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Electrolyte Changes in Contemporary Hemodialysis: A Secondary Analysis of the Monitoring in Dialysis (MiD) Study

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Key Points

- Electrolyte fluxes after contemporary HD and the relationship between serum electrolytes and dialysate prescription remain understudied
- HCO3, Ca, and albumin increased, while K, Mg, and PO4 decreased immediately post-HD. Dynamic changes followed at 15- and 30-minutes post-HD
- We provide predictive models to estimate the pre- to post-HD change in serum electrolytes. Validation of models is warranted

Abstract

Background: There is a paucity of contemporary data examining electrolyte changes during and immediately after hemodialysis (HD), and their relationship with dialysate prescriptions. The present study examines these relationships.

Methods: We analyzed patient- (n=66) and HD session-level pre- and post-dialysis laboratory data (n=1,713) over a six-month period from the Monitoring in Dialysis Study. We fit mixed effects regression models to analyze electrolyte, blood urea nitrogen, creatinine, and albumin levels immediately post-HD, accounting for pre-HD and dialysate prescriptions. In a subset of US patients (n=40), 15-minute post-HD and 30-minute post-HD values were available at one session. Predictive models were fit to estimate electrolyte levels immediately post-HD, accounting for pre-HD concentrations and dialysate prescriptions.

Results: Serum bicarbonate, calcium, and albumin increased (mean increase 4.9±0.3 mEq/L, 0.7±0.1 mEq/L, and 0.4±0.03 g/dL, respectively), whereas potassium, magnesium, and phosphorus decreased immediately post-HD (mean -1.2±0.1 mEq/L, -0.3±0.03 mEq/L, and -3.0±0.2 mg/dL, respectively). Hypokalemia and hypophosphatemia were present in 40% of and

67% of immediate post-HD samples, respectively. Dynamic changes were observed in electrolyte concentrations at 15- and 30-minutes post-HD, compared to immediately post-HD.

Conclusion: We describe the magnitude of post-dialytic changes in serum electrolytes with contemporary HD, reporting a high incidence of electrolyte abnormalities post-HD, and present predictive nomograms relating electrolyte changes immediately post-HD to dialysate prescriptions. Our results may be useful for clinical care and provide insights for future research on dialysate prescriptions.

Introduction

Over 450,000 patients in the United States are dependent on maintenance hemodialysis (HD) for control of serum electrolyte concentrations and acid-base parameters[1]. Traditionally offered as a thrice-weekly therapy, HD utilizes the processes of diffusion and convection to ensure adequate and safe removal of some molecules, while maintaining or replenishing others[2,3]. The dialysate prescription is a critical component in this process and requires a detailed understanding of the dynamic changes and rebound in electrolyte concentrations that occur as a result of HD treatments. This is particularly important, since emerging data implicates the dialysis electrolyte prescription, and both lower and higher serum electrolyte concentrations, as important factors associated with the high incidence of sudden death in patients on maintenance HD[4].

Over the course of the last few decades, several technological advances and changes in clinical practice have been implemented for HD therapy, including the use of higher-efficiency and higher-flux membranes, avoidance of membrane re-use, and shorter treatment times[2]. These may have important implications for the expected peri-dialytic changes in serum electrolytes in modern HD practice. Despite this, a relative paucity of data exists in contemporary practice related to pre-post HD electrolyte changes, shifts in electrolytes during the post-dialysis period, and the influence of the dialysis prescription on such changes.

The aim of the present study was two-fold: 1) to describe the post-dialytic changes in standardly assessed serum electrolyte and biochemical parameters; and 2) to determine the association of the dialysate prescription with electrolyte changes. The present analyses harness the wealth of pre- and post-HD laboratory data from the Monitoring in Dialysis Study (MiD) study, a prospective, multicenter cohort study that used implantable loop recorders to determine the frequency of cardiac arrhythmias over a 6-month period.

Methods

Study design and population

This study is a secondary analysis of the Monitoring in Dialysis (MiD) study[5]. MiD was a prospective cohort study that enrolled 66 maintenance HD patients (n=43 from the United States; n=23 from India) from 10 centers and used implantable loop recorders to record continuous electrocardiographic readings over a 6-month primary observation period. Subjects were enrolled from January 2013 to January 2014 in the US and from March 2014 to December 2015 in India. The primary eligibility criteria were age 21 or older, thrice-weekly in-center HD or eGFR < 15ml/min/1.73 m^2 with expected HD initiation within two months, though no patients were enrolled before their HD initiation. Key exclusion criteria were unsuitability for implantation, expected survival less than 6 months, left-sided HD catheter interfering with implantation, thoracic surgery within 6 months, bacteremia within 60 days or non-bacteremic infection within 14 days, hemoglobin <10 g/dl on consecutive measurements within prior 2 months, end-stage liver failure, transplantation or modality transfer expected within 6 months, existing pacemaker or implantable cardioverter defibrillator. The design and main results of MiD have been reported elsewhere[5,6]. Dialysate prescriptions were not dictated by protocol, but rather as deemed clinically indicated by the patient's nephrologist.

Exposures and outcomes

The primary outcomes of the present study were the changes in electrolyte and laboratory concentrations immediately post-HD, compared with pre-HD. Additionally, we analyzed the association of individual dialysate electrolyte concentrations with changes in serum electrolyte concentrations. As there were differences in several baseline characteristics according to country of origin, we also examined the changes in electrolyte concentration in these sub-groups. In a subset of 40 participants (all from the US), we analyzed electrolyte changes at 15-

minutes post-HD, and 30-minutes post-HD, compared with the immediately post-HD measurements.

Laboratory analysis

In MiD, per the pre-specified protocol[5], blood samples were obtained before and after dialysis twice weekly for the first 4 weeks and then once weekly through the remaining 5 months. Per protocol, additional samples were obtained at 15- and 30-minutes after dialysis on the first session after implantable loop recorder placement in a sub-group of the US participants (n=40). Blood samples were collected at study sites by trained personnel, centrifuged, refrigerated and then shipped to a certified Central Laboratory (DaVita Total Renal Laboratories Inc in the US and a central lab in India) for measurement, using standard techniques.

Statistical analysis

Continuous variables were examined graphically and recorded as means (± standard deviation) for normally distributed data, or medians (25th-75th percentile) for non-normally distributed data. Categorical variables were examined by frequency distribution and recorded as proportions. Pre-HD and post-HD electrolyte and laboratory assessments were described as means (± standard error), accounting for repeated measures across subjects via the use of mixed models with random intercept. The mean differences between post-HD and: 1) pre-HD measurements, 2) 15-minute post-HD, and 3) 30-minute post-HD were estimated and compared using mixed effects regression models. Additionally, as the differences between the pre-dialysis serum and dialysate concentration may influence the post-dialysis serum concentration of any given electrolyte, unadjusted and adjusted models were fit to determine the association of corresponding dialysate prescriptions with change (pre-HD to post-HD) in serum electrolyte concentrations. Model 1 adjusted for the corresponding pre-HD serum electrolyte concentrations; Model 2 additionally adjusted for the dialysis session length. Further, using the linear mixed effect regression models described previously, we predict (and plot) the change

(pre-HD to post-HD) in serum electrolyte concentration, according to the pre-HD serum and dialysate concentrations of the electrolyte of interest. These analyses were carried out for serum sodium, potassium, bicarbonate, and calcium separately. Sub-group analyses were also performed according to country of origin for these plots. Missing data was not imputed. Overall, there was less than 4% missing for any parameter. All analyses were carried out using the statistical software package SAS version 9.4 (Cary, NC). Two-sided P-values of <0.05 were considered statistically significant.

Ethics

The MiD study was approved by applicable institutional review boards or ethical review committees at each participating center and participants provided written informed consent before the beginning of the study.

Results

Baseline characteristics

A total of 66 patients were included in the present analysis, contributing a total of 1,713 HD sessions. The mean age at baseline was 56 ±12 years, 70% were male, 53% were Black and 35% were Asian. A total of 43% of participants had a history of diabetes, 26% had heart failure, and 11% had atrial fibrillation at baseline (Table 1).

Baseline characteristics by country of origin are presented in Supplementary Table 1.

Hemodialysis treatment characteristics

The median duration of HD was 4 hours, with a mean single-pool Kt/V of 1.5 ± 0.4 and ultrafiltration rate of 10 ± 4 mL/kg/hr across all participants (Table 2). In the sub-groups according to country of origin, patients from the US were heavier, had higher blood and

dialysate flow rates, and tended to have a narrower range of dialysate prescriptions than those from India (Supplementary Table 2).

Changes in electrolyte concentrations and other biochemical parameters from pre- to post-HD – descriptive outcomes

The median (25^{th}-75^{th} percentile) number of pre-HD and post-HD sessions analyzed per patient was 28 (25-29) and 27 (24-29), respectively. Compared with pre-dialysis concentrations, serum bicarbonate, calcium, and albumin increased immediately post-HD (mean increase 4.9±0.3 mEq/L, 0.7±0.1 mg/d/L, and 0.4±0.03 g/dL, respectively; Table 3, Figure 1). Conversely, serum potassium, magnesium, and phosphorus decreased immediately following dialysis (mean decrease -1.2±0.1 mEq/L, -0.3±0.03 mg/d/L, and -3.0±0.2 mg/dL respectively). As expected, BUN and creatinine also declined, with mean decline of -39.9±1.2 mg/dL for BUN and -6.3±0.3 mg/dL for serum creatinine (Table 3, Figure 1). Post-HD values were frequently abnormal with 311/1,685 (18.5%) having a post-HD sodium <135 mEq/L, 669/1,689 (39.6%) with post-HD potassium <3.5 mEq/L, 569/1,690 (33.7%) with post-HD bicarbonate >28 mEq/L, 190/1,685 (11.3%) with post-HD calcium >10.4 mg/dL, 162/1,690 (9.6%) with post-HD magnesium <1.7 mg/dL, and 1,129/1,682 (67.1%) with post-HD phosphorus <2.5 mg/dL (Table 3, Figure 1).

Post dialytic changes in electrolyte concentration and other biochemical parameters – descriptive outcomes

Serum laboratory measurements were available at 15- and 30-minutes in a sub-group of patients from the US (n=40). Compared with the immediate post-HD concentration, a post-HD increase at 15 minutes was noted only for serum phosphorus (0.1±0.1 mg/dL), while declines were observed for bicarbonate, calcium, and albumin. However, compared with immediate post-HD concentrations, at 30-minutes post-HD increases were noted for potassium, (0.2±0.1 mEq/L), phosphorus (0.4±0.1mg/dL), BUN (2.5±0.4mg/dL), and creatinine (0.6±0.1 mg/dL). Conversely, declines at 30-minutes post-HD were noted for bicarbonate (-0.7±0.2 mEq/L),

calcium (-0.3±0.1 mg/dL), and albumin (-0.2±0.1 g/dL; Table 4; Figure 1). The proportion of sessions with abnormal serum electrolyte values at 30-minutes post-HD is presented in Table 5.

Association of dialysate prescriptions with changes in pre-to-post HD electrolyte concentrations

The dialysate sodium prescription was significantly associated with the change in serum sodium concentration from pre-HD to immediately post-HD. For example, adjusted for the pre-HD serum sodium, a dialysate sodium prescription of 135 mEq/L was associated with a post-HD decline of 1.4 mEq/L in serum sodium, while a dialysate sodium concentration of 140 mEq/L was associated with a post-HD increase of 0.6 mEq/L. As expected, lower dialysate potassium prescriptions were associated with greater decrease in post-HD serum potassium, while higher dialysate bicarbonate and calcium prescriptions were associated with higher post-HD serum bicarbonate and calcium concentrations, respectively. Results were qualitatively unchanged when further adjusted for dialysis session duration (Table 6). Analogous models are presented in sub-group analyses according to the country of origin (Supplementary table 3). While there are some qualitative and quantitative differences, the precision and stability of these estimates are limited by the small sample size and low variability across dialysate prescriptions among the patients from India.

We developed predictive models to estimate the immediate post-HD serum electrolyte concentration, according to the pre-HD serum concentration and dialysate prescription. In these models, dialysate sodium, potassium, bicarbonate, and calcium were significantly associated with pre- to post-HD changes in the serum concentration of the corresponding electrolyte (Figure 2 and Supplementary Tables 4-8). Sub-group analyses according to country of origin are presented in Supplementary Figure 1.

Discussion

Our secondary analysis of the MiD study describes the immediate and post-HD changes in standardly assessed electrolytes, analyzes the association of dialysate prescription with such changes, and develops initial predictive models to estimate the pre- to post-HD change in serum electrolytes. We observed significant increases in serum bicarbonate, calcium, and albumin and significant decreases in serum potassium, magnesium, and phosphorus immediately following contemporary HD sessions. As post-HD measurements are infrequently performed in clinical practice, our results provide important information on temporal changes and highlight that a significant proportion of values fall outside standard laboratory reference ranges.

Maintenance HD provides a life-saving therapy that has become increasingly available to patients with ESRD across the world. Despite familiarity with this process from over 50 years of clinical use, descriptions of the magnitude of change in serum electrolytes with contemporary practice remain necessary to augment current clinical understanding of the biochemical changes during HD on the one hand, while providing important data for dialysate prescription research on the other.

Dialysate potassium is typically prescribed with the goal of lowering serum (and total body) potassium concentrations that have risen in the inter-dialytic period. Recent research has called particular attention to the observation that post-HD hypokalemia, especially in the setting of pre-HD hypokalemia, is associated with higher all-cause mortality[7]. While the use of dialysate potassium concentrations <2 mEq/L were uncommon in our study, and have become less common in clinical practice more generally, our data clearly outline a greater magnitude of decline in serum potassium with lower dialysate potassium concentrations, with 39.6% of sessions having an immediate post-HD potassium below the lower reference limit and 29% with hypokalemia at 30 minutes post-HD. Although serum potassium continues to ‘rebound’ when measured at 6-hours post-HD,[8] these data support the concept of a higher-risk period peri- and immediately post-HD, which temporally aligns with the periods of highest risk for clinically

significant arrhythmia in the primary analyses of the MiD study[6,9]. Our findings demonstrate that post-HD hypokalemia is common. While prior research demonstrates that rebound in serum potassium continues to occur beyond the post-HD timepoints assessed in our study, more proximal post-HD hypokalemia may partially explain the increased risk of arrhythmia in the immediate post-HD period.

In maintenance HD patients, the intra-dialytic delivery of bicarbonate facilitates buffering of acidic by-products of metabolism, which occurs in the inter-dialytic period. However, this may come at the expense of rapid increases in serum bicarbonate during HD. It has thus been proposed that the optimal dialysate bicarbonate concentration is one that prevents both acidosis between sessions and alkalosis during a HD session[10]. As expected, our results demonstrate a substantial increase in serum bicarbonate concentrations during HD sessions and are consistent with other reports that describe higher post-HD serum concentrations with the use of higher dialysate bicarbonate baths. Interestingly, our data suggest a rebound decrease in serum bicarbonate in the 30-minutes post-HD, which may reflect some element of redistribution. As it is known that HD patients are 1.7-fold more likely to develop sudden death in the 12 hours following HD[11], more data are required to fully understand the changes in acid-base parameters and associated changes in electrolytes that occur during and between HD sessions.

In the present analyses, on average, serum calcium appeared to increase during HD sessions, with higher post-HD serum concentrations noted with use of higher dialysate calcium baths. In recent years, there has been a movement toward the use of lower dialysate calcium concentrations, based on KDIGO guidelines, in an attempt to minimize vascular calcification[12]. As with serum bicarbonate, there seems to be a rebound decease in serum calcium concentrations in the 30-minutes post-HD. Conversely, serum calcium and phosphorus exist in biochemical equilibrium. Phosphorus levels tended to decrease dramatically during HD and, on the basis of our data, we are unable to fully determine the extent to which changes in serum

calcium reflect the influence of dialysate calcium concentration, compared with reduction in serum phosphorus. Additionally, we observed changes in serum albumin, suggesting that the corrected calcium may not change significantly. The saw-tooth pattern of changes in serum albumin and calcium in the post-dialytic period is unusual – whether this reflects true changes or artefact in these samples is unclear, and requires further investigation. Measurement of ionized calcium concentrations would likely provide a better physiological measurement for future studies in this regard.

The development of hyperphosphatemia is a common manifestation of progressive chronic kidney disease and is associated with several adverse outcomes in patients with ESRD on HD[13-15]. However, it is less well appreciated that serum phosphorus is rather efficiently removed by HD, leading to rapid decline in serum concentrations at the end of a HD session. It is notable that the most rapid decline in serum phosphorus occurs early in a HD session[16], which corresponds to the timing of the largest decline in cardiac output and blood pressure[17]. Additionally, hypophosphatemia is associated with the development of ventricular arrhythmias[18]. Though phosphorus-enriched dialysate baths have been employed in the setting of hypophosphatemia[19], to our knowledge no research has assessed this association of this practice with outcomes, such as arrhythmia and mortality[20]. Our data clearly show significant decreases in phosphorus levels during HD, with an average decline in serum phosphorus of 3 mg/dL, while 67.1% of immediate post-HD values were below the lower reference limit. Whether this phenomenon predisposes to arrhythmia or other adverse effects during HD, and further, whether the addition of phosphorus to the dialysate may mitigate this rapid change, is uncertain, but clearly warrants further study. Our data also confirm the presence of a previously reported rebound increase in phosphorus concentrations in the post-HD period[21,22]. This rebound is of course expected, as phosphorus is a largely intracellular cation[23], with the rebound likely occurring as a result of redistribution from the intracellular stores.

Lastly, our data highlight that serum magnesium is lowered during HD but does not appear to have the same degree of rebound toward pre-HD concentrations observed for some other electrolytes. Though perhaps less-appreciated in the HD population, it has been shown that both extremes of higher (>2.1mg/dL) and lower (<1.7mg/dL) serum magnesium concentrations are associated with worse clinical outcomes, including in-hospital mortality[24], while other studies have reported an association of hypomagnesemia with all-cause mortality[25]. Further, it has been demonstrated that contemporary HD patients are generally normo- or hypomagenesemic[26], while magnesium supplementation and higher magnesium concentrations are associated with less vascular calcification[27,28], and, in MiD, higher serum magnesium was associated with a lower incidence rate of arrhythmia[9]. Our data confirm that, with current HD practices, a significant proportion of post-HD magnesium concentrations are abnormal (9.6% below the lower reference limit and 17% above the upper reference limit) and suggest that greater attention to the choice of magnesium bath may be warranted though, again, future studies to assess the associations of changes of dialysate bath with clinical outcomes are warranted. Unfortunately, data on the dialysate magnesium concentration was not recorded in MiD.

While prior studies have assessed intra- and post-HD electrolyte changes[29], and some have even generated predictive models for these changes, our analyses extend prior studies by generating predictive models of multiple post-HD serum electrolytes based on their respective pre-HD serum and dialysate concentrations in the contemporary MiD cohort. We believe that our models provide important data that might be used prospectively and tested in clinical trials to assess whether post-HD electrolyte abnormalities can be prevented and whether arrhythmias can be reduced on that basis. While the sub-group analyses according to country of origin should be interpreted with caution due to small size and a narrower range of dialysate and serum chemistry values, they do highlight the deficiencies of a ‘one-size fits all’ approach to the dialysate prescription. Future studies are warranted to confirm and refine such predictive

models with the goal of providing personalized HD prescriptions that will minimize adverse cardiovascular outcomes and mortality.

There are several strengths to our analyses. The present study uses data from the MiD study, a multicenter prospective cohort with detailed session-level information on pre- and post-HD serum chemistries that were measured at a central laboratory and mandated by protocol. Though prior research has described changes in electrolyte concentrations post-dialysis, the relatively large number of samples in our study allowed prediction models to be developed. Additionally, 15- and 30-minute post-HD measurements were available for a subset of patients, allowing analysis of delayed changes. However, some limitations deserve consideration. The modest sample size and concerns of model over-fitting precluded extensive adjustment for other variables, such as body weight and UF volume. In this respect, although our overall goal was to provide primarily descriptive analyses, the possibility of residual confounding remains, and our results may be underpowered and should be considered with caution. Another limitation is the lack of intra-dialytic measurements and short duration of post-HD lab follow up (labs only obtained at the 15- and 30-minute post-HD time points, in comparison to other studies which drew levels up to the 6-hour post-HD time point)[8]. Future studies should assess electrolyte changes during HD and for a longer duration following HD and should also assess the associations of these electrolyte changes with intra- and post-HD arrhythmia for a longer post-HD time interval. Data regarding the association of intra- and post-HD electrolytes with clinical outcomes will be necessary for understanding the implications of abnormal electrolytes specific to the HD patient population. Neither ionized calcium nor dialysate magnesium were recorded or measured in MiD, precluding further analyses of these parameters. Further, dialysis baths reflected ordered, rather than measured, concentrations of electrolytes. In a typical “three-stream” dialysis system, manipulation of dialysate bicarbonate, for example may affect dialysate sodium slightly. However, this would not be expected to induce a clinically relevant difference in

the sodium concentration delivered. While it is unlikely that the relationship between pre-dialysis values and dialysate chemistry varies widely, our cohort included a modest number of patients from a few centers in the USA and India that may not fully represent the broad range of pre-dialysis concentrations or prescription choices utilized throughout the world. Furthermore, the inclusion and exclusion criteria in this study may have selected potentially ‘healthier’ patients, further limiting the generalizability of our findings to those with more extreme pre-HD electrolyte abnormalities.

In conclusion, this secondary analysis of the MiD study provides a detailed assessment of the changes in electrolytes from pre- to post-HD with contemporary HD treatments. Though the sample size is modest, this data provides information for practicing clinicians who wish to better understand the implications of differing dialysate prescriptions on the changes in serum electrolytes from pre- to immediately post-HD; however, prospective validation of these findings is required. This study highlights several areas of unmet need, which are ripe for development of future interventional studies involving the dialysate prescription.

Disclosures

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Author Contributions

S.C, D.M.C and F.M.C designed the study; D.M.C acquired the study data; K.M.C conducted statistical analyses; S.C and K.M.S drafted the manuscript; all authors analyzed and interpreted the results; D.M.C and F.M.C provided supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Table 1. Characteristics of the participants at baseline

Baseline Characteristics	All subjects (n=66)
Age, years	56 ± 12
Male, n (%)	46 (70)
Race, n (%)	
Asian	23 (35)
Black	35 (53)
White	7 (11)
Other	1 (1)
ESRD vintage, years	2.4 [1.2, 5.3]
Vascular access, n (%)	
AV fistula	46 (71)
AV graft	16 (25)
Catheter	3 (5)
Comorbid conditions, n (%)	
Diabetes mellitus	28 (43)
Hyperlipidemia	40 (61)
Hypertension	56 (85)
Ischemic heart disease	32 (48)
Congestive heart failure	17 (26)
Arrhythmia	21 (32)
Atrial fibrillation	7 (11)
Systolic blood pressure, mmHg	141 ± 23
Diastolic blood pressure, mmHg	77 ± 13
Medication use, n (%)	
Aspirin	30 (45)
Statin	32 (48)
ACEI or ARB	22 (33)
Beta-blockers	36 (55)
Pre-dialysis serum laboratory values	
Blood urea nitrogen, mg/dL	60 ± 18
Creatinine, mg/dL	10.0 ± 3.4
Sodium, mEq/L	137 ± 4
Potassium, mEq/L	5.0 ± 1.0
Calcium, mg/dL	8.7 ± 0.8
Bicarbonate, mEq/L	22 ± 4
Magnesium, mg/dL	2.4 ± 0.5
Phosphorus, mg/dL	5.5 ± 2.0
Hemoglobin, g/dL	11 ± 1
Serum albumin, g/dL	3.9 ± 0.3

Continuous variables are presented as means ± standard deviation or median [25^{th}, 75^{th} percentiles].

Abbreviations: ESRD, end-stage renal disease; AV, arteriovenous; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Characteristics of the dialysis prescription at baseline

Baseline Characteristics	All subjects (n=66)
Duration of hemodialysis, hours	4.0 [3.0, 6.0]
spKt/V	1.5 ± 0.4
Pre-dialysis weight, kg	86.7 ± 28.8
Kg over dry weight target before dialysis	4.2 [-0.4, 12.0]
UFR, ml/kg/h	10 ± 4
Dialysate Flow, mL/min	600 [500, 800]
Blood Flow, mL/min	390 [324, 461]
High-flux dialyzer, n (%)	42 (64)
Membrane reuse, n (%)	18 (27)
Cellulose membrane, n (%)	5 (8)
Dialysate temperature, n (%)	
35.5 Celsius	1 (2)
36.0 Celsius	3 (5)
36.5 Celsius	5 (8)
37.0 Celsius	57 (86)
Dialysate potassium, n (%)	
1.0 mEq/L	1 (2)
2.0 mEq/L	53 (80)
3.0 mEq/L	11 (17)
4.0 mEq/L	1 (2)
Dialysate calcium, n (%)	
1.5 and 1.6 mEq/L	13 (20)
2.0 and 2.5 mEq/L	39 (59)
3.0 and 3.5 mEq/L	14 (21)
Dialysate sodium, n (%)	
135 mEq/L	6 (10)
138 mEq/L	6 (10)
140 mEq/L	49 (80)
Dialysate Bicarbonate, n (%)	
24 - 32 mEq/L	16 (24)
33 - 36 mEq/L	34 (52)
37 – 40 mEq/L	16 (24)

Continuous variables are presented as means ± standard deviation or median [25^{th}, 75^{th} percentiles].
Abbreviations: spKt/V, single-pool Kt/V; UFR, ultrafiltration rate

Table 3. Electrolyte and laboratory values pre- and immediately post-HD

Laboratory Parameter	**Pre-HD value** *mean (SE)* *N subjects* *N HD sessions*	**Post-HD value** *mean (SE)* *N subjects* *N HD sessions*	**Delta (Post-HD minus Pre-HD)** *mean (SE)* *N subjects* *N HD sessions*	**P-value (Post vs. Pre-HD)**	**LLN**	**Frequency of post-HD concentrations below the LLN** *N subjects* *N HD sessions*	**ULN**	**Frequency of post-HD concentrations above the ULN** *N subjects* *N HD sessions*
Sodium (mEq/L)	136.9 (0.5) 66 1708	137.3 (0.3) 66 1685	0.5 (0.4) 66 1648	0.20	<135 mEq/L	38 (57.6%) 311 (18.5%)	>145 mEq/L	2 (3.0%) 2 (0.1%)
Potassium (mEq/L)	4.9 (0.1) 66 1699	3.6 (0.1) 66 1689	-1.2 (0.1) 66 1645	<0.001	<3.5 mEq/L	59 (89.4%) 669 (39.6%)	>5.0 mEq/L	21 (31.8%) 48 (2.8%)
Bicarbonate (mEq/L)	22.3 (0.4) 66 1707	27.1 (0.4) 66 1690	4.9 (0.3) 66 1651	<0.001	<22 mEq/L	28 (42.4%) 141 (8.3%)	>28 mEq/L	58 (87.9%) 569 (33.7%)
Calcium (mg/dL)	8.7 (0.1) 66 1708	9.4 (0.1) 66 1685	0.7 (0.1) 66 1648	<0.001	<8.5 mg/dL	28 (42.4%) 192 (11.4%)	>10.4 mg/dL	29 (43.9%) 190 (11.3%)
Magnesium (mg/dL)	2.4 (0.1) 66 1708	2.1 (0.1) 66 1690	-0.3 (0.03) 66 1653	<0.001	<1.7 mg/dL	29 (43.9%) 162 (9.6%)	>2.4 mg/dL	18 (27.3%) 286 (16.9%)
Phosphorus (mg/dL)	5.2 (0.2) 66 1706	2.2 (0.1) 66 1682	-3.0 (0.2) 66 1645	<0.001	<2.5 mg/dL	65 (98.5%) 1129 (67.1%)	>4.5 mg/dL	8 (12.1%) 8 (0.5%)
BUN (mg/dL)	56.2 (1.6) 66 1713	16.2 (0.6) 66 1695	-39.9 (1.2) 66 1657	<0.001	-	-	-	-
Creatinine (mg/dL)	9.8 (0.4) 66 1713	3.5 (0.2) 66 1695	-6.3 (0.3) 66 1657	<0.001	-	-	-	-
Albumin (g/dL)	3.9 (0.04) 66 1708	4.3 (0.1) 66 1691	0.4 (0.03) 66 1654	<0.001	-	-	-	-

Abbreviations: SE, standard error; BUN, blood urea nitrogen; HD, hemodialysis; LLN, lower limit normal; ULN, upper limit normal.
Mean differences (delta) were calculated using data from subjects who had both pre- and post- measurement for each given electrolyte.
Percent of sessions with a value above or below the limits of normal are calculated as $n_{\text{measurement outside of limits of normal}}/N_{\text{total measurements}}$.

Table 4. Electrolyte and laboratory changes 15- and 30-minute post-HD

Laboratory Parameter	*mean (SE)* *N subjects* *N HD sessions*				P-value (Post vs. 15 mins post)	*mean (SE)* *N subjects* *N HD sessions*		P-value (Post vs. 30 mins post)
	Pre-HD	Post-HD	15 mins post-HD	Delta (15 mins post minus post)		30 mins post-HD	Delta (30 mins post minus post)	
Sodium (mEq/L)	136.9 (0.5) 66 1708	137.3 (0.3) 66 1685	139.2 (0.4) 40 40	0.5 (0.3) 40 40	0.10	138.7 (0.5) 38 38	-0.1 (0.3) 38 38	0.80
Potassium (mEq/L)	4.9 (0.1) 66 1699	3.6 (0.1) 66 1689	3.6 (0.1) 40 40	-0.1 (0.1) 40 40	0.26	3.8 (0.1) 38 38	0.2 (0.1) 38 38	0.03
Bicarbonate (mEq/L)	22.3 (0.4) 66 1707	27.1 (0.4) 66 1690	27.0 (0.7) 40 40	-1.1 (0.5) 40 40	0.02	27.5 (0.5) 38 38	-0.7 (0.2) 38 38	<0.01
Calcium (mg/dL)	8.7 (0.1) 66 1708	9.4 (0.1) 66 1685	8.9 (0.2) 40 40	-0.6 (0.2) 40 40	<0.01	9.2 (0.1) 38 38	-0.3 (0.1) 38 38	<0.01
Magnesium (mg/dL)	2.4 (0.1) 66 1708	2.1 (0.1) 66 1690	1.8 (0.1) 40 40	-0.1 (0.04) 40 40	0.08	1.9 (0.04) 38 38	0.01 (0.02) 38 38	0.59
Phosphorus (mg/dL)	5.2 (0.2) 66 1706	2.2 (0.1) 66 1682	2.4 (0.1) 39 39	0.1 (0.1) 39 39	0.03	2.6 (0.1) 38 38	0.4 (0.1) 38 38	<0.001
BUN (mg/dL)	56.2 (1.6) 66 1713	16.2 (0.6) 66 1695	16.9 (1.2) 24 24	0.8 (0.6) 24 24	0.19	18.9 (1.2) 38 24	2.5 (0.4) 24 24	<0.001
Creatinine (mg/dL)	9.8 (0.4) 66 1713	3.5 (0.2) 66 1695	4.2 (0.3) 39 39	0.2 (0.1) 39 39	0.20	4.7 (0.3) 38 38	0.6 (0.1) 38 38	<0.001
Albumin (g/dL)	3.9 (0.04) 66 1708	4.3 (0.1) 66 1691	4.1 (0.1) 40 40	-0.4 (0.1) 40 40	0.001	4.3 (0.1) 38 38	-0.2 (0.1) 38 38	<0.001

Abbreviations: SE, standard error; BUN, blood urea nitrogen; HD, hemodialysis.
Mean differences (delta) were calculated using data from subjects who had both pre- and post- measurement for each given electrolyte.
The total number of sessions with laboratory data may vary due to missing collections or data recording.
Percentages may not add to 100 due to rounding.

Table 5. Proportion of patients with abnormal serum electrolyte values at 30-minutes post-HD.

Laboratory Parameter	LLN	Frequency of post-HD concentrations below the LLN	ULN	Frequency of post-HD concentrations above the ULN
Sodium (mEq/L)	<135	3/38 (7.9%)	>145	0 (0%)
Potassium (mEq/L)	<3.5	11/38 (29.0%)	>5.0	1 (2.6%)
Bicarbonate (mEq/L)	<22	0 (0%)	>28	13 (34.2%)
Calcium (mg/dL)	<8.5	4/38 (10.5%)	>10.4	1 (2.6%)
Magnesium (mg/dL)	<1.7	7/38 (18.4%)	>2.4	0 (0%)
Phosphorus (mg/dL)	<2.5	17/38 (44.7%)	>4.5	1 (2.6%)

Abbreviations: LLN, lower limit normal; ULN, upper limit normal; HD, hemodialysis. A total of 38 sessions from 38 patients had 30-minute post-HD measurements

Table 6. Unadjusted and adjusted changes in pre-HD to post-HD serum electrolytes according to different dialysate prescriptions

	Change in serum electrolyte (post-HD minus pre-HD) in mEq/L or mg/dL* Mean (SE)					
Dialysate Sodium n/N (%)	**Unadjusted**	**P-value**	**Model 1**	**P-value**	**Model 2**	**P-value**
135 (mEq/L) 191/1511 (13%)	-0.6 (0.6)		-1.4 (0.5)		-1.5 (0.5)	
138 (mEq/L) 146/1511 (10%)	-0.7 (1.2)		-0.4 (0.9)		-0.4 (0.9)	
140 (mEq/L) 1174/1511 (78%)	0.5 (0.4)		0.6 (0.3)		0.6 (0.3)	
		0.10		<0.001		<0.001
Dialysate Potassium						
1 and 2 (mEq/L) 1336/1630 (82%)	-1.3 (0.1)		-1.3 (0.04)		-1.3 (0.04)	
3 and 4 (mEq/L) 294/1630 (18%)	-0.9 (0.1)		-0.9 (0.1)		-0.9 (0.1)	
		<0.001		<0.001		<0.001
Dialysate Bicarbonate						
24 to 32 (mEq/L) 351/1610 (22%)	4.5 (0.5)		3.7 (0.4)		3.5 (0.5)	
33 to 36 (mEq/L) 803/1610 (50%)	4.8 (0.3)		4.4 (0.3)		4.5 (0.3)	
37 to 40 (mEq/L) 456/1610 (28%)	5.1 (0.4)		6.7 (0.4)		6.7 (0.4)	
		0.57		<0.001		<0.001
Dialysate Calcium						
1.5 and 1.6 (mEq/L) 359/1647 (22%)	1.2 (0.2)		0.8 (0.2)		0.8 (0.2)	
2 and 2.5 (mEq/L) 926/1647 (22%)	0.4 (0.1)		0.4 (0.1)		0.4 (0.1)	
3.0 and 3.5 (mEq/L) 362/1647 (22%)	1.1 (0.1)		1.4 (0.1)		1.4 (0.1)	
		<0.001		<0.001		<0.001

Model 1 adjusted for the pre-dialysis serum concentration; Model 2 adjusted for the pre-dialysis serum concentration and dialysis session length.

Changes in serum sodium, potassium and bicarbonate are presented in mEq/L; changes in serum calcium are presented in mg/dL.

P-values for the association between categorical dialysate prescription with electrolyte change.

Footnote 1: Variability in number of sessions may be due to missing collections or data recording.

Footnote 2: Negative sign (-) indicates a decrease.

Figure legends

Fig 1. Serum electrolyte and laboratory parameter changes over time.

Abbreviations. HD, hemodialysis; min, minute.

Fig 2. Predicted change in A) serum sodium, B) serum potassium, C) serum bicarbonate and D) serum calcium according to baseline serum electrolyte and dialysate prescription (mEq/L).

Each graph is based on a model that adjusted for the pre-HD concentration of the electrolyte of interest. For instance, the predictive graph for serum sodium is adjusted for pre-HD serum sodium.

Figure 1

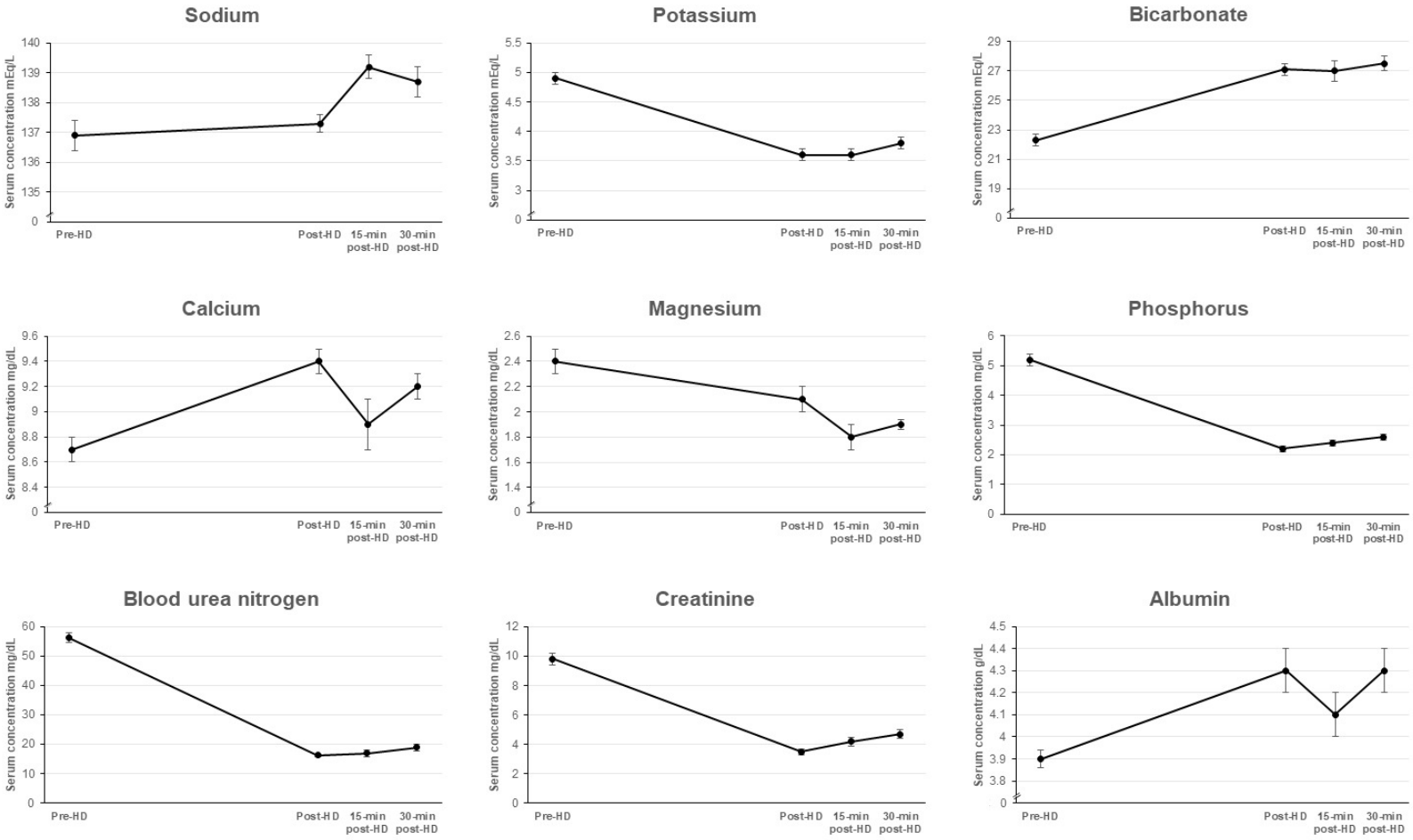
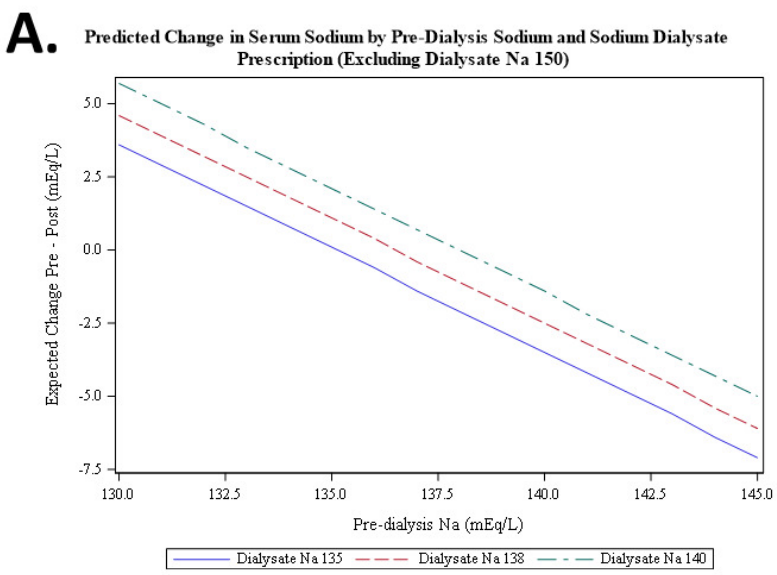
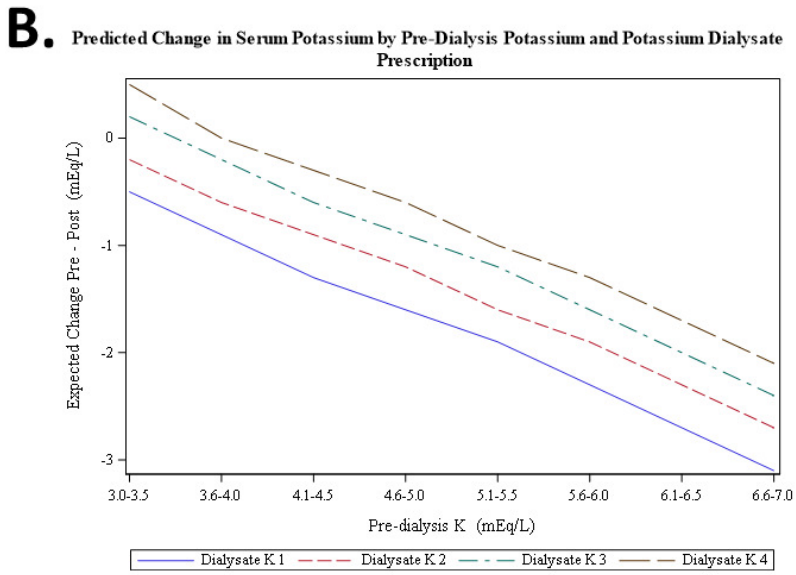
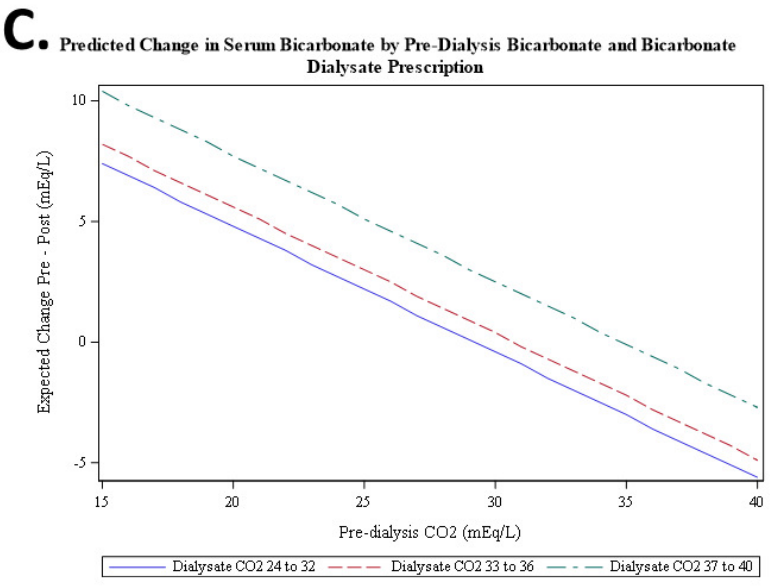
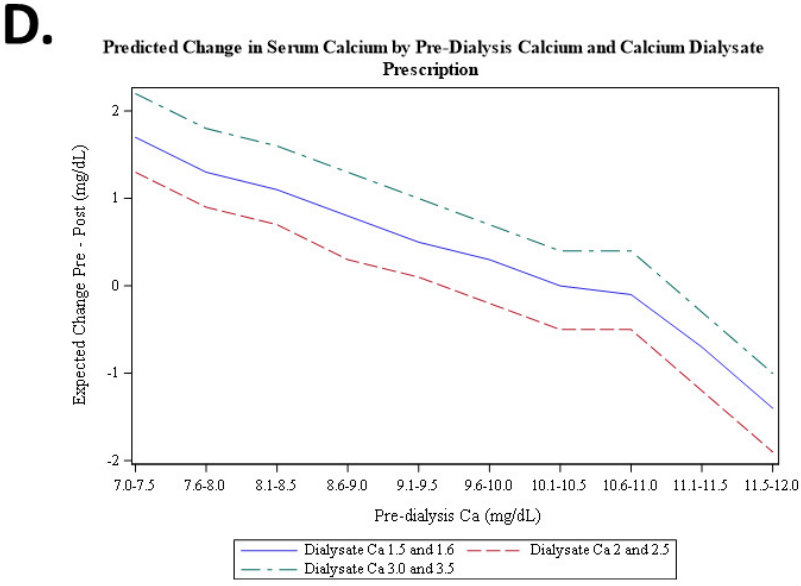

Sodium
Serum concentration mEq/L
140
139
138
137
136
135
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD
Potassium
Serum concentration mEq/L
5.5
5
4.5
4
3.5
3
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD
Bicarbonate
Serum concentration mEq/L
29
27
25
23
21
19
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD
Calcium
Serum concentration mg/dL
9.6
9.4
9.2
9
8.8
8.6
8.4
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD
Magnesium
Serum concentration mg/dL
2.6
2.4
2.2
2
1.8
1.6
1.4
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD
Phosphorus
Serum concentration mg/dL
6
5
4
3
2
1
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD
Blood urea nitrogen
Serum concentration mg/dL
60
50
40
30
20
10
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD
Creatinine
Serum concentration mg/dL
12
10
8
6
4
2
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD
Albumin
Serum concentration g/dL
4.5
4.4
4.3
4.2
4.1
4
3.9
3.8
0
Pre-HD
Post-HD
15-min post-HD
30-min post-HD

Figure 2


A.
Predicted Change in Serum Sodium by Pre-Dialysis Sodium and Sodium Dialysate Prescription (Excluding Dialysate Na 150)
Expected Change Pre - Post (mEq/L)
5.0
2.5
0.0
-2.5
-5.0
-7.5
130.0
132.5
135.0
137.5
140.0
142.5
145.0
Pre-dialysis Na (mEq/L)
Dialysate Na 135
Dialysate Na 138
Dialysate Na 140


B.
Predicted Change in Serum Potassium by Pre-Dialysis Potassium and Potassium Dialysate Prescription
Expected Change Pre - Post (mEq/L)
0
-1
-2
-3
3.0-3.5
3.6-4.0
4.1-4.5
4.6-5.0
5.1-5.5
5.6-6.0
6.1-6.5
6.6-7.0
Pre-dialysis K (mEq/L)
Dialysate K 1
Dialysate K 2
Dialysate K 3
Dialysate K 4


C.
Predicted Change in Serum Bicarbonate by Pre-Dialysis Bicarbonate and Bicarbonate Dialysate Prescription
Expected Change Pre - Post (mEq/L)
10
5
0
-5
15
20
25
30
35
40
Pre-dialysis CO2 (mEq/L)
Dialysate CO2 24 to 32
Dialysate CO2 33 to 36
Dialysate CO2 37 to 40


D.
Predicted Change in Serum Calcium by Pre-Dialysis Calcium and Calcium Dialysate Prescription
Expected Change Pre - Post (mg/dL)
2
1
0
-1
-2
7.0-7.5
7.6-8.0
8.1-8.5
8.6-9.0
9.1-9.5
9.6-10.0
10.1-10.5
10.6-11.0
11.1-11.5
11.5-12.0
Pre-dialysis Ca (mg/dL)
Dialysate Ca 1.5 and 1.6
Dialysate Ca 2 and 2.5
Dialysate Ca 3.0 and 3.5