls, $P < 0.05$).
χ^2 test for trend except for race (χ^2 goodness-of-fit).

hematocrit was 32.8% (10%, 90% limits 28.8 and 36.3%). Patients of longer vintage were significantly more likely to be younger, African American, and nondiabetic (Table 1).

Body composition and dialysis vintage

The mean body weight was 74.3 kg. There was a significant relationship between weight and vintage ($P < 0.0001$). Body weight tended to be lower among patients of longer dialysis vintage, particularly among those on dialysis for more than 10 years (Table 1). The linear estimate per year of vintage beyond year 2 was −0.66 kg body wt ($P < 0.0001$). These values were adjusted for age, gender, race, and diabetes status, all of which, except for gender, varied widely by vintage category.

The mean estimated TBW was 40.8 kg. The relationship between TBW and vintage was of borderline significance, with the largest differences observed among individuals whose vintage was more than 10 years. The mean estimated BCM was 26.1 kg. Trends in estimated BCM were noted among individuals whose vintage was more than five years. The linear estimate per year of vintage beyond year 2 was −0.17 kg TBW ($P = 0.0003$) and −0.14 kg BCM ($P < 0.0001$).

The largest relative differences by vintage were observed for phase angle. The relationship between phase angle and vintage was significant ($P < 0.0001$), with the peak phase angle (5.09°) observed among patients in the two- to three-year vintage category. The phase angle of patients in the greater than 10 years vintage group was significantly different than all other groups. The linear estimate per year of vintage beyond year 2 was −0.07 degrees.

Biochemical indicators and dialysis vintage

The serum albumin, prealbumin, and cholesterol concentrations were the biochemical indicators of nutritional status evaluated in these analyses. These were measures recently deemed valid and clinically useful in a preliminary report of the NKF-DOQI Nutrition Practice Guidelines [15]. Although the predialysis serum creatinine concentration has been strongly linked to mortality in patients on hemodialysis [4] and is a marker of muscle bulk, its level is confounded by residual renal function and the dose of dialysis. Since residual renal function is known to vary by vintage, the serum creatinine concentration could not be considered as a nutritional surrogate in these analyses.

There were significant relationships between albumin and vintage ($P < 0.0001$) and prealbumin and vintage ($P = 0.0007$). For albumin, the relation was curvilinear (Table 1). The positive coefficient for the linear term (3.25×10^{-2}, $P < 0.0001$) and the negative coefficient for the quadratic term (-1.51×10^{-3}, $P < 0.0001$) of vintage confirmed the reverse U-shaped relationship (that is, patients early and late in their dialysis experience tended to have the lowest serum albumin concentrations). The percentage of patients with albumin <3.5 was 12.8%, 5.0%, 2.9%, 3.7%, 4.0%, and 4.1% in the <1, 1 to 2, 2 to 3, 3 to 5, 5 to 10, and >10 years vintage groups, respectively. For prealbumin (obtained on more than half of the study subjects), the major differences were observed among individuals whose vintage was more than 10 years ($P < 0.05$ for >10 years vintage compared with all other categories; Table 1). This is especially noteworthy because prealbumin concentra-

tions tend to increase with reduced residual renal function [16], and reduced residual renal function would be expected among the patients of longest vintage.

The mean cholesterol concentration tended to decrease slightly with increasing vintage ($P < 0.0001$). The percentage of patients with serum cholesterol concentrations <100 mg/dL was 17.2%, 10.9%, 10.6%, 12.0%, 10.5%, and 14.2% in the corresponding vintage categories.

Dialysis vintage and survival

In unadjusted analyses, vintage was not associated with survival, either as a linear or higher order term. Adjustment for case mix yielded a vintage term associated with an increased RR of death (RR 1.04, 95% CI, 1.01 to 1.07 per year). The relationship between vintage and survival was not influenced by age, gender, race, or diabetes (interaction terms $P = 0.67$ to 0.86). In other words, the vintage-associated RR was similar across major case-mix categories (for example, African American RR 1.05 (95% CI, 1.00 to 1.10), non-African American RR 1.06 (95% CI, 1.02 to 1.10), diabetes RR 1.07 (95% CI, 1.01 to 1.15), and no diabetes RR 1.05 (95% CI, 1.02 to 1.09).

Further adjustment for laboratory data (that is, albumin, prealbumin, creatinine, cholesterol, hemoglobin, ferritin, and dialysis dose, expressed either as URR and URR^2 or Kt) yielded a RR of 1.06 (95% CI, 1.03 to 1.09 per year). In other words, there was a 6% increased risk of death with each additional year on dialysis. As with case mix adjustment, the relationship between vintage and survival was not significantly dependent on any of the included laboratory measurements.

To explore whether the increased RR of death associated with increasing vintage could be explained by the associations among vintage and body composition, we fit "saturated" multivariable models with adjustment for case mix and laboratory variables, along with body weight, phase angle, and TBW or BCM. In all cases, there was no material change in the RR estimate (vintage RR 1.05, 95% CI, 1.02 to 1.08). We observed significant interactions between vintage and body weight ($P = 0.002$) and vintage and TBW ($P < 0.02$), such that the adverse "effect" of vintage was more pronounced among persons of higher weight or TBW. In other words, if one compared patients above and below the median weight (72 kg), the increase in RR per year of vintage was roughly 9% among heavier patients and roughly 3% among lighter patients.

To obviate the assumption of linearity and the possibility that patients of very long vintage exerted excessive influence on the analysis, we compared patients whose vintage was two to five and ≥five years with a referent category of patients whose vintage was <two years. Relative to patients whose vintage was <two years, the multivariable RR of death was 1.57 (95% CI, 1.21 to 2.05) for patients whose vintage was two to five years and 1.99 (95% CI, 1.48 to 2.67) for patients whose vintage was ≥five years.

DISCUSSION

Relatively little is known about the associations of dialysis vintage with most outcomes relevant to hemodialysis patients, including survival and nutritional status. It is difficult to draw conclusions regarding a "vintage effect" because of confounding (positive and negative), as well as selection and lead-time bias. It is conceivable that prolonged dialysis vintage, at least in the range of 5 to 15 years, could be associated with either adverse or favorable clinical characteristics. For example, patients who are well enough to survive many years on dialysis may have some unmeasured qualities (for example, "determination") that directly influence survival, but cannot be adjusted for in any statistical analysis or accounted for in any nonrandomized clinical trial. Alternatively, extended dialysis vintage could indicate noncandidacy for kidney transplantation. While some factors prompting nonacceptance into transplant programs can be well adjusted for, others cannot (for example, the physician's assessment of anticipated adherence with immunosuppressive drug therapy).

Numerous studies have shown clinically meaningful and statistically significant associations among indicators of nutritional status and mortality and morbidity in prevalent and incident hemodialysis patients. However, since these studies were cross-sectional, they failed to describe expected changes in nutritional status or their downstream effects (that is, morbidity) over time. In this study, we found that several body composition parameters (body weight, TBW and BCM estimated by BIA, and phase angle) and biochemical indicators of nutritional status (albumin, prealbumin, and cholesterol) varied significantly by dialysis vintage. These observations probably underestimate the true effect of time on nutritional status. It is extremely likely that selection effects would bias against an inverse relationship between a nutritional parameter and vintage. For example, in the case of albumin, patients with lower serum albumin concentrations tend to "die off" early, leaving a sample of longer vintage enriched with subjects whose average serum albumins are higher than the initial cohort's values might have been.

The curvilinear relationship between albumin and vintage confirms our clinical impressions that the serum albumin concentration tends to increase during the first year of dialysis therapy. Some investigators have used this observation to support the earlier initiation of dialysis ("healthy start") to prevent worsening protein-energy malnutrition from prolonged uremia. While this hypothesis is attractive, it cannot be proved by this study. Pa-

tients early in their dialysis experience may be more volume overloaded, thereby diluting the serum, or hypoalbuminemia may prompt initiation of dialysis, and the subsequent increase seen in the vintage one- to two-year and two- to three-year categories might indicate regression to the mean.

The observation that phase angle decreases significantly with increasing vintage is of great interest. We have previously shown that phase angle is inversely related to age and significantly lower in whites, women, and patients with diabetes [10]. The changes in phase angle with increasing vintage were relatively large and clearly reflect a change in body composition (or at least the distribution of intracellular and extracellular water) that is independent of demographic factors. Phase angle is directly related to survival in hemodialysis patients [17]. In nonuremic populations, the phase angle has also proved to be a useful prognostic tool. Ott et al found that a narrow phase angle was a potent predictor of death in a cohort of 75 HIV-positive patients, explaining more variability than CD4 lymphocyte count, age, serum albumin, or other parameters [18]. In bone marrow transplant recipients, a narrow phase angle was related to the length of hospital stay, total number of days on total parenteral nutrition (TPN), and the cumulative dose of steroids and antibiotics [19]. More research is required to define the utility of phase angle in the hemodialysis population.

The recognition of an increased death risk with increasing vintage has important practical implications. For instance, most transplant programs do not evaluate candidacy based on vintage, and vintage is not included in the United Network of Organ Sharing (UNOS) organ allocation algorithm [20]. The relationship between dialysis vintage and patient and graft survival after kidney transplantation needs to be evaluated. There may also be important implications of the vintage-body composition relationship. It might be advisable for dietitians to include "long vintage" among the nutritional risk factors, prompting more intensive evaluation, counseling, and potentially nutritionally directed therapy.

It is unclear why we show an adverse association of increasing vintage, while Lowrie and Lew showed a favorable association a decade ago [4, 5]. It is possible that the relative influence of selection is reduced compared with the biological effects of vintage on a variety of body systems, including the somatic and visceral protein pools. Analysis of prevalent FMCNA cohorts from 1996 and 1997 confirms the increased multivariable RR of death with increasing vintage in the present era (data not shown). It is noteworthy that adjustment for body composition did not extinguish the increased RR of death observed with increasing vintage. Clearly, the interplay among these factors is complex. Progressive atherosclerosis with increasing vintage, followed by death due to cardiovascular disease is an alternative hypothesis for the observed vintage–mortality associations. The vintage–comorbidity association, if confirmed, could explain the findings of Bloembergen et al [6]. Unfortunately, these authors did not report the unadjusted RR of vintage or the RR without adjustment for comorbid conditions.

There are several important limitations to this study. Mortality was the only nonintermediate outcome evaluated. The relationships among dialysis vintage and hospitalization, functional status, and health-related quality of life, among other outcomes, would have been of interest. The exclusion of patients with major amputations may have affected the results, particularly for the subgroup of patients with diabetes. However, if patients with major amputations tend to become more disabled and wasted over time than the average patient (as we suspect), exclusion of these patients would have lessened the strength of the associations among vintage and nutritional parameters. Analysis of cause-specific death may have clarified the pathway of the vintage-mortality relationship (for example, cardiovascular disease). TBW and BCM estimated by BIA are not the most sensitive indicators of altered body composition. In longitudinal studies, dual-energy x-ray absorptiometry (DXA) or other more precise measures of body composition should be evaluated. For the purpose of this analysis, it is worth noting that misclassification or information bias induced by BIA would have biased the relation between vintage and body composition parameters toward the null. Finally, the sample size was relatively small, so the power to explore potential interactions among vintage and other clinical characteristics was limited.

In summary, dialysis vintage is directly related to unfavorable changes in nutritional status, including body weight and composition, in hemodialysis patients. A year accrued on hemodialysis is associated with a 6% increase in the risk of death, all else equal. Cross-sectional analyses probably underestimate these effects because of selection and lead-time bias. Longitudinal assessments of nutritional status, including body composition, are required to understand better the natural history of wasting with ESRD and its implications for long-term survival.

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