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The Effect of Diffusive and Convective Sodium Balance During Hemodialysis on Interdialytic Weight Gain

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Graduate Program in Medical Biophysics
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

THE EFFECT OF DIFFUSIVE AND CONVECTIVE SODIUM BALANCE DURING HEMODIALYSIS ON INTERDIALYTIC WEIGHT GAIN

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ABSTRACT

Patients with end stage renal disease (ESRD) often require hemodialysis treatments in which blood's water and dissolved solutes undergo diffusion and convection by exposure to an extracorporeal membrane. The leading cause of death in this population is cardiovascular, and how hemodialysis is prescribed alters total sodium balance, a critical determinant of cardiovascular health. We performed retrospective and prospective analysis of data from patients in the Southwestern Ontario Regional Hemodialysis Program. An increased Dialysate sodium (Dial-Na+) to Pre-dialysis plasma sodium (Pre-Na+) concentration difference (DPNa+) leads to adverse clinical outcomes in hemodialysis patients. The post- to pre-dialysis plasma sodium difference (PPNa+) predicts clinical outcomes equally well as DPNa+ so long as Dial-Na+ is within 3 mmol/L of Pre-Na+. Calculation of DPNa+ requires determination of the Pre-Na+, historically thought to be stable in hemodialysis patients and thus termed "setpoint" (SP). However, we determined that SP is modifiable by hemodialysis prescription. Finally, an equation to predict interdialytic weight gain was created, confirming Dial-Na+, dialysis frequency and duration to be modifiable factors affecting IDWG. Further research is required to validate this equation prospectively, and to determine the impact of changes of SP on cardiovascular morbidity and mortality.

KEYWORDS

Hemodialysis, end stage renal disease, end stage kidney disease, interdialytic weight gain, cardiovascular mortality, sudden cardiac death, dialysate sodium, sodium setpoint, diffusive sodium balance, ultrafiltration, osmotic sodium balance, quotidian hemodialysis, nocturnal hemodialysis, home hemodialysis.

CO-AUTHORSHIP STATEMENT

This thesis contains three published papers (Chapters 3, 4, and 5) and two submitted manuscripts (Chapters 6 and 7). These published papers and submitted manuscripts form the major scientific work of this thesis. Each published paper and submitted manuscript has several authors who may or may not have been members of the thesis advisory committee.

Chapter 1: Benjamin Thomson was instrumental in conception, design, and writing of initial and final versions of Chapter 1. Dr. Robert Lindsay provided intellectual input and helped to revise the final version.

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Quotidian and Nocturnal Hemodialysis. Submitted to: *Nephrology Dialysis Transplantation.*

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LIST OF ABBREVIATIONS

ADH	Anti-Diuretic Hormone
BP	Blood Pressure
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence Intervals
DeltaPRENA100	(PRENA100+) – (PRENA-50)
DeltaPRENA100-150	(PRENA100-150) – (PRENA-50)
Dial-Na+	Dialysate Sodium Concentration
DPNa+	(Dialysate Sodium Concentration) – (Pre-Hemodialysis Plasma Sodium Concentration)
DPRENA-50	(Dialysate Sodium Concentration) – (PRENA-50)
ESRD	End Stage Renal Disease
FHN	Frequent Hemodialysis Network
FNHD	Frequent Nocturnal Hemodialysis
GFR	Glomerular Filtration Rate
H20	Water
HD	Hemodialysis
HIGHDialSOD	Study Period in which Dialysate Sodium Concentration was 3 mmol/L Higher Than Patient's Sodium Setpoint
ICHD	Intermittent Conventional Hemodialysis
IDWG	Interdialytic Weight Gain
IDWG%BW	Interdialytic Weight Gain as a Percentage of Body Weight
INHD	Intermittent Nocturnal Hemodialysis
KDOQI	Kidney Disease Outcomes Quality Initiative
LOWDialSOD	Study Period in Which Dialysate Sodium Concentration was 3 mmol/L Lower Than Patient's Sodium Setpoint
MDRD	Modificd Diet in Renal Disease
mM	Millimoles Per Liter
NKF	National Kidney Foundation
PD	Peritoneal Dialysis

Post-Na+	Post-Hemodialysis Plasma Sodium Concentration
PPNa+	(Post-Hemodialysis Plasma Sodium Concentration) – (Pre-Hemodialysis Plasma Sodium Concentration)
Pre-Na+	Pre-Hemodialysis Plasma Sodium Concentration
PRENA-50	Mean Pre-Dialysis Plasma Sodium Concentration in the 50 Days Prior to Transition to Home Hemodialysis
PRENA100+	Mean Pre-Dialysis Plasma Sodium Concentration, from 100 Days After Transition to Home Hemodialysis, to the End of the Home Hemodialysis Modality
PRENA100-150	Mean Pre-Dialysis Plasma Sodium Concentration from 100 to 150 Days After Transition to Home Hemodialysis
RP	Pearson's Correlation Coefficient
RTx	Renal Transplant
SCD	Sudden Cardiac Death
SHD	Short Hours Daily Hemodialysis
SP	Sodium Setpoint, also known as Mean Pre-Dialysis Plasma Sodium Concentration
US	United States

LIST OF SYMBOLS

D	Fick's Diffusion Coefficient (m^2/s)
δc	Difference in Concentration Across Membrane, Commonly Referred to as "Concentration Gradient" (mol/m^3)
δn	Difference in Sodium Movement Across Membrane (mol)
δP	Pressure Difference Between Two Points Along a Dialyzer Hollow Fiber (Pa)
δt	Change in Time (s)
δd	Distance for Molecule to Move for Diffusion Out of Dialyzer Hollow Fiber (m)
κ	Boltzmann's Coefficient (1.3806×10^{-23} $m^2kg/s^2Kelvin$)
L	Dialyzer Hollow Fiber Length (m)
M	Molecular Weight (g/mol)
N	Avogadro's Number ($6.02214 \times 10^{23}/mol$)
Na+	Sodium
η	Viscosity [kg/(m s)]
Q	Blood Flow Rate (m^3/s)
R	Resistance [$kg/(s\ m^4)$]
r	Dialyzer Hollow Fiber Radius (m)
τ	Sheer Stress on Dialyzer Hollow Fiber Wall [$kg/(m\ s^2)$]
T	Temperature (Kelvin)
u	Partial Molar Volume (m^3/mol)
v	Velocity (m/s)
[x]	Concentration of Substance x (mmol/L)

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Chapter 1: General Introduction

1.0 General Introduction

Prevalence of kidney disease in the United States (U.S.) has increased by over 60 times from 1973 to 2011.[1,2] Now approximately 15% of the population is affected by kidney disease,[3-5] translating to over 4 million Canadians[6] and 40 million Americans.[7] Prevalence estimates have been difficult without a uniform definition of kidney disease; fortunately, this was formalized in 2002 (Table 1.1).[8]

Stage	Glomerular Filtration Rate*	Kidney Damage**	Prevalence (%)
1	> 90 mL/min/1.73 m^2	+	1.8
2	60-89 mL/min/1.73 m^2	+/-	3.2
3	30-59 mL/min/1.73 m^2	+/-	7.7
4	15-29 mL/min/1.73 m^2	+/-	0.4
5 "End Stage"	<15 mL/min/1.73 m^2 OR renal replacement therapy ***	+/-	2.4

Table 1.1: Kidney Disease Outcomes Initiative Definition of Kidney Disease

* Glomerular Filtration Rate defined by a Serum Creatinine, as per Cockcroft-Gault,[9] Modification of Diet in Renal Disease (MDRD)[10] or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[11] equations

** Kidney Damage may include urinary abnormality (eg. Microalbuminuria, hematuria) or structural abnormality of the kidney

*** Renal replacement therapy may include peritoneal dialysis, hemodialysis, or renal transplantation

Critical in the formal definition is the recognition that kidney disease exists on a continuum, and that patients can progress from one stage to the next. Though 15% of the population suffers from kidney disease, 2.4% (Table 1.1) have the most advanced "end stage" 5, and many of these patients require renal replacement therapy. There are three types of renal replacement therapy, being peritoneal dialysis (PD), hemodialysis (HD), and renal transplantation (RTx). Hemodialysis is a process in which a patient's blood is exposed to a man-made dialyzer membrane to remove waste products, to restore the proper balance of electrolytes such as potassium and phosphate, and to eliminate extra fluid from the body. Most recent estimates suggest there are 23,188 Canadians[12] and 398,861 Americans[13] with Stage 5 kidney disease so severe that they require renal replacement with hemodialysis treatments.

Patients with all stages of kidney disease are at higher risk of cardiovascular death than the general population.[14-16] The most common cause of death in patients with end stage kidney disease is indeed cardiovascular (Figure 1.1).[2]

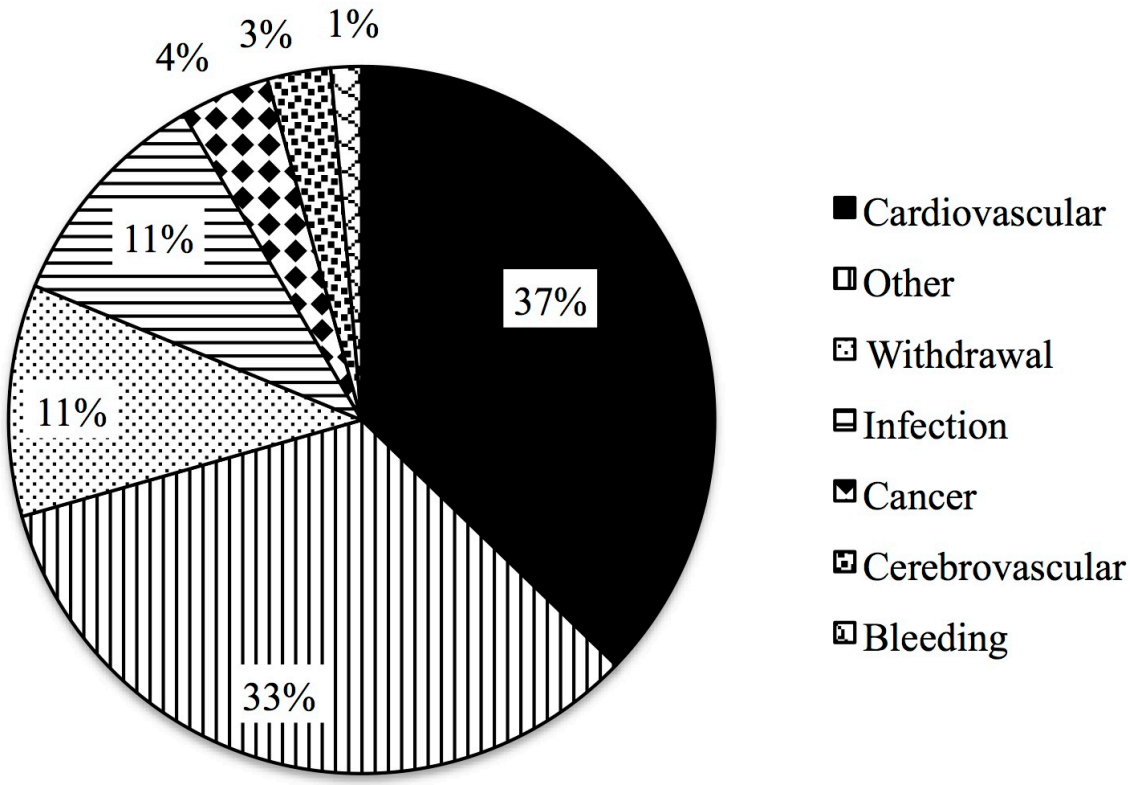

Figure 1.1: Causes of Death in Patients with End Stage Renal Disease

Cardiovascular disease encompasses a wide spectrum of pathologies, but in end-stage kidney disease patients using hemodialysis (ESRD-HD), up to 60% of cardiovascular deaths are by sudden cardiac death (SCD).[17] It is well established that SCD risk increases as renal function worsens;[18] Several mechanisms have been proposed, including hemodialysis prescription,[19-26] anemia and vascular access,[27-31] atherosclerosis,[19,32] arteriolosclerosis,[33,34] volume and pressure overload.[20,35-40]

1.1 Hemodialysis

Of special importance in hemodialysis patients are the separate effects of volume overload and pressure exerted upon the left ventricular output,[20,35-40] which ultimately lead to left ventricular hypertrophy[41-49] and death.[50,51] In conventional hemodialysis

patents, urine output is either absent or insufficient, so hemodialysis is performed three times a week to remove solutes and fluids. The increase in weight from the end of a hemodialysis session to the start of the next session is called interdialytic weight gain (IDWG) (Figure 1.2).

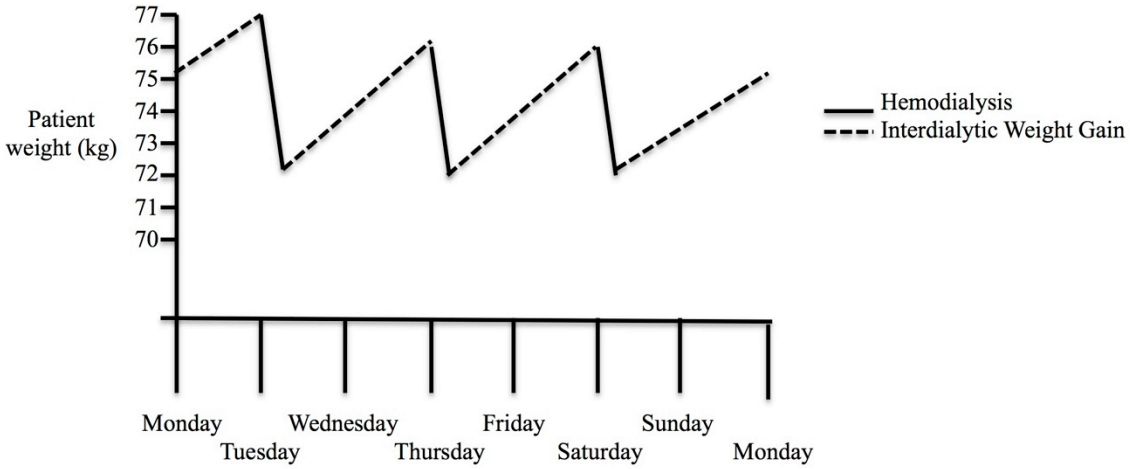

Figure 1.2: Interdialytic Weight Gain in Patients Undergoing Hemodialysis Tuesdays, Thursdays and Saturdays

Overwhelming evidence suggests that, when corrected for confounding factors such as nutritional status,[52,53] increases in IDWG lead to increased morbidity and mortality in hemodialysis patients.[37,38,53-56] Thus, defining strategies that effectively control interdialytic weight gain is of clinical importance, and likely will lead to improved survival of hemodialysis patients.

Total body volume is regulated through sodium balance,[57] and thus the major determinant of IDWG is a patient's total sodium balance (Equation 1.1).

Equation 1.1: Total Sodium Balance

IDWG ~ [Na+] Balance = [Na+] intake (oral or intravenous)

- Urinary [Na+] excretion - Other (fecal/sweat) [Na+] excretion

+ [Na+] balance in hemodialysis

In hemodialysis patients, urinary [Na+] excretion is either non-existent or negligible, and fecal and sweat sodium excretion is negligible. Thus, the [Na+] balance in a hemodialysis

patient is determined by [Na+] intake (oral or intravenous) and by [Na+] balance in hemodialysis. It is well established that dietary oral sodium restriction decreases IDWG and left ventricular mass.[58,59] Likewise, administration of intravenous sodium chloride solution increases IDWG.[60,61] However, the effect of [Na+] balance, during hemodialysis, on IDWG, is less well understood. An understanding of the biological and physical processes involved in hemodialysis, and their effects on total sodium balance, is therefore essential to determine how to reduce IDWG, and ultimately, hemodialysis patient morbidity and mortality.

Hemodialysis is a process in which a patient's blood is exposed to a man-made dialyzer membrane to remove waste products, to restore the proper balance of electrolytes such as potassium and phosphate, and to eliminate excess body fluid (Figure 1.3). Blood leaves the patient (Figure 1.3- blue curved arrow) from an intravenous catheter, into a hemodialysis machine, where it enters "pre-membrane" into the top of a dialyzer, simultaneous to clean dialysate fluid entering the bottom of the same dialyzer. After the waste products and excess water are removed, blood leaves the dialyzer, and is pumped back into the patient (Figure 1.3- red curved arrow).[A]

As blood flows through the parallel array of small caliber cylindrical tubes in the operational core of a dialysis machine (the dialysis "membrane"), the material walls of the tubing are the hemodialysis membrane. The flow in each tube is approximately parabolic in velocity profile, the fastest in the center, and slowest at the wall. The friction between these fluid layers is known as viscosity, or less formally as "stickiness." Mathematically, the viscosity (η), is defined as the ratio of the fluid shear stress (τ,in Pa), divided by the fluid shear rate ($\delta v/\delta r$, in s^{-1}) [$\eta = \tau /(\delta v/\delta r)$, thus having units of Pa.s]. If the viscosity of a fluid is independent of shear rate, then the viscosity is said to be a Newtonian fluid. While blood does have a minor dependence of its viscosity on shear

[A] There are many components to the standard hemodialysis machine, including heaters, deaeration, blood tubing, blood and dialysate pumps, blood leak detector, flow meter, conductivity cell and display, pH probes, filters, dialysis membrane, and electrical supply. However, it is not the objective of this thesis to discuss each individual component. Instead, only those components that have a role in sodium balance in hemodialysis are discussed. Furthermore, the dialysis machine and components are kept relatively constant from one instrument to another. These instruments are also kept relatively constant whether a patient performs their treatment in a hospital, or at home. Therefore, the biophysical forces involved in hemodialysis are similar regardless of the location of the treatments.

rate at very low shear rates, it is considered to be Newtonian in the larger blood vessels and within the dialysis instrumentation.

The removal of waste products and water relies upon passage of blood inside one of thousands of hollow fibers,[B] with dialysate fluid moving in the opposite direction on the opposite side (Figure 1.4). Since sodium removal during hemodialysis is critical to the total body sodium balance, which in turn is important in cardiovascular and all-cause mortality, a detailed understanding of all the factors that contribute to intradialytic

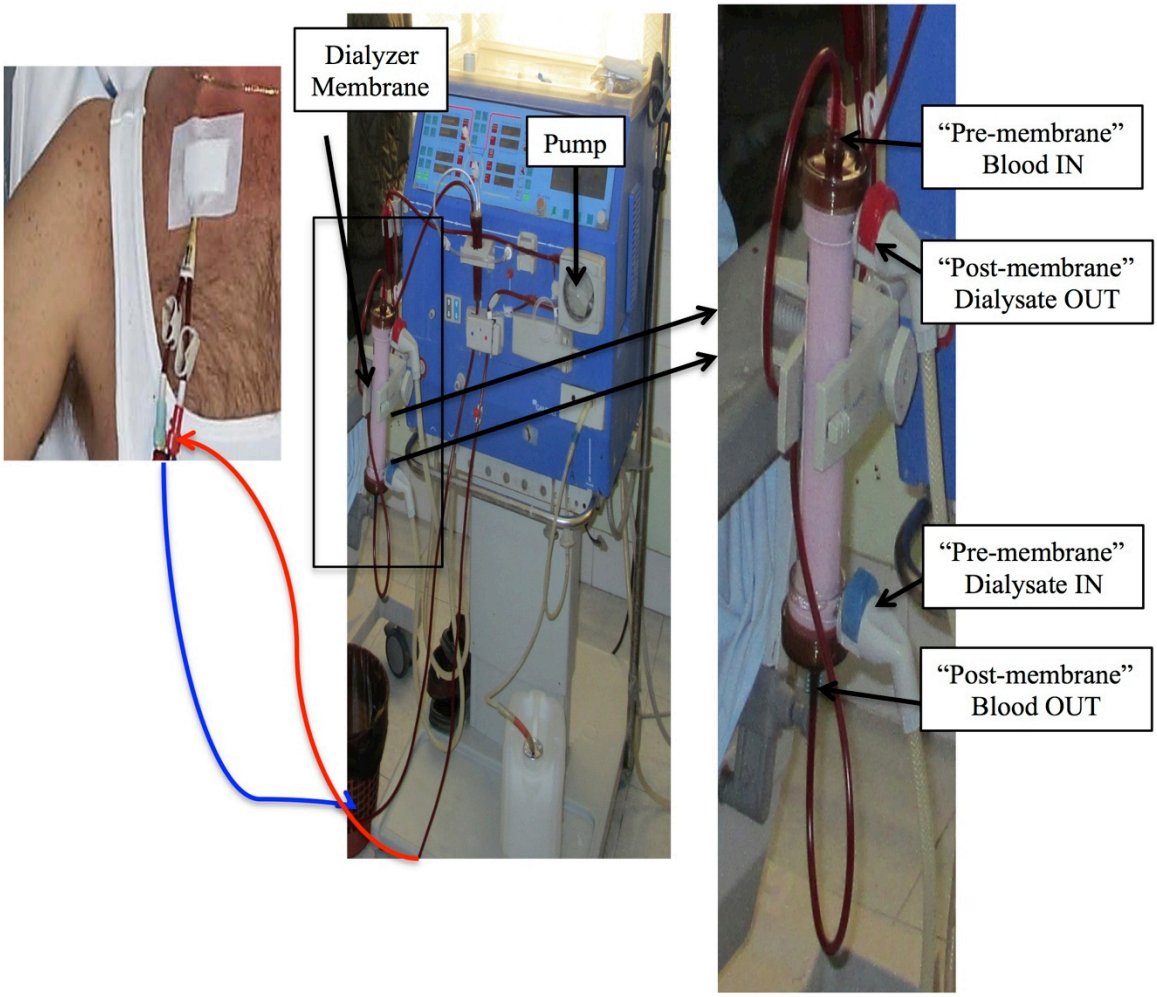

Figure 1.3: Hemodialysis Process

sodium balance is essential. Sodium balance during hemodialysis occurs by both diffusion and convection.

[B] In nephrology clinical settings, a hemodialysis hollow "fiber" is one of thousands of cylindrical "tubes" encased within a hemodialysis "membrane."

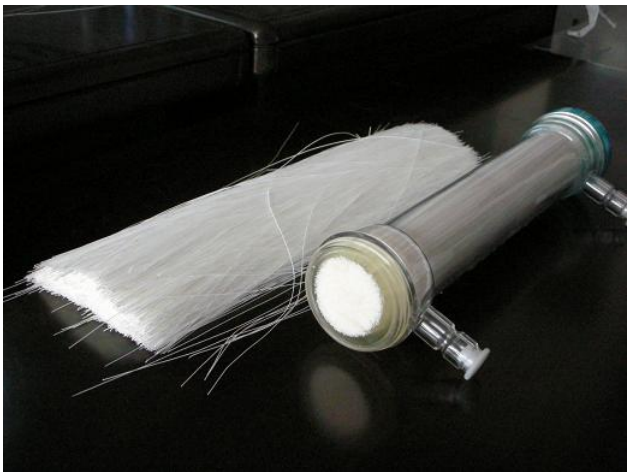

Figure 1.4: Dialyzer Hollow Fibers Through Which Blood Flows.

1.1.1 Diffusion

The rate of diffusive sodium removal across dialyzer membranes is determined by Fick's law (Equation 1.2). In turn, Fick's diffusion coefficient depends on a number of factors (Equation 1.3). Combining equations 1.2 and 1.3 to determine the rate of diffusive sodium removal leads to equation 1.4.

Equation 1.2: Fick's Law

$$\delta n/\delta t = -D(A)\ \delta c/\delta d$$

Equation 1.3: Fick's Diffusion Coefficient

$$D = (\kappa T/6\pi\eta)(4\pi N/3Mu)^{1/3}$$

Equation 1.4: Combination of Equations 2 and 3

$$\delta n/\delta t = (-A)\ (\delta c/\delta d)(\kappa T/6\pi\eta)(4\pi N/3Mu)^{1/3}$$

where $\delta n/\delta t$ = the rate of movement of sodium molecules per unit time (mol/s); D = Fick's diffusion coefficient (m^2/s); A = membrane surface area (m^2); δc = concentration difference (mol/m^3) and δd = the distance a sodium molecule must move (m). κ = Boltzman's constant (J/K); T = absolute temperature (Kelvin); η = viscosity [Pa s]; N =

Avogadro's number (mol^{-1}); M = molecular weight (g/mol); u = partial molar volume (m^3/mol).

Boltzmann's constant ($\kappa = 1.3806 \times 10^{-23}\ m^2kg/s^2$ deg.K.) and Avogadro's number ($N = 6.0221 \times 10^{23}\ mol^{-1}$) are known. Furthermore, dialyzed blood must be returned to the patient at a tolerable temperature, between 35.5 and 38.0 degrees Celsius. This prevents patient discomfort and hypothermia at low temperatures,[62,63] and intradialytic hypotension at high temperatures.[64-67] Thus, there is only a narrow range for the temperature (T), which will be simplified to 36.5 ^oC, or 309.65 ^oK. Simplifying for δn yields Equation 1.5.

Equation 1.5: Rate of Molecular Movement During Hemodialysis

$$\frac{\delta n}{\delta t} = \frac{(3.09 \times 10^{-14})\,(A)\,(1/Mu)^{1/3}}{\eta}\,\frac{(\delta c)}{(\delta d)}$$

where δn = movement of molecules (mol); δt = time (s); A = the area of the dialyzer membrane through which molecules move (m^2); δc = concentration difference (mol/m^3); δd = the distance a sodium molecule must move (m); η = viscosity [Pa s)]; M = molecular weight (g/mol); u = partial molar volume (m^3/mol)

Thus, diffusive loss of a substance can be increased on hemodialysis by a larger dialyzer surface area (A), a shorter distance for a molecule to travel (δd), a greater concentration difference (δc), longer time on hemodialysis (δt), and lower blood viscosity (η). While the design of dialysis machines and dialyzer membranes is not the goal of the research performed for this thesis, a basic understanding is required to establish the rationale of our research design.

1.1.1.1 Dialyzer Area

Dialyzer membrane fiber area is a function of both fiber radius and length (equation 6).

Equation 1.6: Hemodialyzer Fiber Area

$$A = 2\pi rL$$

Where A = fiber surface area (m^2), r = fiber radius (m),
L = fiber length (m).

1.1.1.2 Dialyzer Fiber Radius

Laminar flow of a Newtonian fluid at constant velocity can be modeled using Poiseuille's equation (equation 1.7). On the one hand, a small inner diameter is desirable because it decreases the diffusive distance for solute mass transfer (equation 1.5). However, the flow along the length of a hollow fiber is governed by the Poiseuille equation (equation 1.7), which can be rearranged for blood flow (equation 1.8).

Equation 1.7: Poiseuille's Law

$$\Delta P = \frac{8(\eta)(Q)(L)}{\pi r^4}$$

Equation 1.8: Blood Flow as per Poiseuille Equation

$$Q = \Delta P/R \qquad \text{where } R = 8\eta L/\pi r^4$$

Where ΔP = pressure difference between two points (P2 and P1) along a tube, η = fluid viscosity [Pa s)], Q = volumetric flow rate (m^3/s), r = radius of tube (m), R = resistance to blood flow, L = fiber length (m)

R and r^4 are inversely related; small decreases in hollow fiber radius (r) cause large increases in flow resistance (R). In general, however, the principal resistance to molecular movement out of dialysis tubing is the hollow fiber material itself with a minor

contribution to the radial distance within the blood itself. Since blood flow rate is constant during hemodialysis, an increase in flow resistance is matched with a large increase in pressure drop. This pressure drop is problematic; osmotic clearance is optimized by maximizing a dialyzer membrane's water permeability. Therefore, high flow resistance and associated large pressure drop associates with backfiltration of dialysate into the blood compartment.[68] This is undesirable, as backfiltration is associated with endotoxin exposure, activation of complement, cytokines, inflammation, malnutrition and death.[69-73] Modifications in hollow fiber radius are thus limited, reflecting a compromise between these opposing forces;[74] most hollow fibers have a relatively standard inner diameter (180-220 μm).

1.1.1.3 Dialyzer Fiber Length

Like dialyzer fiber radius, the fiber length represents a compromise between opposing forces.[74] On the one hand, an increase in diffusive capacity can be achieved by increasing the fiber area (equation 1.3), which is dependent upon the fiber length (equation 1.6). On the other hand, increased fiber length associates with higher flow resistance (equation 1.8) and larger pressure drop, which leads to backfiltration of dialysate into the blood compartment.[68] This is undesirable, as backfiltration leads to endotoxin exposure, activation of complement, cytokines, inflammation, malnutrition and death.[69-73] The spectrum of hollow fiber length is thus narrow, reflecting a compromise between these opposing forces;[74] most hollow fibers have a standard length (20-24 cm).

1.1.1.4 Distance for Molecule to Travel

The distance for a molecule in blood to travel, to enter the dialysate, is determined by the hollow fiber radius, and the fiber wall thickness (Figure 1.5). Considerations for hollow fiber radius are discussed above (Section 1.1.1.2).

The hollow fiber thickness reflects three competing manufacturing constraints. Firstly, the fiber wall must withstand the shear stresses of high blood flow under pressure. Shear stress is the external force that blood acts upon the hollow fiber, parallel to the plane in which the fiber lies. This relationship is dictated by the Poiseuille equation

(equation 1.9). Shear stress against the hollow fiber wall also exerts itself against red blood cells, making them susceptible to hemolysis. However, the risk of hemolysis in modern hemodialysis machines is very low; thus, shear stress lies within well tolerated physiological limits. Secondly, greater membrane biocompatibility leads to improvements in complement activation,[75] inflammation,[76] nutritional status,[77] cardiovascular outcomes[72] and mortality.[72,78,79] The earliest hemodialysis membranes, made of modified or unmodified cellulose,[68] had low biocompatibility. These had a wall thickness of 6-15 μm.[80] The major constituent of these membranes was cellobiose,[81] which contained a high density of hydroxyl groups that activated the alternative complement pathway.[82] Newer synthetic membranes have successfully replaced the hydroxyl group and improved biocompatibility.

Equation 1.9: Shear Stress on Hollow Fiber Wall

$\tau = 4\eta v/r$ or $\tau = 4\eta Q/\pi r^3$

Where τ = shear stress on hollow fiber wall (Pa), η = blood viscosity [Pa s)],
v = average blood velocity within hollow fiber (m/s), r = fiber radius (m),
Q = blood flow rate (m^3/s)

Thirdly, earlier hemodialysis membranes had a low mean pore size, limiting clearance to only lower molecular weight toxins.[83,84] On the other hand, a number of synthetic membranes have been developed, including polysulfone,[85] polyamide,[86] polymethylmethacrylate,[87] polyethersulfone,[88] and polyethersulfone combined with polyamide.[89] These membranes have higher water permeability and larger pore size, permitting improved clearance of higher molecular weight proteins.[85,90] Increased clearance of higher molecular weight proteins, such as β2-microglobulin, is desirable since it has been strongly linked to decreased incidence of neuropathy,[70,91,92] cardiovascular disease[93-95] and less strongly to death.[94,96] In light of these manufacturing limitations and clinical outcomes, newer hemodialysis membrane fibers tend to be thicker-walled (≥ 20 μm).[74]

1.1.1.5 Concentration Difference

The hemodialysis membrane concentration difference is determined by the concentration of substance inside hollow fibers (blood) and outside the fiber (dialysate) (Figure 1.5).[C] However, hemodialysis is needed thrice weekly to achieve a minimal weekly hemodialysis clearance to achieve benefits in patient morbidity and mortality.[93,97-102] Therefore, patients' maximal blood substance concentration reflects two things, being the duration and the rate of substance production in the interdialytic interval.

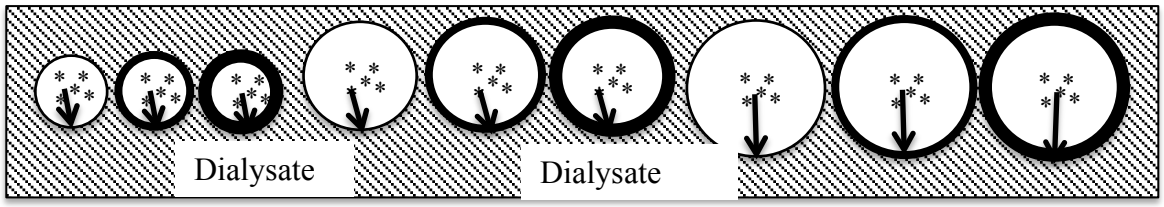

Figure 1.5: Schematic of Solute (*) Inside Dialyzer, Crossing Distance of Hollow Fiber Radius and Fiber Wall to Dialysate

As the interdialytic interval duration increases, substance concentration increases. However, changes in dialysis frequency have more pronounced impacts on the interdialytic interval duration (Table 1.2). For example, a 50% increase in dialysis duration from 4 to 6 hours (hemodialysis prescription 1 to 2) decreases interdialytic interval 5.3% (38 to 36 hours), but a similar 50% increase in dialysis frequency from 4 to 6 times per week (hemodialysis prescription 1 to 3) decreases interdialytic interval 36.8% (38 to 24 hours). More frequent hemodialysis schedules have been associated with improved blood pressure,[103,104] phosphate control,[103] physical function,[105] left ventricular mass,[42,103] and cardiac function.[106] However, frequent (>4 sessions per week) dialysis modalities of short (<4 hours per session) duration may in fact increase patient mortality, compared to equal frequency but similar or longer duration.[107] This is probably because of increased dialysis access related complications[108] and increased myocardial stunning secondary to higher fluid removal rates.[26,64,109-111] Thus, it is likely that both hemodialysis

[C] Nephrologists, and indeed nephrology literature, refers to the concentration difference between dialysate and pre-dialysis sodium, or between post- and pre-dialysis sodium as the DPNa+ or PPNa+ "gradient." However, the term "gradient" implies a distance factor, which is not included in the nephrology "gradient" description. To avoid confusion, this thesis uses the term concentration "difference" whenever possible, except in published nephrology work, which interchangeably uses "gradient."

frequency and duration impact diffusive sodium balance, and thus cardiovascular and overall patient mortality. The rate of substance production during the interdialytic period is determined by body mass, body composition, nutritional status and general health.[98] Indeed, a U shape curve is found for intradialytic urea reduction rate (x-axis) and survival (y-axis); lower survival rates at the lower urea reduction rates reflect poor nutritional status, anorexia, and muscle wasting, all of which are low toxin generation states.

Hemodialysis Prescription	Frequency (sessions per week)	Duration (hours per session)	Interdialytic Interval (hours)
1	4	4	38
2	4	6	36
3	6	4	24
4	6	6	22

Table 1.2: Interdialytic Interval of Four Hemodialysis Prescriptions

Maximal concentration difference requires a low concentration in the dialysate concentration (Figures 1.3 and 1.5). For most toxins, a low pre-membrane dialysate concentration facilitates maximal diffusive removal. However, rapid concentration shifts during hemodialysis are associated with patient morbidity and mortality for some substrates, requiring standard dialysate concentrations of sodium and chloride,[112,113] calcium,[112,114-116] potassium,[117] bicarbonate and acetate,[118,119] magnesium[112] and glucose (Table 1.3).[120] Maximal concentration difference is supported by the countercurrent flow of blood inside and dialysate outside of the hollow fibers (Figures 1.3 and 1.6). Blood flow rate of 350-400 mL/min and dialysate flow rates of 500 mL/min are standard, since higher flow rates do not significantly increase small molecular weight solute (eg. Urea) clearance.[121]

1.1.1.6 Concentration Difference - Sodium

In patients without kidney disease, plasma sodium concentration is stabilized by thirst and ADH responsive osmoreceptors located in the hypothalamus[122] and the organum vasculosum of the lamina terminalis.[123,124] Plasma osmolality is calculated by concentrations of glucose, urea and sodium (Equation 1.10).

Equation 1.10: Calculated Plasma Osmolality

Osmolality = 2 [Sodium] + [Urea] + [glucose]

Where Sodium, urea and glucose are in mmol/L, and osmolality is in mOsm/kg.

Dialysate Constituent	Concentration (mEq/L)
Sodium (Na+)	135 to 145 mmol/L
Chloride (Cl-)	105 mmol/L
Calcium (Ca++)	2.5 to 3.5 mEq/L
Acetate	4.0 mEq/L
Potassium (K+)	1.5 to 3.0 mmol/L
Bicarbonate (HCO3-)	33 to 38 mmol/L
Magnesium (Mg++)	0.75 mEq/L
Glucose	5 to 10 mmol/L

Table 1.3: Dialysate Composition

Tight regulation maintains body fluid osmolality between 280 and 295 mOsm/kg water by restoring plasma sodium to a patient specific "setpoint" that is stable over time (Figure 1.7).[125,126,127] While the sodium setpoint is well established in people with normal renal function,[126] it was not until 1991 that it was confirmed in patients with severe kidney disease,[128] and until 2007 that is was confirmed in conventional ($\leq$ 4 hour per session) thrice weekly hemodialysis patients.[129-131] However, recent evidence suggests that thehemodialysis procedure can alter intradialytic plasma sodium concentrations.[132] Moreover, previous reports of sodium setpoint stability in hemodialysis patients excluded patients with certain comorbid illnesses, had limited plasma sodium measurements, and only considered patients whose hemodialysis sessions were 4 hours or less in duration, and 3 times a week. Establishing if the sodium setpoint can be modified in frequent or longer hemodialysis is essential, since hyponatremia (low plasma sodium) has been associated with increases in all-cause mortality.[133,134] The results of previous trials that show a survival advantage in longer hemodialysis[135,136] and increased mortality in more frequent hemodialysis[107] may relate to changes in the pre-dialysis plasma sodium setpoint (hypothesis 2.1).

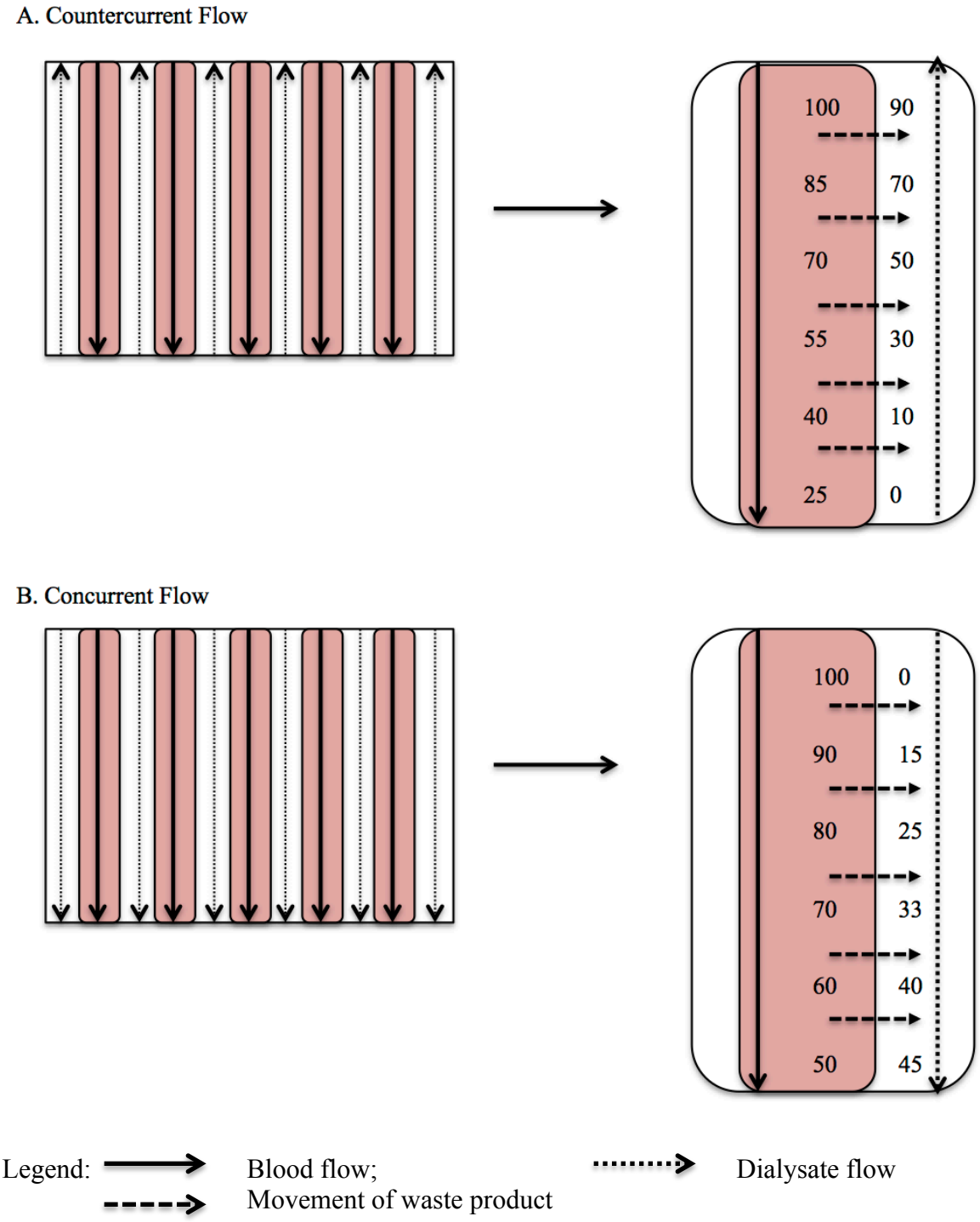

Figure 1.6: Waste Product Concentration with Countercurrent (A) and Concurrent (B) Flow

Diffusive balance of sodium during hemodialysis is determined by the concentration difference between the pre-hemodialysis plasma sodium concentration (Pre-Na+) inside, and the dialysate sodium concentration (DialNa+) outside the hollowfiber. In conventional thrice weekly hemodialysis patients, a positive dialysate to plasma sodium difference (Dial-Na++ > Pre-Na+) is associated with increased blood pressure, IDWG and cardiovascular morbidity and mortality.[137-140] On the other hand, a negative dialysate to plasma sodium difference (Dial-Na++ < Pre-Na+) is associated with intradialytic hypotension, which is an independent predictor of death.[132,141] Given these factors, considerable debate persists regarding the appropriateness of personalizing dialysate sodium concentration to minimize adverse outcomes. It is uncertain whether the dialysate to pre-dialysis plasma sodium concentration difference, or the pre-dialysis to post- dialysis plasma sodium concentration difference is preferable to predict clinical outcomes. Furthermore, the predictive value of dialysate, pre- and post-dialysis plasma sodium concentrations has not been evaluated in

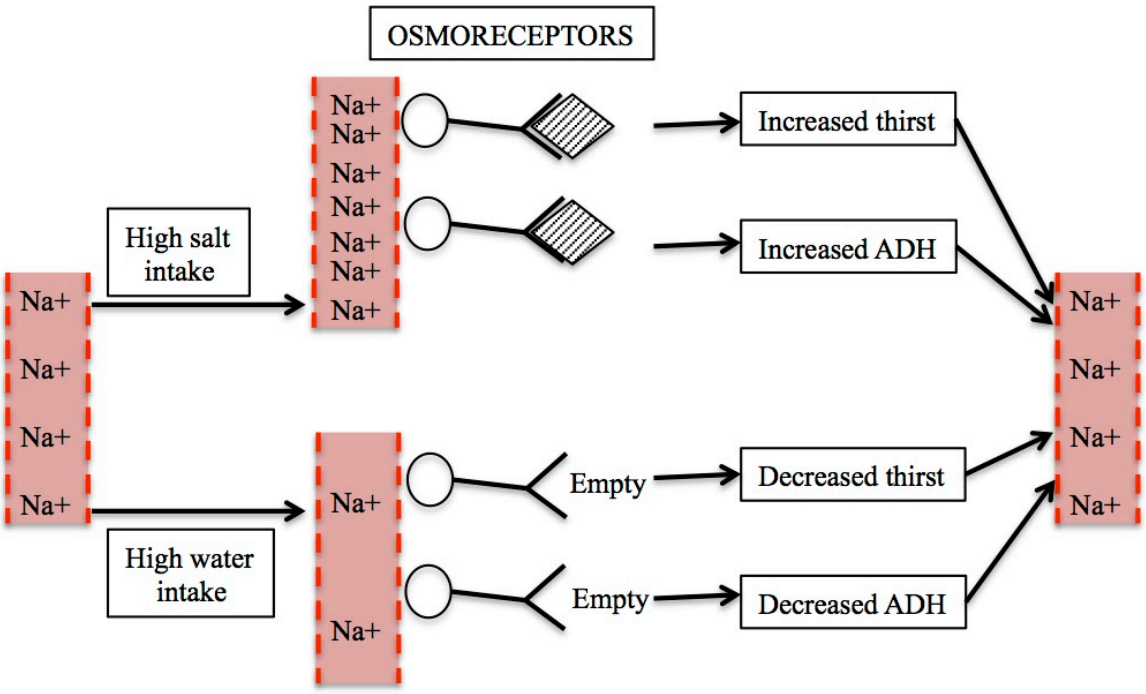

Figure 1.7: Homeostatic Mechanism for Plasma Osmolality

a hemodialysis population on longer or more frequent hemodialysis sessions. This has special relevance in the design of prospective clinical trials in frequent hemodialysis modalities, and in the clinical monitoring of such patients (hypothesis 2.2).

A hemodialysis patient's albumin concentration influences the amount of sodium available for diffusion. Since the anionic albumin is impermeable across hemodialysis membranes, its negative charge leads to an electrochemical gradient, leaving less than 100% of plasma sodium available for diffusion.[142] Since plasma albumin concentration is variable, this "Gibbs-Donnan effect" may be relevant to diffusive sodium loss during hemodialysis (hypothesis 2.3).

One of the other two components of calculated osmolality is blood glucose (equation 1.10). In diabetes mellitus, a quantitative or qualitative insulin deficiency prevents glucose movement into cells, leading to hyperglycemia in the extracellular space. As hyperglycemia worsens, extracellular fluid osmolality increases (equation 1.10) and exceeds that of the intracellular fluid, leading to movement of water out of cells into the extracellular fluid. Plasma sodium concentration falls in proportion to the dilution of the extracellular fluid, falling approximately 1.6 mEq/L per 5.5 mmol/L increase in blood glucose concentration.[143] It is thus plausible that the hyperglycemic milieu of diabetes alters water and sodium balance during hemodialysis; this has not been well studied (hypothesis 2.3).

1.1.1.7 Time on Hemodialysis

The maximal duration for conventional hemodialysis treatment was, until recently, dictated by facility resources, and ultimately by cost; personnel costs, laboratory tests, building maintenance, electricity, water, and administrative costs limited most patients to a maximum of four hours per session,[144-147] within one of the three hemodialysis shift times (8 AM to 12 PM, 12:30 PM to 4:30 PM, 5 PM to 9 PM). However, when compared to conventional hemodialysis, sessions longer than 4 hours associate with improvement of multiple ESRD-associated conditions. While improved phosphate balance,[104,148-151] renal anemia,[148,152] and fertility[153] are well accepted, the pathophysiology of improved blood pressure,[148,150] left ventricular hypertrophy,[42,103,154,155] and mortality[135,136,156,157]

remain controversial. There are also cost reductions with home nocturnal (6 to 8 hours per session) hemodialysis ($36,840 to $61,220 per annum), compared to in-center conventional (4 hours maximum per session) thrice weekly hemodialysis of four hours ($58,959 to $100,198 per annum).[158-161] However, longer hemodialysis treatments are not preferable for all patients, as the quality of life has not consistently shown differences between hemodialysis modalities.[162] Health care administrators have thus advocated for more patients to undergo their hemodialysis treatments at home, while many nephrologists have advocated for those home treatments to be of longer duration than 4 hours. Understanding how to optimize hemodialysis duration, within the confines of cost and patient comfort, has the potential to improve patient morbidity and mortality.

In the London Daily Nocturnal Dialysis study,[148] IDWG was higher in frequent nocturnal ($\geq$4 sessions per week, $\geq$6 hours per session) than in short hours daily ($\geq$ 4 sessions per week, $\leq$ 4 hours per session) hemodialysis patients using a standard dialysate sodium concentration of 140 mmol/L, suggesting that the time of exposure to a higher dialysate sodium may affect IDWG. On the other hand, the Frequent Hemodialysis Network (FHN) showed lower IDWG in the frequent nocturnal hemodialysis patients,[150] but the patients in this study had variable dialysate sodium concentrations and higher residual urinary volumes. This raised the possibility that the time of exposure to a diffusive sodium difference was of importance to IDWG (hypothesis 2.3). Likewise, whether residual urinary volume affected IDWG was unknown (hypothesis 2.3). Since longer hemodialysis duration translates to longer exposure of blood to a diffusive sodium difference (equation 1.1), this will alter IDWG and thus cardiovascular morbidity and mortality.[37,38,53-56]

1.1.1.8 Viscosity

As blood viscosity increases, diffusive solute loss from blood into dialysate decreases (Equation 1.5). The major determinants of blood viscosity are temperature,[163] hematocrit[164,165] and plasma protein concentration.[166] Tables of blood viscosity based on plasma albumin and blood hematocrit[167,168] are accurate at low shear rates, but may not apply to hemodialysis patients whose blood flows from and back into an arteriovenous

fistula, graft or intravenous catheter during hemodialysis (Figure 1.3). However, even at the conditions of hemodialysis, the major predictors of blood viscosity have consistently been confirmed to be the same.[169-172] Since temperature is determined by patient hemodynamic stability and symptoms (35.5 to 38.0 degrees Celsius, see section 1.1.1, equation 1.4), the remaining factors of importance are hematocrit and plasma protein concentration.

Progression of kidney disease leads to an erythropoietin deficiency and anemia.[173,174] Correction of anemia is associated with increases in hematocrit, blood viscosity and reduced diffusive hemodialysis clearance.[175] However, it is other clinical endpoints that determine current guidelines for target hemoglobin of 11.0 to 12.0 g/dL in hemodialysis patients;[176,177] considerable evidence shows that normalization of hemoglobin >13.0 g/dL associates with increased rates of cerebrovascular disease, myocardial infarction and death.[178-183]

Under most physiologic circumstances, plasma protein concentration is determined by the most abundant plasma protein albumin. Hypoalbuminemia (<35 g/L) is associated with cirrhosis, chronic inflammation or infection, and malnutrition.[184-186] Hyperalbuminemia (>50 g/L) is much less common,[187] being described in high protein diets.[188]

Concerns have arisen in studies showing that blood viscosity does not consistently decrease with decreasing vessel diameter. This Fahreus-Lindqvist effect has been conclusively confirmed *in vitro*;[169,189-196] when blood flows in tubes of decreasing diameter, relative viscosity decreases.[197] This effect is exaggerated once tube diameter falls below 1.0 mm; the dialyzer hollow fiber diameter of 0.18 to 0.22 μm (section 1.1.1.2) means a ~20% reduction in relative blood viscosity, due to the Fahreus-Lindqvist effect.[195,198]

Poiseuille's law and each of its derivations (equations 1.7 and 1.8) make a number of assumptions. Firstly, blood should be an incompressible Newtonian fluid with constant viscosity.[199] However, blood is non-Newtonian in at least two ways;[195] the pressure-flow curve is probably not linear,[200,201] and shear stress is dependent on blood viscosity.

However, blood viscosity still has the same predictors despite the non-Newtonian factors;[163,202] while the relationship may not be perfectly linear, equations 1.7 and 1.8 still provide a reasonable first estimation to identify clinical factors of importance. Secondly, there should not be acceleration of fluid in the pipe. This condition holds true for standard hemodialysis, since a set blood flow rate from the patient maintains a constant blood flow rate through thousands of standardized hollow dialyzer fibers.[74] Thirdly, the hollow fiber length must be substantially greater than the diameter to avoid the entrance-length effect[203,204]; a length of greater than 10 times diameter is usually sufficient to overcome this issue.[205] Since the average hollow fiber radius is 180 to 220 μm (section 1.1.1.2), and the hollow fiber length 20 to 24 cm (section 1.1.1.3), the entrance-length effect is insignificant in hemodialysis. Fourthly and finally, blood flow through a dialyzer should be laminar, which holds true under most circumstances.[206,207] This can be confirmed by calculation of a Reynolds number for the conditions of blood flowing through a hollow fiber in a dialyzer for a standard hemodialysis patient.

Equation 1.11: Reynolds Number for Blood Flow in Dialyzer Hollow Fiber

$$R_e = \frac{\rho \, v \, d_H}{\eta}$$

Where R_e = Reynolds number, ρ = density (kg/m^3), v = velocity (m/s), d_H = diameter, η = viscosity (Pa s).

Dialyzer fiber diameter is approximately 400 mm (section 1.1.1.2), the whole blood density ranges from 1043 to 1057 kg/m^3, and blood viscosity ranges from 3 to 4 x 10^{-3} (Pa s) at 37 degrees Celsius.[208] Blood flow during hemodialysis is set to 400 mL/min; assuming 12,500 hollow fibers per dialyzer and a fiber radius of 200 mm, the blood velocity is 0.00424 m/s. Using these values, the R_e of blood in a hollow fiber during dialysis is 0.5088, well below the upper limit cutoff for laminar flow, which Reynolds initially described to be approximately 2100.[209,210]

1.1.2 Convection

Convection, also known as ultrafiltration, is the movement of water across a semi-permeable membrane due to hydrostatic or osmotic pressure.[211] The dialysis machine pump exerts a negative pressure on the dialysate compartment and a positive pressure in the blood compartment, leading to water and dissolved substances leaving the blood into the dialysate ("solvent drag") (Figure 1.8).[212] When dialysate and patient plasma sodium concentrations are equal, no diffusive difference is present. Intradialytic sodium loss is then entirely dependent on negative convective balance.[211]

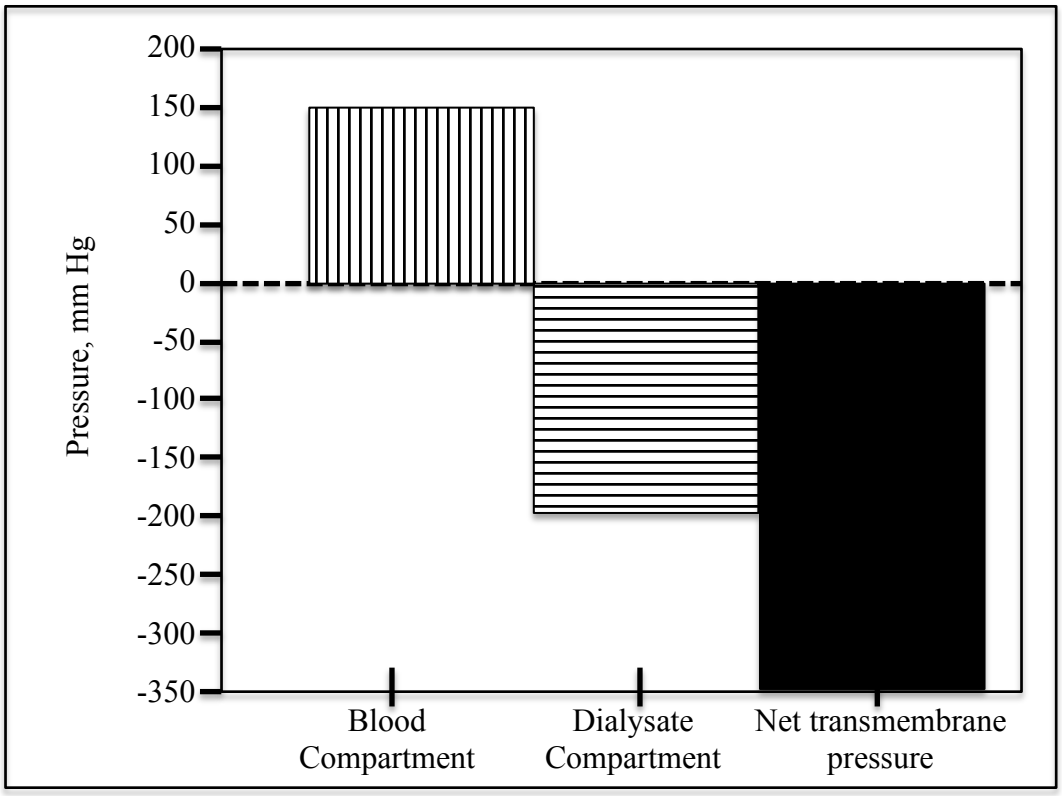

Figure 1.8: Blood and Dialysate Compartment Pressures Leading to Net Transmembrane Pressure for Convection.

Convective fluid losses during hemodialysis have pronounced impact on the compartments that make up total body water. In an average healthy 70 kg man, approximately 60% of body mass (42 kg) is made up of water, of which 2/3 (28 kg) is intracellular and 1/3 (14 kg) is extracellular.[213] However, if the same man becomes anuric and hemodialysis-dependent, interdialytic weight gains lead to expansion of both

intracellular and extracellular fluid compartments (Figure 1.9). Fluid expansion forms the basis of clinical dry weight assessment by examining for interstitial fluid expansion (edema) and intradialytic hypotension (Figure 1.9).[213] However, it is well recognized that a hemodialysis patient can have fluid excess without clinical evidence of volume expansion, commonly called "silent overhydration."[214-216] Furthermore,

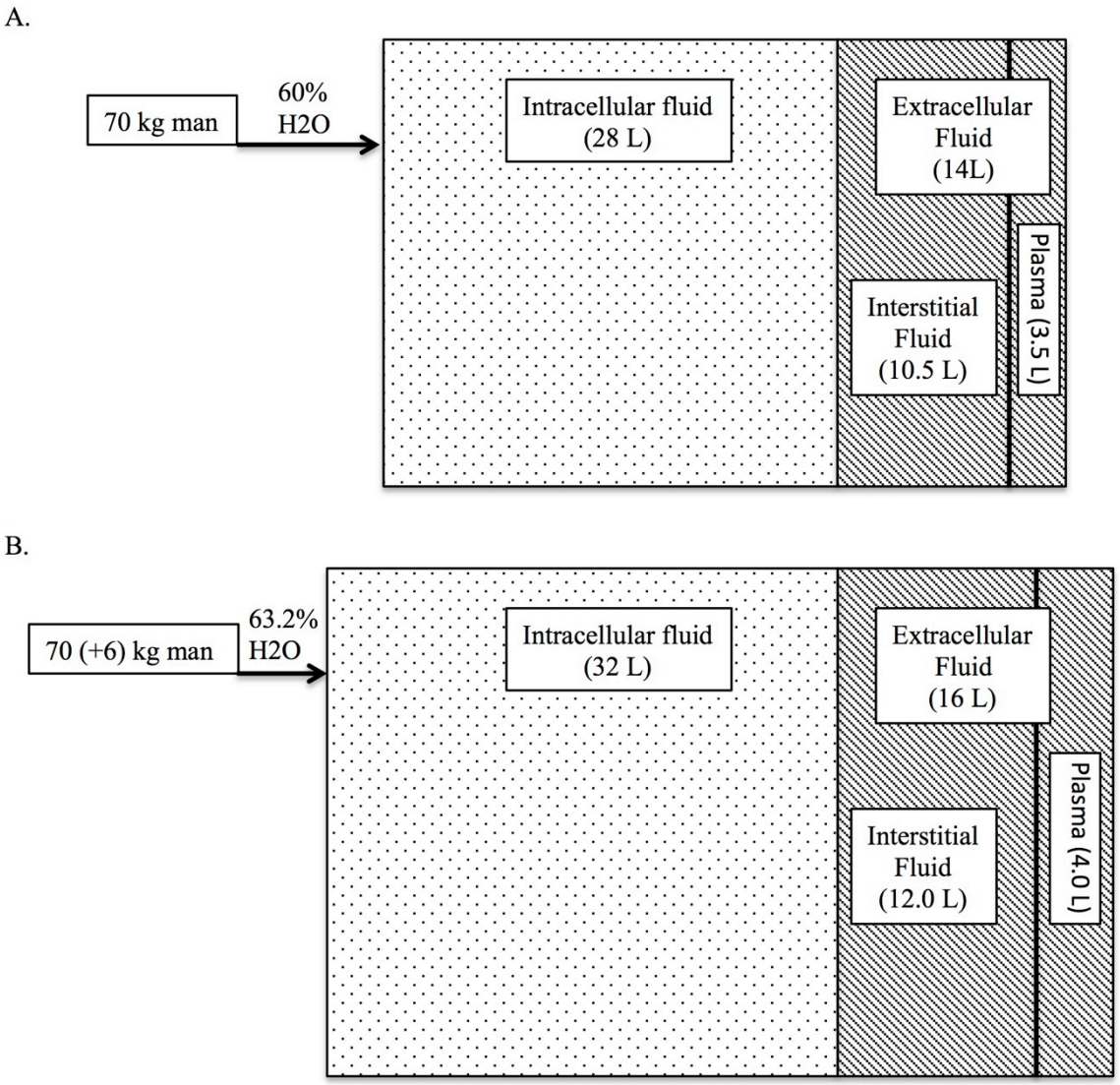

Figure 1.9: Total Body Water in Healthy 70 kg Man (A) and Hemodialysis Patient With Dry Weight of 70 kg but with 6 kg Interdialytic Weight Gain (B)

relative proportions of compartments of total body water differ significantly depending on sex, race and body habitus (hypothesis 2.3).[217] Likewise, intradialytic hypotension occurs when increases in plasma volume from compartments outside plasma occur slower than hemodialysis reduces plasma volume.[64,218] Refilling from the interstitial fluid

continues until 4 hours after a hemodialysis session; intradialytic hypotension is therefore a poor marker for total body volume status. Expansion of these compartments leads to volume overload, pressure overload,[20,33,35,37-40] left ventricular hypertrophy,[41-49] and death.[50,51] This effect is even more pronounced when dry weight is clinically assessed inaccurately as in "silent overhydration", since hemodialysis will return a patient to a persistently volume overloaded state (Figure 1.10).[219,220] Given the inaccuracies of clinical volume assessment, a great deal of research has focused on improving evaluation of hemodialysis patient's total body water status and dry weight. However, natriuretic peptides,[221-229] diameter of inferior vena cava,[222,227,230] and CRIT-line monitoring[231-239] have limited specificity and generalizability ,[220,229] and their use may even increase mortality.[236] Perhaps the most promising is the current "gold

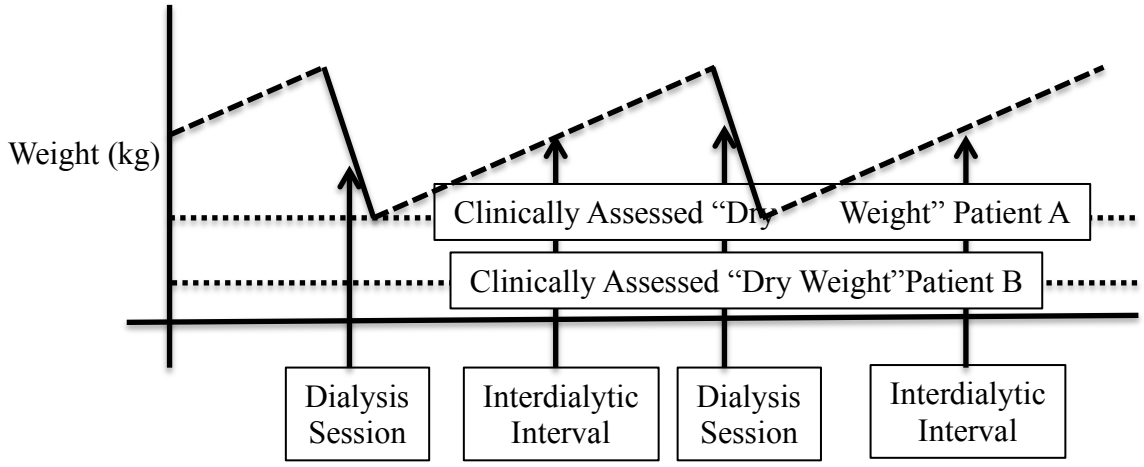

Figure 1.10: Hemodialysis Patients Oscillate from "Wet" to "Dry" State if Clinical Assessment of Dry Weight is Accurate (A). If Dry Weight is Lower Than Clinically Estimated (B), Patient Will Remain "Volume Overloaded" After Hemodialysis

standard" of multiple-frequency bioimpedance spectroscopy. The resistance of body fluid compartments can be measured, with the ratio of the resistances of the intracellular and extracellular water reflecting the relative volume of these compartments.[240] As hemodialysis patients accumulate excess fluid in their extracellular compartment, this ratio proves useful in the evaluation of dry weight. Considerable evidence confirms that bioimpedance-guided volume assessment of hemodialysis patients is associated with improved clinical outcomes,[219,241-243] including mortality.[219] While evaluation of these technologies is not the objective of this document, it should be mentioned that

bioimpedance has confirmed that IDWG reduction is insufficient to reduce cardiovascular mortality if "silent overhydration" persists. This is one inherent limitation of any clinical work designed to identify strategies to reduce IDWG.

1.2 Historical Context

"Optimal" dialysate sodium concentration has changed more frequently and for more reasons than likely any other hemodialysis parameter.[244] Early prescriptions relied on a negative DPNa+ to increase diffusive sodium loss. A Dial-Na+ of 125 to 130 mmol/L was standard, and osmotic loss of plasma water was promoted by using high dialysate glucose concentrations.[244,245] However, treatment times decreased over time, necessitating increases in Dial-Na+ to decrease intradialytic symptoms such as disequilibrium syndrome.[246,247] A Dial-Na+ of 140 mmol/L became standardized for patients undergoing hemodialysis thrice weekly. This increase in Dial-Na+ was further supported when acetate-based solutions were replaced with bicarbonate-based dialysate,[64] with the observation that higher Dial-Na+ were associated with less intradialytic hypotension.[53,248,249] With higher Dial-Na+, sodium removal on hemodialysis occurred by convection only, with diffusive losses often replaced with diffusive sodium gain. Decisions regarding Dial-Na+ became based upon minimizing patient symptoms within the confines of having only 4 hours three times a week to assure all sodium and fluid removal. This formed the basis of "sodium ramping," in which higher Dial-Na+ were used for all or part of a dialysis session.[248-250] Sodium ramping successfully reduced symptoms such as cramping, headaches and intradialytic hypotension.[248,249] However, significant increases in thirst, pre-dialysis blood pressure and interdialytic weight gain (IDWG) raised concern that such prescriptions might exacerbate volume overload and cardiovascular mortality.[244] As such, the use of sodium ramping has largely fallen out of favor.

As the burden of cardiovascular disease persisted in hemodialysis patients, new strategies to counteract the chronic state of volume and pressure overload were sought. This led to reevaluation of the standard prescription of thrice weekly hemodialysis of 3 to 4 hours each session. More frequent and longer hemodialysis are associated with improvements in anemia control,[152] calcium and phosphate balance,[149,251,252] fertility,[153] and volume and pressure overload.[42,154,155,253,254] Indeed, nocturnal therapies associate

with improved survival by uncertain mechanisms. This thesis examines the impact of the present day hemodialysis prescriptions, on diffusive and convective sodium balance. This will ultimately establish the effect of sodium balance on cardiovascular morbidity and mortality in hemodialysis patients.

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Chapter 2: Hypotheses

2.0 Hypotheses

Hypothesis 2.1:

Hemodialysis of a duration greater than 4 hours or a frequency greater than 3 times weekly has no effect on the pre-dialysis plasma sodium setpoint. This hypothesis was evaluated retrospectively in Chapters 3 and prospectively in Chapter 7.

Hypothesis 2.2:

The dialysate to pre-dialysis plasma sodium difference and the pre- to post-dialysis sodium plasma differences will predict clinical outcomes (blood pressure, interdialytic weight gain, intradialytic hypotension) equally effectively in a hemodialysis population with frequency greater than thrice weekly and session duration greater than 4 hours per session. This hypothesis was evaluated retrospectively in Chapter 4 and prospectively in Chapter 6.

Hypothesis 2.3:

IDWG can be predicted by several demographic and clinical factors, which each impact sodium balance on hemodialysis. These factors may include patient factors (age, sex, body habitus, diabetes status, dietary salt intake), laboratory factors (patient hematocrit, plasma albumin and pre-hemodialysis plasma sodium concentration, residual renal function), and dialysis factors (dialysate temperature and sodium concentration, dialysis time and duration, dialysis membrane hollow fiber length and radius and wall thickness). This was evaluated in Chapter 5.

Chapter 3: Plasma Sodium Setpoint: Is it Constant or Changed by Hemodialysis Prescription?

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3.1 Introduction

Patients with normal renal function have a specific osmolality value, above which thirst is generated and fluid ingested. This "setpoint" results in a relatively stable and reproducible plasma sodium level over time, not only in patients without kidney disease,[1] but also in patients with advanced renal disease.[2] Evidence of this sodium setpoint is also seen in thrice weekly conventional hemodialysis patients.[3-5] However, hemodialysis patients lack the mechanisms to regulate body osmolality and fluid balance. While previous trials examining the clinical effects of different dialysate sodium concentrations have treated pre-dialysis sodium "setpoint" as stable, this assumption has not been confirmed in quotidian hemodialysis patients.

Lower pre-dialysis sodium "setpoint" and higher dialysate sodium concentrations lead to important clinical outcomes such as increased blood pressure and IDWG,[6-13] which may effect cardiovascular and all-cause mortality.[14,15] Lower pre-dialysis plasma sodium is independently associated with increased all-cause mortality,[16,17] thus a change in sodium "setpoint," might need ongoing monitoring to minimize IDWG, and associated cardiovascular morbidity and mortality.

The objective of this study was to determine if the sodium setpoint changed with longer or more frequent exposure to the same dialysate sodium concentrations, when patients transitioned from thrice weekly conventional hemodialysis to dialysis modalities differing in duration and frequency.

3.2 Materials and Methods

Study Population

We performed a retrospective observational design that included all patients in the home hemodialysis program of the Southwestern Ontario Regional Renal Program, from 1998 to December 31, 2011. A total of 87 patients, 23 still current and 64 no longer on home hemodialysis, were included. All patients in our study were on conventional thrice weekly hemodialysis in-center (ICHD) prior to home hemodialysis; some continued

ICHD while others changed hemodialysis modality upon transferring from in-center to home hemodialysis.

Dialysis Modality

The modality of home hemodialysis was defined by the duration of dialysis therapy, and the frequency of treatments. Short-hours daily (SHD) hemodialysis was defined as a minimum of 5 treatments per week, with a treatment time of 1.5 hours to 4.0 hours. Intermittent conventional hemodialysis (ICHD) implied a maximum of 4 treatments per week, with treatment times of 1.5 hours to 4 hours. Frequent nocturnal hemodialysis (FNHD) was a minimum of 5 treatments per week, with a minimum treatment time of 6.0 hours. Intermittent nocturnal hemodialysis (INHD) meant a maximum of 4 treatments per week, with a minimum treatment time of 6.0 hours. Dialysate sodium concentration was not individualized as it was a standard 140 mmol/L for all patients at all times.

Blood sample collection

In the 50 days prior to initiation of home hemodialysis, while the patient is on in-center thrice weekly conventional hemodialysis (ICHD-IC), pre and post dialysis blood samples are taken every one to two weeks. Upon transition to home hemodialysis, pre and post dialysis blood samples are routinely taken each month. Home patients are trained to take blood from the arterial blood line at the start of dialysis and post-dialysis, using a standard slow blood and stop dialysate method. The samples are centrifuged and then stored and refrigerated until delivered to the local laboratory for that patient. All patient blood tests are measured using automated and standardized methods. Of interest to this study were pre-dialysis plasma sodium concentrations. Only outpatient blood tests were used, to assure that the patient was at their baseline health status, so that the plasma sodium concentration would not be confounded by acute illness.

Sodium concentration measurement

Plasma sodium concentration was measured using Beckman-Coulter LX20 Pro Chemistry Analyzer with Ion Selective Electrodes prior to, and Roche Modular P Chemistry Analyzer with Ion Selective Electrodes after November 4, 2008. This change

was made by the London Health Sciences Center because of a need for higher volume of laboratory testing. Both plasma Na+ concentration methods were regularly calibrated; thus, the measurements were treated as equivalent on data analysis. Dialysate sodium concentration was determined using online conductivity measurements built into the Fresenius H series hemodialysis machine, which was used for all patients. Blood glucose was not measured simultaneous to Na+ concentration; thus, plasma sodium levels were not corrected for glucose. Dialysate Na+ concentration measurement is regularly calibrated, to assure stability and accuracy of dialysate Na+ concentrations. Home hemodialysis machines were evaluated and calibrated at least once, and usually twice annually, by the program's water engineer or one of the trained home hemodialysis nurses.

Database Creation

Blood test results were available from the electronic patient record (PowerChart by Cerner) of London Health Sciences Centre.

Age (years), sex, diabetes status, residual renal function (mL/min/1.73m^2) and months of renal replacement therapy prior to initiation of home hemodialysis were determined from chart review. Residual renal function was calculated within 3 months of conversion to home hemodialysis, as previously described.[18]

Weights (kg), dialysis treatment times and frequency were obtained from archived dialysis treatment run sheets. The average values for these per month were calculated and entered into the study database. For this analysis, a single value for each patient data point was used; the average of the monthly values was used regardless of time period on hemodialysis modality. There were no duplicate observations for any patient.

Ethics

Because of concerns regarding the use of a standard dialysate of 140 mmol/L sodium concentration and prompted by the observation of high IDWGs in patients undergoing FNHD, a quality assurance investigation was instituted. All laboratory tests had been taken as per routine care protocols; demographic and dialysis treatment information were

available from patient records. Once extracted, all data were de-identified before analysis. No patient had to provide blood samples, answer questionnaires or do anything specific for this study which was conducted in accordance with the Declaration of Helsinki. Thus, informed written consent was not obtained from the current patients.

Statistics

Data were analyzed using the Statistical Package for Social Sciences (SPSS, IBM, Armonk, New York, U.S.) version 19.0.

Patients exposed to different dialysis modalities were compared using two-tailed student T-tests for continuous variables, and Fisher's exact test for categorical variables. Statistical significance was achieved with $\alpha<0.05$.

The objective of this study was to determine if the sodium setpoint changed with longer and more frequent exposure to the same dialysate sodium concentrations, when patients transitioned from thrice weekly conventional hemodialysis to dialysis modalities differing in duration and frequency (SHD, ICHD, INHD, FNHD). The "sodium setpoint" was defined as the average pre-dialysis plasma sodium concentration over the time period specified for each of three endpoints. The three endpoints were DeltaPRENA100, DeltaPRENA100-150, and M100 (Figure 3.1). They are defined as follows:

DeltaPRENA100 is the difference between PRENA100+ and PRENA-50. PRENA100+ is the average pre-dialysis plasma sodium concentration, after 100 days of home hemodialysis, for the life of the patient while still on the same dialysis modality. PRENA-50 is the average of all pre-dialysis plasma sodium values in the 50 days prior to transition to home hemodialysis and while on ICHD.

Each patient's period of time on home hemodialysis differed after the first 100 days. Thus, DeltaPRENA100-150 was also calculated as the difference between PRENA100-150 and PRENA-50. The PRENA100-150 is the average pre-dialysis plasma sodium concentration, between 100 and 150 days post-transition to home hemodialysis.

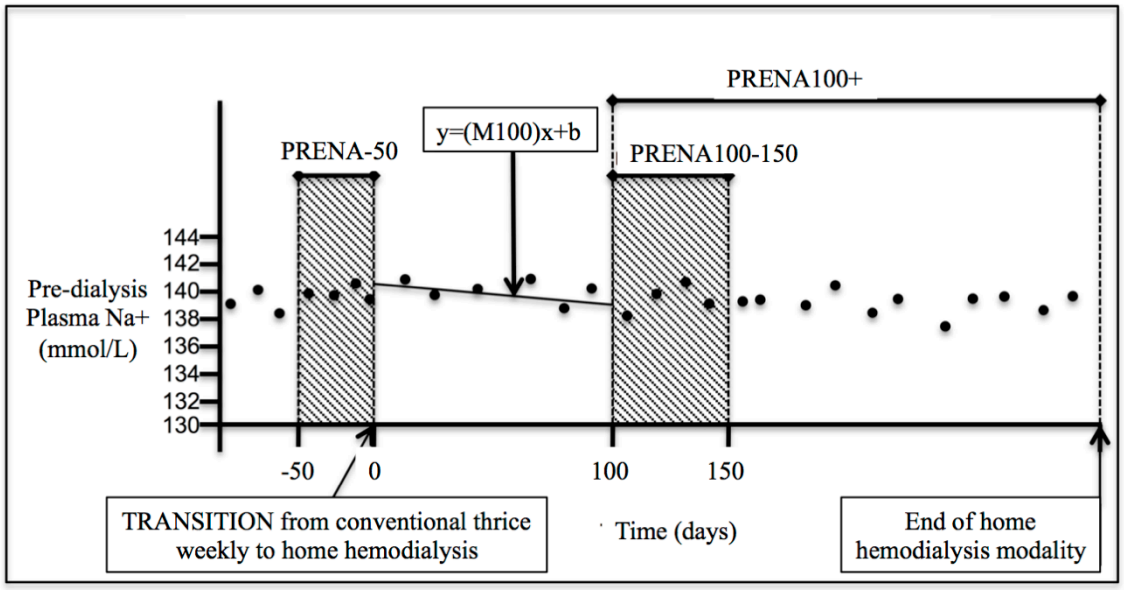


Figure 3.1: Endpoints to Determine Existence of Sodium Setpoint

PRENA100+ and PRENA-50 were compared, as were PRENA100-150 and PRENA-50 in each dialysis modality group, for all patients, and separately for patients with PRENA-50 values a) greater than or equal to, or b) less than the dialysate sodium concentration of 140 mmol/L. A statistically significant change between Pre and Post-Na+ values implied a change in sodium setpoint.

A line of best fit was then calculated from the pre-dialysis plasma sodium values versus time plot for each patient over the first 100 days after transitioning to home hemodialysis. The slope of these lines of best fit was measured with its confidence intervals (M100). The mean M100 values found in different dialysis modality groups were compared overall, and again by PRENA-50/dialysate-Na+ relationship. A M100 with 95% confidence intervals that did not cross zero was evidence for a change in sodium setpoint.

We chose the time period of 100 days because we wanted a minimum of 3 plasma sodium measurements for each patient to calculate slope of pre-dialysis plasma sodium concentration. Since each home hemodialysis patient undergoes monthly blood work, most patients have a minimum of 3 pre-dialysis sodium concentrations within 100 days.

Regression models were used to identify an association between the primary outcome DeltaPRENA100 and a series of covariates. Specifically, univariate regression analyses were performed using DeltaPRENA100, DeltaPRENA100-150, and M100 as separately evaluated dependent variables. Independent variables evaluated included dialysis frequency and duration, dialysate to (PRENA-50) difference (DPRENA-50), and (DPRENA-50) times dialysis duration. We evaluated (DPRENA-50) times dialysis duration, as an independent variable, since we have previously shown that this covariate is predictive for interdialytic weight gain in a similar patient population.

Multivariate regression was used in an attempt to determine how DeltaPRENA100 was associated with dialysis frequency, duration, the dialysate to PRENA-50 difference, and the dialysate to PRENA-50 difference times dialysis duration. Here all patients were used regardless of dialysis modality.

VARIABLE	Short Hours Daily (mean, SE)	Intermittent Conventional (mean, SE)	Frequent Nocturnal (mean, SE)	Intermittent Nocturnal (mean, SE)
n	31	13	30	13
At Home Hemodialysis Initiation:				
Age (years)	43.6 (2.2)	48.7 (4.0)	43.6 (1.8)	44.9 (3.1)
Weight (kg)	83.5 (4.9)	68.5 (3.6)	87.5 (4.5)	77.7 (6.4)
Residual Renal function (ml/minute)	0.27 (0.11)	1.94 (0.48)	0.84 (0.34)	1.85 (0.82)
Presence of diabetes (%)	19.4	7.1	33.3	16.7
Female sex (%)	45.2	50	36.7	41.7
Vintage of Renal Replacement (months)	73.5 (11.6)	54.5 (16.3)	96.6 (17.1)	104.0 (32.0)
While on new dialysis modality:				
Albumin (g/L)	38.5 (0.6)	37.3 (0.7)	38.2 (0.7)	36.7 (1.4)
Phosphate (mmol/L)	1.76 (0.07)	1.68 (0.10)	1.56 (0.07)	1.74 (0.10)
Dialysis Duration (minutes per session)	142.3 (5.1)	202.3 (13.6)	408.6 (12.4)	372.5 (21.8)
Dialysis Frequency (sessions per week)	5.7 (0.1)	3.1 (0.1)	5.2 (0.1)	3.1 (0.1)
Weekly Dialysis Duration (minutes per week)	803.4 (27.1)	633.7 (43.2)	2052.1 (103.9)	1148.5 (47.1)
Weekly Ultrafiltration (L)	10.4 (0.7)	6.5 (0.7)	12.0 (0.6)	6.6 (0.7)

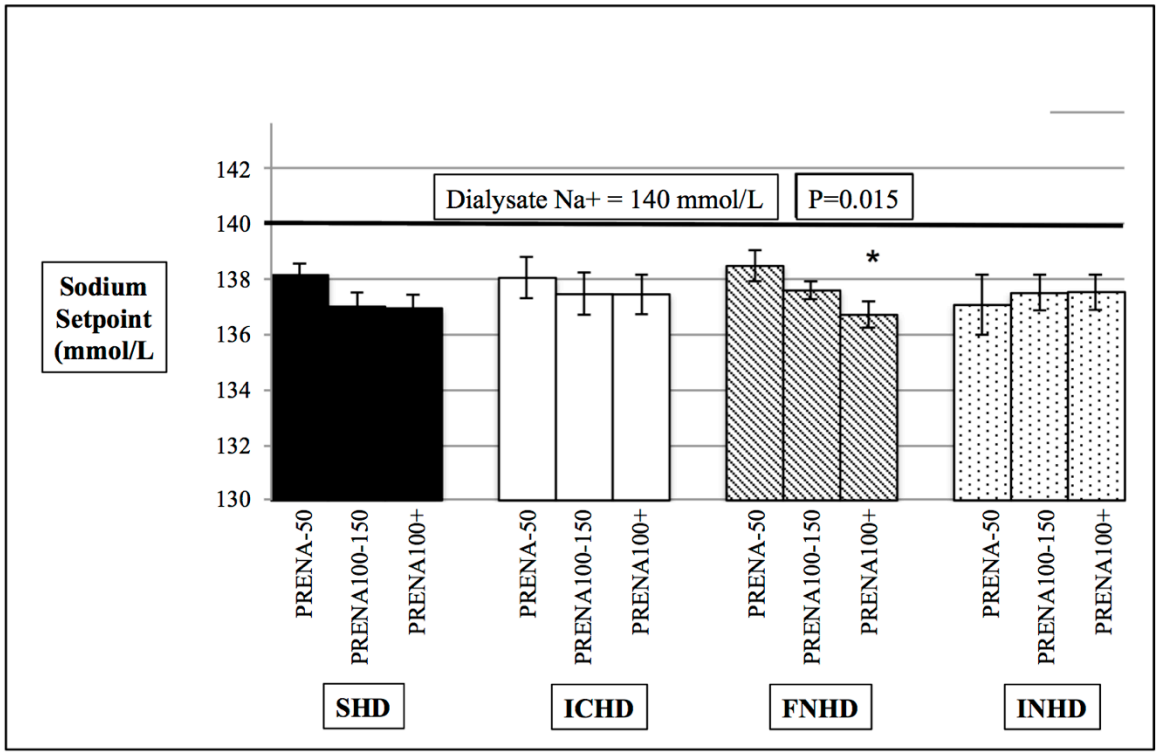
Table 3.1: Demographic Factors of Dialysis Modality Groups

3.3 Results

A total of 87 patients made up the database, with 31, 13, 30 and 13 from SHD, ICHD, FNHD and INHD. There were 29, 13, 28 and 12 patients with sufficient data for DeltaPRENA100 and DeltaPRENA100-150, and 31, 10, 26 and 11 patients with sufficient data for M100 from SHD, ICHD, FNHD and INHD, respectively. A total of 29 patients had pre-transition pre-dialysis sodium setpoint greater than or equal to 140 mmol/L, with 12,3,12, 2 from SHD, ICHD, FNHD and INHD.

There were no statistically significant differences between dialysis modalities for age, diabetes status, sex, or vintage of renal replacement prior to initiation of home hemodialysis (Table 3.1). However, FNHD patients were heavier than ICHD patients (87.5 versus 68.5 kg, $p = 0.008$). Residual renal function was higher in ICHD patients than SHD patients (1.94 versus 0.27 mL/min/1.73 m^2, $p < 0.001$). While on the assigned dialysis modality, plasma albumin did not differ between groups. Pre-dialysis phosphate concentration was lower in FNHD than SHD patients (1.56 versus 1.76 mmol/L, $p = 0.044$). Dialysis duration was shorter in SHD patients (142.3 min) than ICHD (202.3 min, $p <0.001$), FNHD (408.6 min, $p<0.001$) and INHD patients (372.5 min, $p<0.001$), and shorter in ICHD patients than FNHD ($p<0.001$) and INHD patients ($p<0.001$). Dialysis frequency was greater in SHD patients (5.7 per week) than ICHD (3.1 per week, $p<0.001$), FNHD (5.2 per week, $p<0.001$) and INHD patients (3.1 per week, $p<0.001$), and greater in FNHD than ICHD ($p<0.001$) or INHD patients ($p<0.001$). Weekly dialysis duration was lower in ICHD than SHD (633.7 vs. 803.4 minutes, $p=0.001$), lower in SHD than INHD (803.4 vs. 1148.5 minutes, $p<0.001$) and lower in INHD than FNHD (1148.5 vs. 2128.1 minutes, $p<0.001$). Weekly ultrafiltration volume was lower in ICHD and INHD than SHD (6.5 and 6.6 vs. 10.4 L, $p<0.001$ and $p=0.004$) and lower in ICHD and INHD than FNHD (6.5 and 6.6 vs. 12.0 L, $p<0.001$ for both).

Sodium setpoint decreased in FNHD patients when all pre-dialysis sodium concentrations from 100 days post-transition onwards were considered (PRENA-50 > PRENA100+)(138.5 to 136.7 mM, $p=0.015$)(Figure 3.2).



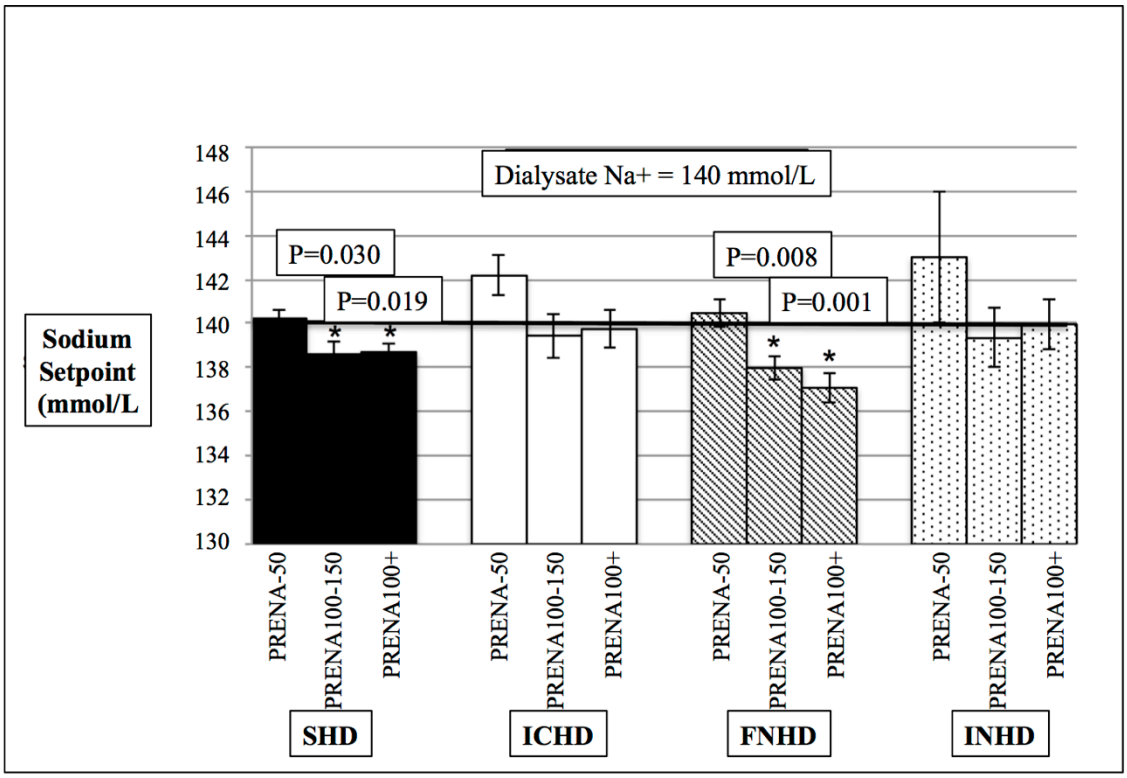
FNHD = frequent nocturnal hemodialysis; ICHD = intermittent conventional hemodialysis; INHD = intermittent nocturnal hemodialysis; SHD = short hours daily hemodialysis.

Figure 3.2: Pre-Dialysis Plasma Sodium Concentration Before (PRENA-50), Between Days 100 to 150 After (PRENA100-150) and All Days from 100 days After (PRENA100+) Transition to Home Hemodialysis

In both SHD and FNHD patients whose pre-transition pre-dialysis sodium (PRENA-50) was greater than or equal to the dialysate sodium of 140 mM, sodium setpoint decreased when post-transition pre-dialysis sodium concentrations from 100 days onwards were considered (PRENA-50 > PRENA100+) (SHD 140.2 to 138.7 mM, p=0.019; FNHD 140.5 to 137.1 mM, p=0.001) (Figure 3.3). When pre-dialysis plasma sodiums were restricted to post-transition days 100 to 150, the sodium setpoint still decreased in both SHD and FNHD patients (SHD 140.2 to 138.6 mM, p=0.030; FNHD 140.5 to 138.0 mM, p=0.008) (Figure 3.3).

There was no difference in any dialysis modality group, between PRENA-50 and PRENA100+, or between PRENA-50 and PRENA100-150, if the pre-transition pre-

dialysis sodium (PRENA-50) was less than the dialysate sodium concentration of 140 mM (Figure 3.4).



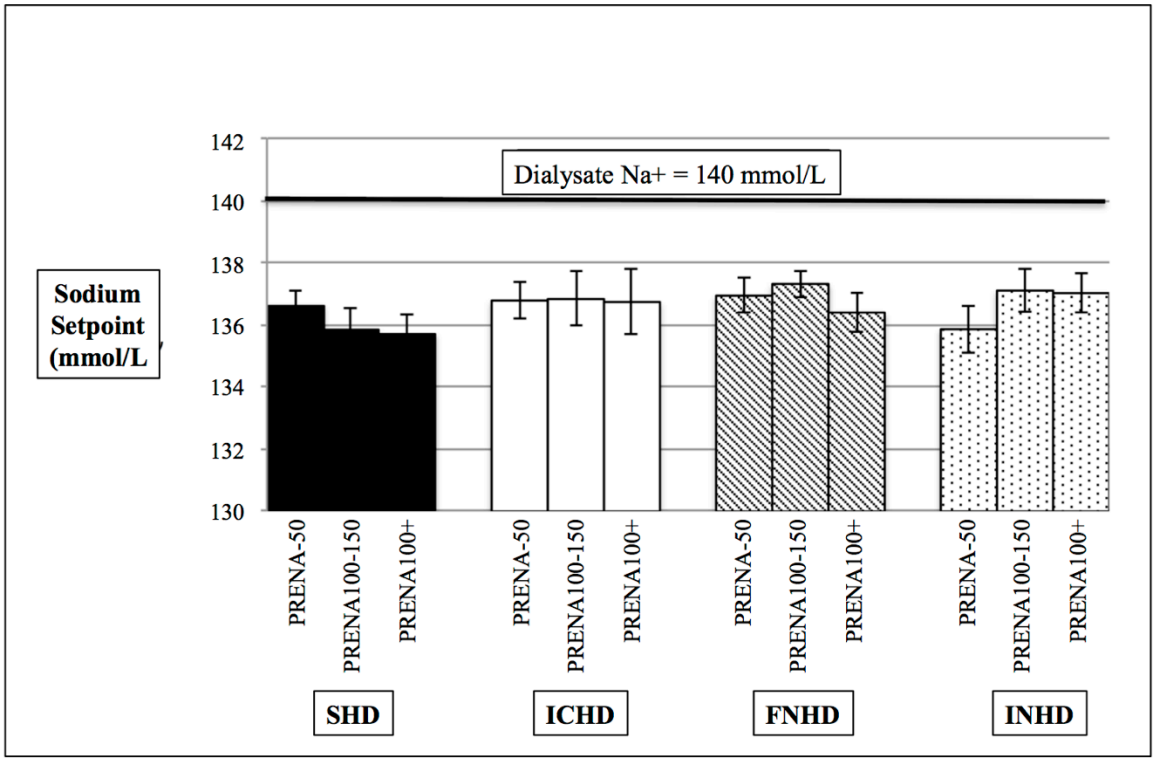
FNHD = frequent nocturnal hemodialysis; ICHD = intermittent conventional hemodialysis; INHD = intermittent nocturnal hemodialysis; SHD = short hours daily hemodialysis.

Figure 3.3: Pre-Dialysis Plasma Sodium Concentration Before (PRENA-50), Between Days 100 to 150 After (PRENA100-150) and All Days From 100 Days After (PRENA100+) Transition to Home Hemodialysis, with Pre-Transition Setpoint > 140 mmol/L

The slope of pre-dialysis plasma sodium in the first 100 days post-transition (M100) was less than zero in all SHD (95% CI, -0.0055 to -0.0318 mM/day) and FNHD (95% CI, -0.0010 to -0.0394 mM/day) patients, and in SHD (95% CI, -0.0081 to -0.0351 mM/day) and FNHD (95% CI, -0.0209 to -0.0695 mM/day) patients whose pre-transition pre-dialysis sodium (PRENA-50) was greater than or equal to 140 mM (Figure 3.5).

Univariate regression analysis was performed to predict M100 using 73 data-sets from 29 SHD, 9 ICHD, 24 FNHD and 11 INHD patients. Univariate correlation coefficients and p values are shown (Table 3.2). The strongest predictor of M100 was the

dialysate to pre-dialysis plasma sodium difference (DPRENA-50)(R^2 = 12.65%) although no independent factor reached statistical significance (Table 3.1).



FNHD = frequent nocturnal hemodialysis; ICHD = intermittent conventional hemodialysis; INHD = intermittent nocturnal hemodialysis; SHD = short hours daily hemodialysis.

Figure 3.4: Pre-Dialysis Plasma Sodium Concentration Before (PRENA-50), Between Days 100 to 150 After (PRENA100-150) and All Days From 100 Days After (PRENA100+) Transition to Home Hemodialysis, With Pre-Transition Setpoint < 140 mmol/L

Univariate regression analysis was performed to predict DeltaPRENA100 and DeltaPRENA100-150 using 82 data-sets from 29 SHD, 13 ICHD, 28 FNHD and 12 INHD patients. Univariate correlation coefficients and p values are shown (Table 3.2). The covariate of (DPRENA-50)(dialysis time) had a correlation of 31.8% and 42.0% for DeltaPRENA100 and DeltaPRENA100-150, respectively. However, this was entirely due to the DPRENA-50 component; elimination of dialysis duration from the covariate improved the correlation coefficient and p value in both DeltaPRENA100 (R^2 = 31.8 to 32.8%, p = 0.540 to 0.030) and DeltaPRENA100-150 (R^2 = 42.0 to 42.0%, p = 0.859 to

0.002). Dialysis frequency (R^2 = 6.19%, p = 0.060) and dialysis duration (R^2 = 2.15%, p = 0.085) trended towards a relationship with DeltaPRENA100.

A multivariate model was created to investigate the association of DeltaPRENA100 with dialysis frequency and DPRENA-50.

Model 1

DeltaPRENA100 = 0.4765 (DPRENA-50)
- 0.3506 (dialysis frequency per week) – 0.2807

R^2 = 35.44% (adjusted R^2 = 33.8%)

F-statistic = 21.68 (on 2 and 79 degrees of freedom, p<0.001)

DeltaPRENA100 = ($Post_{100}$-Na+) – (PRENA-50)

DPRENA-50 = (Dialysis Na+) – (PRENA-50),
adjusted p value < 0.001, R^2 = 32.8% in univariate model

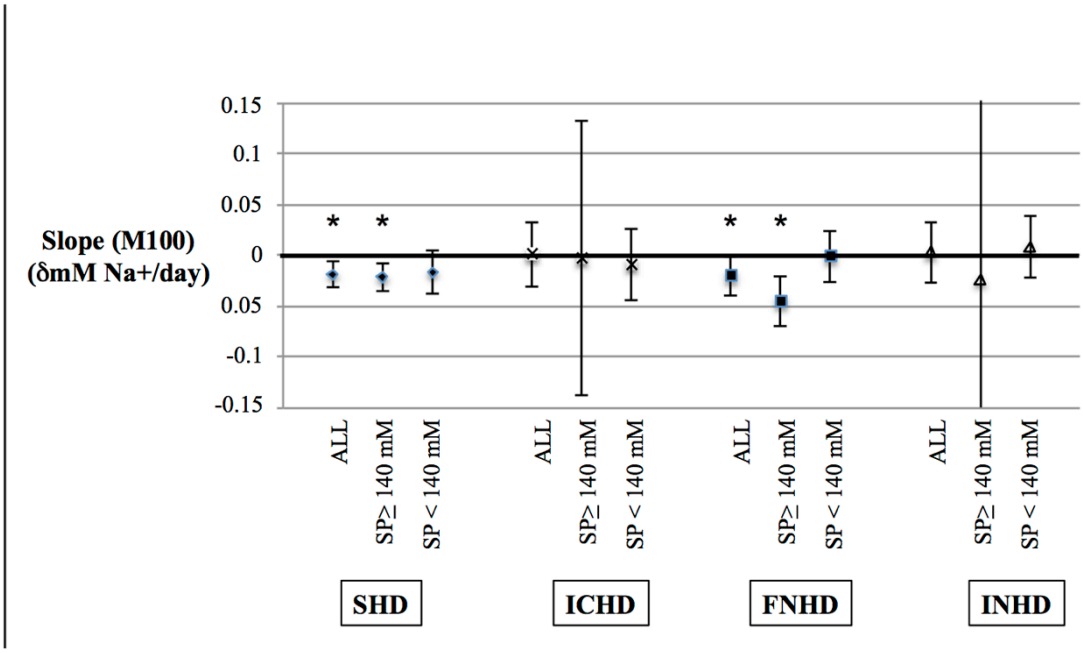
Dialysis frequency = Dialysis sessions per week,
adjusted p value = 0.077, R^2 = 6.2% in univariate model

	M100			DeltaPRENA100+			DeltaPRENA100-150		
Independent Factor	R^2 (%)	P	Coefficient	R^2 (%)	P	Coefficient	R^2 (%)	P	Coefficient
Dialysis Frequency (sessions per week)	2.26	0.31	-2.59 x 10^-3	6.19	0.06	-0.402	4.05	0.15	-2.82 x 10^-1
Dialysis Duration (minutes)	0.6	0.98	-5.86 x 10^-5	2.15	0.09	-0.216	0.15	0.3	-2.00 x 10^-3
DPRENA-50 (mmol/L)	12.65	0.66	2.69 x 10^-4	32.82	0.03	0.083	42.04	0.002	1.77 x 10^-3
(DPRENA-50) (Dialysis Duration)	9.24	0.26	3.59 x 10^-3	31.78	0.54	0.013	42.04	0.86	3.20 x 10^-2

Table 3.2: Univariate Regression Coefficients and P values for Independent Variables Predicting Slope of Predialysis Na+ in first 100 days (M100), Difference in Pre and Post-100 Days Post-Transition Pre-Dialysis Na+ (DeltaPRENA100+) and Differences in Pre- and Days 100-150 Post-Transition Pre-Dialysis Na+ (DeltaPRENA100-150)

3.4 Discussion

The sodium setpoint is considered to be stable in hemodialysis patients. The results of this study suggest that this is true at least with ICHD. According to model 1, this assumption is reasonable in ICHD patients; a pre-dialysis sodium between 133.0 and 141.0 mmol/L would be associated with DeltaPRENA100 between -2 and 2 mmol/L. This difference could be attributed to changes in total body water, or to laboratory measurement variability. In Keen and Gotch's initial description of the stability of the pre-dialysis sodium setpoint,[3] 89% of patients had an average pre-dialysis plasma sodium from 133.0 mM to 141.0 mM.



FNHD = frequent nocturnal hemodialysis; ICHD = intermittent conventional hemodialysis; INHD = intermittent nocturnal hemodialysis; SHD = short hours daily hemodialysis.

Figure 3.5: Slope of Pre-Dialysis Plasma Sodium Concentration, in First 100 Days After Transition from Conventional Thrice Weekly (ICHD) to Home Hemodialysis for All patients, and for Patients with Initial Sodium Setpoint (SP) > or < 140 mmol/L

However, there are scenarios in which a sodium setpoint change may occur on the basis of model 1. Patients whose dialysate sodium is personalized to be equal or less than pre-dialysis sodium may decrease their sodium setpoint. For example, in a patient dialyzed 5 times weekly, with a pre-dialysis plasma sodium of 135 mmol/L, whose dialysate sodium is personalized to 132 mmol/L, in an attempt to "desalt," the associated DeltaPRENA100 would be -3.5 mmol/L (model 1), which would bring the pre-dialysis plasma sodium setpoint down to 131.5 mmol/L, a level associated with increased mortality.[16,17]

Furthermore, patients dialyzed in units using a "standard dialysate sodium concentration" may increase their pre-dialysis plasma sodium setpoint. For example, a patient dialysed 3 times weekly, with a setpoint of 130 mmol/L, whose dialysate sodium is 140 mmol/L would have an associated DeltaPRENA100 of +3.4 mmol/L (model 1), setting the new pre-dialysis plasma sodium setpoint to 133.4 mmol/L. These patients would not have been observed in the Keen and Gotch's description, since none of their patients had sodium setpoints under 131 mmol/L. It is unknown whether the increased interdialytic weight gain observed in patients with a large dialysate to pre-dialysis plasma sodium difference, is offset by any improvement in mortality by increasing the sodium setpoint. If so, this may in part explain the unexpected results of Hecking et al, [15,19] who discovered that patients whose pre-dialysis sodium was less than 137 mmol/L had improved mortality when dialyzing against a higher dialysate sodium concentration, and reduced hospitalization and mortality with higher dialysate sodium concentrations, in units that did not individualize dialysate sodium concentrations. Dialysate sodium prescriptions may have changed some of the pre-dialysis sodium concentrations from a low level to a level associated with improved mortality. Prospective trials should evaluate the effect of intentionally increasing pre-dialysis plasma sodium setpoints, on cardiovascular and all-cause mortality.

Determining the pathophysiology of a change of plasma sodium setpoint is not the objective of this study, and will need to be established prospectively. Stability in blood glucose, lipid and paraprotein concentrations needs to be initially assumed. Then if a patient has a pre-dialysis plasma sodium concentration greater than the dialysate sodium

concentration, one could hypothesize that the post-dialysis plasma sodium concentration would decrease towards the dialysate sodium concentration, since sodium loss would occur relative to the isosmotic ultrafiltration, leaving the plasma with relative sodium to water loss. It is possible that equilibration back to sodium setpoint homeostasis requires an interdialytic interval longer than patients on quotidian, but not intermittent hemodialysis modalities. This hypothesis would need to be evaluated prospectively. However, this would explain why adding (dialysis time) to (DPRENA-50) did not improve (DPRENA-50) prediction of DeltaPRENA100 (Table 3.2), since dialysis frequency is a much greater determinant of interdialytic interval duration. For example, doubling a patient's dialysis duration from 4 to 8 hours (at dialysis frequency 3 times a week) only marginally decreases interdialytic time interval from 39.0 to 36.0 hours, whereas doubling a patient's dialysis frequency from 3 to 6 weekly sessions (at dialysis duration 4 hours a session) significantly decreases interdialytic time interval from 39.0 to 20.6 hours. Indeed, a patient with a pre-dialysis plasma sodium setpoint of 140 mmol/L, dialyzing 7 days weekly with a dialysate sodium of 140 mmol/L, would decrease their pre-dialysis plasma sodium setpoint to 137 mmol/L; this is a surprising and unexpected finding, the etiology of which will need to be elucidated with prospective investigations.

Finally, quotidian dialysis therapies appear from these results to be associated with an increased chance of decreasing the sodium setpoint when the initial pre-dialysis plasma sodium setpoint is equal to or greater than the dialysate sodium (Figure 3.3). For example a patient on 6 nights a week hemodialysis, with an initial pre-dialysis plasma sodium of 143 mmol/L, and a dialysate sodium concentration of 140 mmol/L will have a DeltaPRENA100 of -3.8, bringing the pre-dialysis plasma sodium setpoint to 140.2 mmol/L. Targeting the dialysate sodium concentration to below the pre-dialysis sodium setpoint could lead to repeated drops in the pre-dialysis sodium with every change in dialysate concentration. This may be undesirable from an outcome perspective.

Any statistically significant changes in pre-dialysis plasma sodium setpoint were observed with 150 days after transition from thrice weekly conventional to home hemodialysis (Figure 3.3). It is thus unlikely that any decreases in pre-dialysis sodium setpoint related to patients developing comorbidities associated with lower plasma

sodium concentrations such as heart or liver disease. Indeed, the strongest associations with change in plasma sodium setpoint were iatrogenic, specifically the choices of dialysis frequency and the dialysate sodium to pre-dialysis plasma sodium difference (Table 3.2). Furthermore, only outpatient blood tests were considered, so acute illness or comorbid illness is unlikely to be a confounding factor.

In light of numerous studies that suggest personalizing dialysate sodium concentrations can decrease interdialytic weight gain,[6-13] these data give reason for caution. If dialysate sodium is intentionally decreased to the pre-dialysis plasma sodium concentration, the IDWG may fall, but any benefit in morbidity and mortality may be offset by a decrease in sodium setpoint.

There are weaknesses to this study. Firstly, all data in this study were retrospective and measurements did not occur at exact time intervals in all patients. Thus, it remains unclear whether any change in sodium setpoint is a continuous process, or if any change is upon initiation of dialysis and complete after a short interval of time. However, the pre-dialysis plasma sodium setpoint change was completed within 150 days in our study, suggesting that patients reach a new "steady state" in which the effects of dialysis frequency and dialysate to pre-dialysis plasma sodium difference offset each other. Secondly, data points used were aggregates of variable numbers of dialysis and laboratory values occurring between variable time periods. This may explain why model 1 only provides 35% explanation for the change in DeltaPRENA100. Thirdly, there were baseline differences between dialysis modality groups, such as residual renal function and patient weight, which may be confounders. The study also has strengths in that numerous pre-dialysis plasma sodium values are available and that modalities differing in frequency and duration were used with this home hemodialysis population. While the sample size of patients was small (n=87), the findings were statistically significant and likely of clinical importance.

Further studies are indicated in quotidian hemodialysis patients that will vary prospectively the dialysate sodium to establish the effect of dialysate sodium and sodium setpoint on cardiovascular morbidity and all cause mortality.

3.5 Conclusions

In hemodialysis patients, the pre-dialysis plasma sodium "setpoint" is dynamic and correlated to the dialysate sodium concentration and dialysis frequency. Nephrologists should consider how the selected dialysate sodium concentration affects the dialysate to pre-dialysis plasma sodium concentration difference, and should also continue to monitor pre-dialysis plasma sodium concentrations. Prospective trials are needed to establish when the benefits of a decrease in interdialytic weight gain are offset by a decrease in sodium setpoint, and how dialysate sodium concentration should be targeted to minimize cardiovascular and all-cause mortality.

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Chapter 4: Pre to Post-Dialysis Plasma Sodium Change Better Predicts Clinical Outcomes Than Dialysate to Plasma Sodium Gradient in Quotidian Hemodialysis.

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4.1 Introduction

The amount of sodium removed from a patient on hemodialysis is the sum of convective loss and the diffusive gain or loss on dialysis.[1] Diffusive sodium balance on thrice weekly intermittent conventional hemodialysis (ICHD) is associated with important clinical outcomes, including interdialytic weight gain (IDWG), blood pressure, intradialytic hypotension, cardiovascular morbidity and mortality.[2-6] Which aspect of sodium balance is best to follow (and perhaps influence) is controversial; while decreasing dialysate sodium decreases thirst, IDWG and blood pressure,[1-8]post-dialysis minus pre-dialysis plasma sodium (PPNa+) may be superior to dialysate sodium minus pre-dialysis plasma sodium (DPNa+) in predicting mortality.[6]

While the effects of PPNa+ and DPNa+ in ICHD have been reported, those in more frequent dialysis modalities remain unknown. The objective of this study was to determine whether DPNa+ or PPNa+ better predicted clinical outcomes in patients on short hours daily (SHD) and frequent nocturnal home hemodialysis (FNHD) and to define these outcomes in FNHD and SHD.

4.2 Materials and Methods

All patients who received treatment through the Southwestern Ontario Regional Home Hemodialysis program base in London Ontario, from 1985 to December 31, 2011 were considered (n=101). A retrospective observational study was used. Patients were required to be on an assigned dialysis modality for a minimum of 120 days, to facilitate adequate record collection (n=92). All patients included in this trial initiated home hemodialysis after January 1, 1998. Patients who were on either short hours daily (SHD) (n=35) or frequent nocturnal hemodialysis (FNHD) (n=38) were included. Intermittent conventional hemodialysis (ICHD) (n=11) and intermittent nocturnal hemodialysis (INHD) (n=8) patients were excluded because of their low numbers.

Dialysis Modality and Characteristics

SHD home (n=35) was defined as a minimum of 5 treatments per week, with a minimum treatment time of 1.5 hours and a maximum treatment time of 4.0 hours. FNHD home

(n=38) was defined as a minimum of 5 treatments per week, with a minimum treatment time of 6.0 hours.

Dialysate sodium concentration was 140 mmol/L for all patients. Dialysate bicarbonate and potassium concentrations were personalized for each patient, to normalize pre-dialysis potassium and bicarbonate concentrations. Dialysate calcium concentration was 1.25 mEq/L for all SHD patients. From December, 2001 onwards, all FNHD patients dialyzed using a 1.75 mEq/L Ca++ dialysate concentration, as is now considered standard practice.[9] Prior to December, 2001, patients' dialysate calcium concentration was either 1.25 or 1.75 mEq/L. Thus, the majority of FNHD patients (26/38, 68.4%) used a dialysate calcium concentration of 1.75 mEq/L for the entire duration of this trial, and for those patients who initiated home hemodialysis prior to December 2001, 40.6% of data were collected while dialysate calcium concentration was 1.75 mEq/L.

Blood sample collection

Pre and post-dialysis blood samples are routinely taken each month. Home patients are trained to take blood from the arterial blood line at the start of dialysis and post-dialysis, using a standard slow blood and stop dialysate method. The samples are centrifuged and then stored and refrigerated until delivered to the local laboratory for that patient. All patient blood tests are measured using automated and standardized methods. Of interest to this study were pre-dialysis plasma sodium, bicarbonate and albumin, and post-dialysis plasma sodium values.

Sodium concentration measurement

Plasma sodium concentration was measured using Beckman-Coulter LX20 Pro Chemistry Analyzer with Ion Selective Electrodes prior to, and Roche Modular P Chemistry Analyzer with Ion Selective Electrodes after November 4, 2008.

Dialysate sodium concentration was determined using online conductivity measurements built into the Fresenius H series hemodialysis machine, which was used for all patients.

Database Creation

Blood test results were obtained from the hospital electronic patient record (PowerChart by Cerner). Data from individual patients were only used in the study if a minimum of 3 pre- and post-dialysis plasma sodium sets were available.

IDWG, pre and post-dialysis systolic and diastolic blood pressures, dialysis treatment times, and ultrafiltration volumes were obtained from archived dialysis treatment run sheets. These were the defined outcomes. The average values for these per month were calculated and entered into the study database. Summary measures were used at the patient level to avoid issues of correlation within patients. As such, a single value representing the average monthly value for each outcome per person was used in the analyses regardless of patient hemodialysis vintage.

Demographic patient information, including age, sex, weight (kg) at initiation of therapy, presence of diabetes, months of renal replacement therapy prior to initiation of home hemodialysis, and date of initiation of home hemodialysis were recorded by chart review. The blood pressure before initiation of home hemodialysis was recorded from the pre-home hemodialysis assessment clinic, which is within 1 month of initiation.

Residual glomerular filtration rate at initiation of home hemodialysis (Kr in mL/min/1.73m^2), was calculated using 24 hour urine collections for urinary urea and creatinine, as previously described.[10] Residual urinary volume was not commonly recorded, and thus residual renal function was used instead. Patients who urinated less than 250 mL urine daily were recorded to have no residual renal function.

Ethics

Because of concerns regarding the use of a standard dialysate of 140 mmol/L sodium concentration and prompted by the observation of high IDWGs in patients undergoing FNHD, a quality assurance investigation was instituted. All laboratory tests had been taken as per routine care protocols; demographic and dialysis treatment information were available from patient records. Once extracted, all data were de-identified before analysis. No patient had to provide blood samples, answer questionnaires or do anything

specific for this study that was conducted in accordance with the Declaration of Helsinki. Thus, informed written consent was not obtained from the current patients.

Statistics

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 19.0. The average for all demographic factors was calculated. To compare FNHD and SHD patients at baseline, *p*-values were calculated using two tailed student t-test for continuous variables and Fisher's exact test for categorical variables. Each baseline demographic and clinical factor's distribution was assessed. When a non-normal distribution was found, that factor's median and interquartile ranges were calculated.

To evaluate which of DPNA or PPNA better predicted the clinical endpoints, univariable analyses using dependent variables of IDWG, pre-dialytic systolic and diastolic blood pressures, intradialytic change in systolic and diastolic blood pressures, and ultrafiltration rate were conducted SHD and FNHD patients were considered collectively, then separately. R^2 and *p*-values were calculated, and a *p*-value of less than or equal to 0.05 was considered statistically significant.

Gradient	Mean	Median	Interquartile range (quartile 2 to 3)	Standard Deviation
DPNa+(n)	41.1	27.0	27-48	35.5
PPNa+ (n)	28.3	16.0	16-42	23.3
Clinical Outcome				
Interdialytic Weight Gain (n)	13.1	8.0	8-19	11.0
Pre and post-hemodialysis blood pressure pairs (n)	12.9	8.0	8-19	10.9
Ultrafiltration volume (n)	13.5	8.0	8-20	11.7

DPNa+ = dialysate minus pre-dialysis plasma sodium concentration; PPNa+ = Post-minus Pre-dialysis plasma sodium concentration.

Table 4.1: Number of Observations for Pre- to Post Hemodialysis (PPNa+) and Dialysate to Pre-Hemodialysis (DPNa+) Sodium Gradient, and for Each Clinical Outcome

The mean, median, range, interquartile ranges and variance in the number of observations for DPNa+ and PPNa+, and for each clinical outcome, were calculated. The effects of DPNa+ and PPNa+ on IDWG, pre-dialytic systolic and diastolic blood pressures, intradialytic change in systolic and diastolic blood pressures, and ultrafiltration rate were compared between SHD and FNHD using two tailed student t-tests. Statistical significance was considered at $p \leq 0.05$.

4.3 Results

A total of 73 sets of time-averaged pre- and post-dialysis plasma sodium values were made from 2065 matched pre- and post-dialysis plasma sodium values. There were a mean and median number of 28.3 and 16.0 observations for each patient's PPNa+ and 41.1 and 27.0 observations for each patient's DPNa+ (Table 4.1). The majority of all patients combined (90.4%), and each of SHD (88.6%) and FNHD (92.1%) had pre-dialysate plasma sodium values less than the dialysate sodium of 140 mmol/L(Figure 4.1). The majority of all patients combined (96.5%) and each of SHD (97.1%) and FNHD (94.7%) had post-dialysis plasma sodium levels less than the dialysate sodium of 140 mmol/L (Figure 4.2).

There were a mean and median of 13.1 and 8.0 observations for each patient's IDWG, 12.9 and 8.0 observations for each patient's paired pre and post hemodialysis BP, and 13.5 and 8.0 observations for each patient's ultrafiltration volume (Table 4.1).

All background demographic and clinical factors had a normal distribution (Table 4.2), except for residual renal function (mL/min) and vintage of renal replacement prior to initiation of home hemodialysis (months). The mean, median and first to third interquartile ranges for dialysis vintage (months) were 67.0, 50.0 and 18.0 to 102.0 for SHD and 94.5, 71.0, and 24.0 to 121.0 for FNHD. The mean, median and first to third interquartile ranges for residual renal function (mL/min) were 0.47, 0.00 and 0.00 to 0.00 for SHD and 0.78, 0.00, and 0.00 to 0.84 for FNHD.

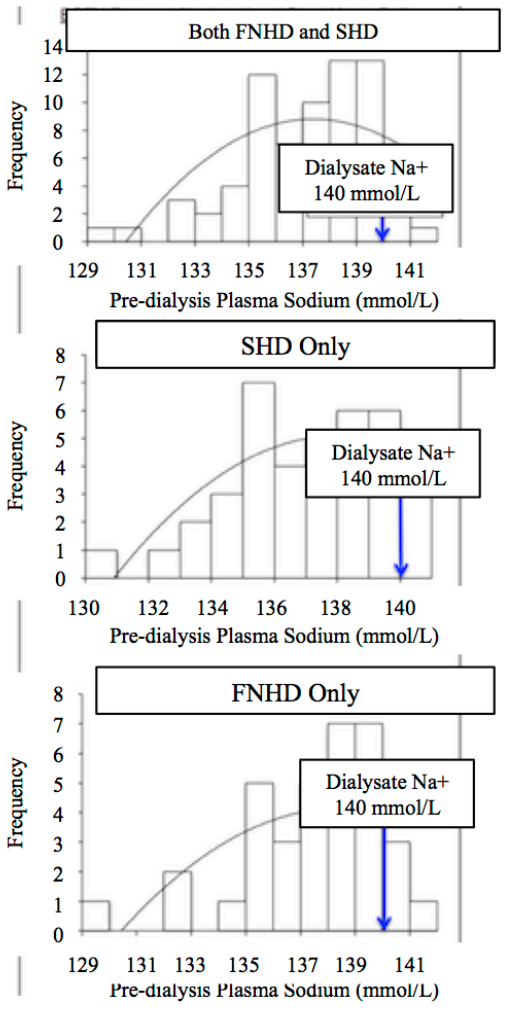

Figure 4.1 Pre-Dialysis Plasma Sodium Concentration

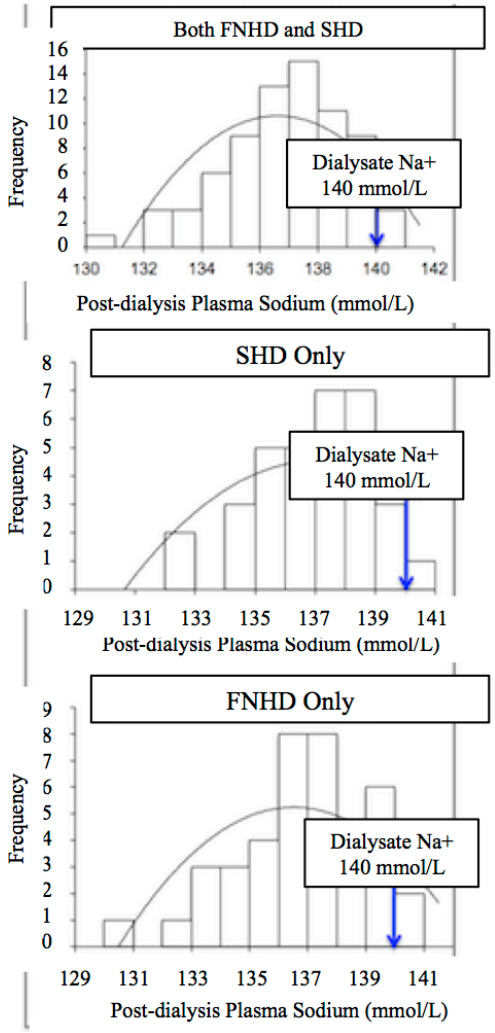

Figure 4.2: Post-Dialysis Plasma Sodium Concentration

FNHD = frequent nocturnal hemodialysis; SHD = short hours daily hemodialysis

SHD patients had a slightly higher dialysis frequency (Table 4.2) (5.54 vs. 5.26 sessions per week, p=0.03), and as expected, a lower dialysis duration (146.0 vs. 402.8 minutes, p<0.001) than FNHD patients.

VARIABLE	Short Hours Daily (mean, SE)	Frequent Nocturnal (mean, SE)	p value
n	35	38	
At Home hemodialysis Initiation			
Age (years)	45.6 (2.2)	45.4 (1.4)	0.22
Sex (% female)	45.7	36.8	0.48
Diabetic Status (%)	20	26.3	0.59
Vintage of Renal replacement (months)	67.0 (10.5)	94.5 (15.0)	0.13
Residual renal function (mL/min)	0.47 (0.18)	0.78 (0.26)	0.11
Systolic Blood Pressure (mm Hg)	147.0 (3.4)	148.3 (3.3)	0.98
BP diastolic (mm Hg)	83.7 (2.1)	84.3 (2.3)	0.52
Date of Initiation (%):			
1998-2002	37.1	31.6	0.63
2003-2007	28.6	29.0	1.00
2008-2012	34.3	39.5	0.81
While on Home hemodialysis			
Pre-dialysis Serum Albumin (mg/dL)	38.4 (0.5)	37.5 (0.6)	0.26
Pre-dialysis Serum Bicarbonate (mmol/L)	25.8 (0.3)	26.0 (0.7)	0.65
Dialysis Frequency (sessions per week)	5.54 (0.09)	5.26 (0.08)	0.03
Dialysis Duration (minutes per session)	146.0 (5.2)	402.8 (8.1)	<0.001

Table 4.2: Demographic and Clinical Factors of Patients on Short Hours Daily and Frequent Nocturnal Home Hemodialysis

PPNa+ was superior to DPNa+ in predicting IDWG (Table 4.3) in SHD patients (R^2 = 0.105 vs. 0.019, p=0.04 vs. 0.68), FNHD patients (R^2 = 0.223 vs. 0.020, p=0.002 vs. 0.76) and combined (R^2 = 0.147 vs. 0.024, p=0.001 vs. 0.75). PPNa+ was superior to DPNa+ in predicting pre-dialysis systolic blood pressure in SHD patients (R^2 = 0.103 vs. 0.007, p = 0.02 vs. 0.82). PPNa+ was superior to DPNa+ in predicting intradialytic change in systolic BP in FNHD patients (R^2 = 0.100 vs. 0.002, p=0.02 vs. 0.16) and combined patients (R^2 = 0.042 vs. 0.015, p = 0.002 vs. 0.02). PPNa+ was superior to DPNa+ in predicting intradialytic change in diastolic BP in FNHD patients (R^2 = 0.066 vs. 0.019, p = 0.02 vs. 0.06) and combined patients (R^2 = 0.014 vs. 0.060, p=0.004 vs. 1.0). PPNa+ was superior to DPNa+ in predicting ultrafiltration rate in FNHD patients

		DPNA+			PPNa+		
		R^2	P	Slope	R^2	P	Slope
Interdialytic Weight Gain (Liters)	SHD (n=35)	0.019	0.68	0.041	**0.105**	**0.04**	**0.134**
	FNHD (n=38)	0.020	0.76	0.042	**0.223**	**0.002**	**0.166**
	Combined (n=73)	0.024	0.75	0.047	**0.147**	**0.001**	**0.150**
Pre-dialysis BP systolic (mm Hg)	SHD (n=35)	0.007	0.82	0.525	**0.103**	**0.02**	**2.742**
	FNHD (n=38)	0.013	0.72	0.781	0.003	0.50	-0.473
	Combined (n=73)	0.003	0.81	-0.354	0.003	0.19	0.493
Pre-dialysis BP diastolic (mm Hg)	SHD (n=35)	0.004	0.73	0.904	0.028	0.13	0.904
	FNHD (n=38)	0.087	0.84	-1.269	0.098	0.89	-1.623
	Combined (n=73)	0.032	0.82	-0.716	0.024	0.71	-0.812
Interdialytic change in BP systolic (mm Hg)	SHD (n=35)	0.023	0.09	0.728	0.028	0.09	-0.999
	FNHD (n=38)	0.002	0.16	0.191	**0.100**	**0.02**	**-1.847**
	Combined (n=73)	**0.015**	**0.01**	**-0.579**	**0.042**	**0.002**	**1.254**
Interdialytic change in BP diastolic (mm Hg)	SHD (n=35)	**0.101**	**0.02**	**0.786**	0.003	0.13	-0.035
	FNHD (n=38)	0.019	0.06	0.383	**0.066**	**0.02**	**-0.866**
	Combined (n=73)	0.060	1.00	-0.651	**0.014**	**0.004**	**0.402**
Ultrafiltration rate (L/hour)	SHD (n=35)	0.055	0.25	0.025	0.052	0.27	0.034
	FNHD (n=38)	0.036	0.52	0.010	**0.296**	**0.001**	**0.035**
	Combined (n=73)	0.003	0.73	0.006	**0.038**	**0.05**	**0.029**

DPNa+ = Dialysate minus Pre-dialysis plasma sodium concentration; FNHD = frequent nocturnal hemodialysis; PPNa+ = Post- minus Pre-dialysis plasma sodium concentration; SHD = short hours daily hemodialysis

Table 4.3: PPNa+ and DPNa+ Versus Clinical Outcomes in Short Hours Daily and Frequent Nocturnal Hemodialysis

(R^2 = 0.296 vs. 0.036, p = 0.001 vs. 0.52) and combined patients (R^2 = 0.038 vs. 0.003, p = 0.05 vs. 0.73).

DPNa+ was superior to PPNa+ in predicting intradialytic change in diastolic BP in SHD patients (R^2 = 0.101 vs. 0.003, p=0.02 vs. 0.13). No other statistically significant differences were found between DPNa+ and PPNa+, for any clinical endpoints.

Ultrafiltration rate was significantly lower in FNHD than SHD patients (0.035 vs. 0.77 L/hour, $p < 0.001$) (Table 4.4). While IDWG appeared higher in FNHD than in SHD patients (2.25 vs. 1.92 L), this approached but did not reach statistical significance (p=0.06). There were no other statistically significant differences in clinical outcomes between SHD and FNHD patients.

	Short Hours Daily (mean, SE)	**Frequent Nocturnal (mean, SE)**	**p**
Interdialytic Weight Gain (L)	1.92 (0.14)	2.25 (0.11)	0.06
Pre-dialysis BP systolic (mm Hg)	140.9 (2.8)	139.7 (2.7)	0.77
Pre-dialysis BP diastolic (mm Hg)	79.8 (1.8)	79.7 (1.7)	0.96
Intradialytic change in BP systolic (mm Hg)	11.0 (2.1)	9.7 (1.9)	0.64
Intradialytic change in BP diastolic (mm Hg)	6.8 (1.1)	3.8 (1.1)	0.06
Ultrafiltration Rate (L/hour)	**0.77 (0.04)**	**0.35 (0.02)**	**<0.001**

Table 4.4: Clinical Endpoints of Standardized Dialysate Bath of 140 mmol/L in Short Hours Daily Versus Frequent Nocturnal Hemodialysis Patients

PPNa+ correlated with increased interdialytic weight gain in both SHD and FNHD patients, but this correlation was stronger in FNHD patients (R^2 = 0.105 vs. 0.019), with greater statistical significance (p = 0.04 vs. 0.68) and with greater slope (0.166 vs. 0.134) (Figure 4.3).

In FNHD patients, PPNa+ associated with greater drops in systolic (slope= -1.847, R^2 = 0.100, p = 0.02) and diastolic (slope = -0.866, R^2 = 0.066, p = 0.02) blood pressures on dialysis (Figure 4.4). This was in contrast to SHD patients, in whom a greater DPNa+ associated with a decreased drop of diastolic blood pressure (slope =0.786, R^2 = 0.101, p=0.02) (Table 4.3). This is shown graphically (Figure 4.4); as post-dialysis plasma sodium increases relative to pre-dialysis plasma sodium in FNHD patients, there is more of a drop in systolic and diastolic blood pressures on dialysis. On the other hand, as dialysate sodium increases relative to pre-dialysis plasma sodium in SHD patients, the magnitude of diastolic blood pressure fall on dialysis decreases.

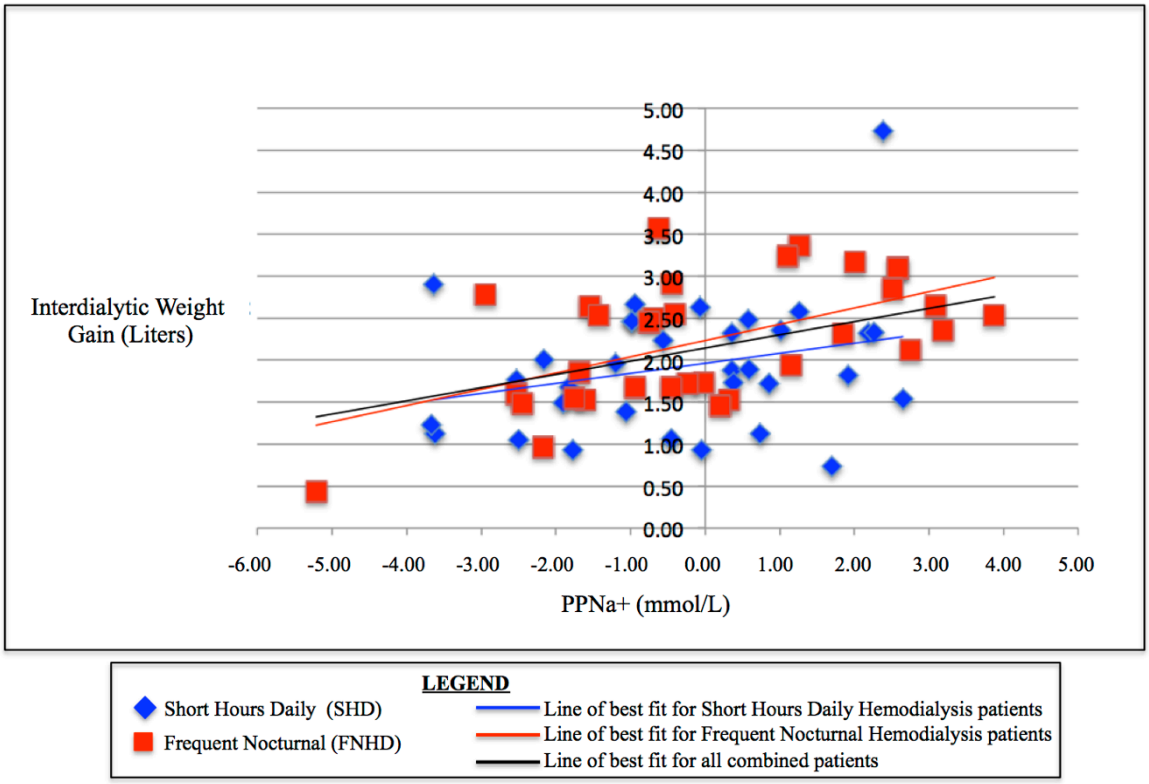

Figure 4.3: Effect of PPNa+ on Interdialytic Weight Gain for Short Hours Daily and Frequent Nocturnal Hemodialysis Patients

4.4 Discussion

Total sodium balance on hemodialysis is determined by the net of convective loss and diffusive sodium gain or loss.[1] Positive sodium balance in patients on thrice weekly conventional hemodialysis is associated with IDWG, and, in turn hypertension, left ventricular hypertrophy and cardiovascular morbidity and mortality.[1,5-8,13] Both low and high pre-dialysis systolic blood pressures are associated with increased mortality in patients undergoing thrice weekly hemodialysis. However, the clinical effects of more frequent and longer duration exposure to a dialysate higher than the pre-dialysis plasma sodium has not been described.

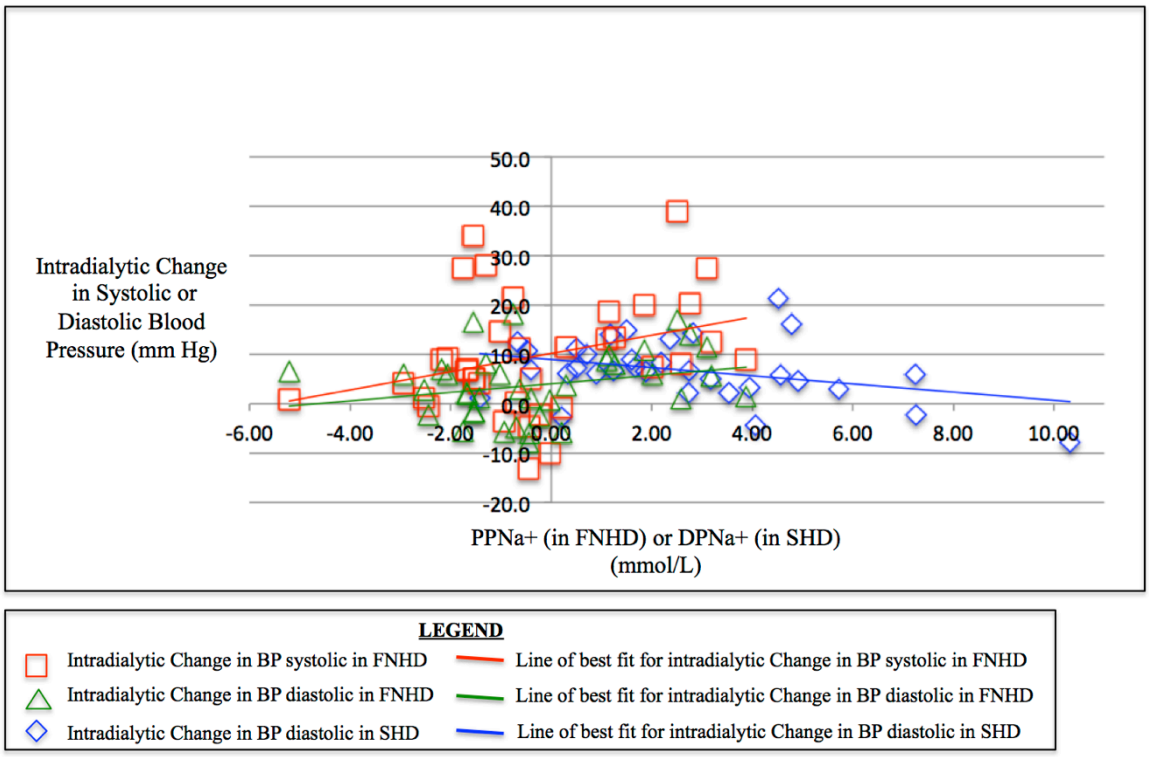

Figure 4.4: Intradialytic Change in Blood Pressure in Short Hours Daily and Frequent Nocturnal Hemodialysis Patients

Understanding which of DPNa+ or PPNa+ better predicts clinical outcomes is important not only in determining which factors are modifiable, but also to design prospective trials aimed at improving outcomes. Reducing dialysate sodium has been shown to improve IDWG and blood pressure,[1,3-7]and DPNa+ has been correlated to IDWG.[16] However, in large population observational data, PPNa+ appears superior to DPNa+ in predicting IDWG in ICHD.[17] Our study confirms that in quotidian dialyzed patients, PPNa+ has a stronger association than DPNa+ with IDWG, intradialytic change in blood pressure, and ultrafiltration rates, consistent with recent work of Hecking et al.[17] IDWG was more strongly correlated to PPNa+ in FNHD than SHD patients (R^2=0.223 vs. 0.105), and with greater statistical significance (p=0.002 vs. 0.04) and slope (0.166 vs. 0.134) (Table 4.3) (Figure 4.3). This reflects the longer exposure to a positive diffusive difference (402.8 vs. 146.0 minutes, $p < 0.001$) (Table 4.2). This is consistent with the recent work of Munoz-Mendoza et al, who showed decreased IDWG and blood pressure in thrice weekly nocturnal patients exposed to lower dialysate sodium concentrations.[18]

DPNa+ was more correlated than PPNa+ with intradialytic change in blood pressure, in SHD patients. This was the only clinical variable associated more with DPNa+ than PPNa+. This was in contrast to FNHD patients, where PPNa+ was more associated with change in BP on dialysis, only in the opposite direction (Figure 4.4). This may result from a variety of factors. Firstly, FNHD patients are exposed to a diffusive difference longer and thus have a more positive sodium balance. While the higher IDWG in FNHD patients in our trial did not reach statistical significance (2.25 vs. 1.92 L, p=0.06)(Table 4.4), patients in the London Daily Nocturnal Dialysis Study with a dialysate sodium of 140 mM had higher IDWG in FNHD vs. SHD patients. This may cause the intradialytic change in blood pressure to reflect relative ultrafiltration requirements, which are higher with more positive sodium balance (Table 4.3). Secondly, it's possible that the recumbent position of FNHD patients has different effects on the effective circulating volume (ECV), and that time upright is needed before this approximates the ECV of SHD patient undergoing ultrafiltration of a similar volume. Finally, FNHD patients may have greater restoration in homeostasis of hormones involved in blood pressure regulation. The generation of intradialytic hypotension is associated with autonomic neuropathy[17]which may be improved by nocturnal dialysis modalities.[20]

Intradialytic hypotension is associated with increased mortality in patients undergoing thrice weekly hemodialysis.[20] However, the increased intradialytic drop in blood pressure in FNHD patients with an increased PPNa+ is of uncertain clinical significance. FNHD patients are on less anti-hypertensive medications than SHD patients, and suffer from fewer dialysis related symptoms like cramping, headaches, dizziness, dyspnea, and self-reported intradialytic hypotension.[22] The study provides clinically important information. Firstly, the majority of quotidian patients (90.4%) are exposed to a positive diffusive difference for sodium (Figure 4.1). Ideally, this dialysate sodium should be targeted to minimize IDWG, to improve blood pressure and to minimize risk of intradialytic hypotension. This can be achieved by personalizing the dialysate sodium so that PPNa+ is zero or even slightly negative. This effect appears more crucial in FNHD than SHD patients, because of the longer duration of therapy. Furthermore, a negative

DPNa+ or PPNa+ does not seem to predispose FNHD patients to the risk of intradialytic hypotension as it does in SHD patients.

This study does have limitations. A relatively small number of patients of variable dialysis vintage were studied in a retrospective fashion. All data points were aggregates of variable numbers of dialysis and laboratory values, occurring between variable time periods, corresponding to patients' attendance at clinics, when data were entered into the electronic patient record. However, numerous pre- and post-dialysis sodium values were available from two quotidian dialysis modalities. The active plasma sodium available for diffusion could not be quantified precisely in this study. However, the concentration of major plasma anions albumin and bicarbonate were not statistically different pre-dialysis (Table 4.2), suggesting that the Gibbs-Donnan effect[23] did not operate disproportionately in one dialysis modality.

In conclusion, the PPNa+ has a greater association than DPNa+ to IDWG, pre-dialysis systolic blood pressure, intradialytic blood pressure change and ultrafiltration rates in SHD and FNHD patients. However, DPNa is associated with intradialytic diastolic blood pressure change in SHD, but not in FNHD patients. In the latter, a positive sodium balance increases the risk of large blood pressure drops on dialysis. Further work is needed to establish the effect of altering dialysate sodium concentration, on long-term cardiovascular outcomes, in quotidian dialyzed patients.

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Chapter 5: Modifiable Variables Affecting Interdialytic Weight Gain Include Dialysis Time, Frequency, and Dialysate Sodium.

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5.1 Introduction

Intradialytic sodium (Na+) removal leads to decreased blood pressure[1-3] and decreased interdialytic weight gain (IDWG).[4-8] This may lead to better outcomes[9] in hemodialysis patients, although this is controversial.[12] The amount of Na+ removed from a patient during hemodialysis is the net of that lost by convection with that lost or gained by diffusion.[4] Diffusive gain occurs when the dialysate Na+ exceeds the pre-dialysis plasma Na+. In the London Daily Nocturnal Dialysis study,[10] IDWG was higher in frequent nocturnal (FNHD) than short hours daily hemodialysis (SHD) patients, using a standard dialysate concentration of 140 mmol/L, suggesting that the time of exposure to a higher dialysate Na+ may affect IDWG. In contrast, the Frequent Hemodialysis Network (FHN)[11] showed less IDWG in FNHD patients but they had variable dialysate Na+ concentrations and higher urinary volumes. Thus, factors that determine IDWG may include residual urinary volume, dialysis time and frequency, and the dialysate to plasma diffusion difference (DPNa+). A recent study determined that pre to post dialysis change in plasma Na+ (PPNa+) better correlated to clinical outcomes than did the δDPNa+.[8] However, the effect of DPNa+ on mortality remains controversial, with one large prospective cohort study showing positive DPNa+ associated with decreased mortality,[12] contrary to the findings of previous studies.[13] However, PPNa+ is likely the result of both DPNa+ and time of exposure to the diffusive Na+ difference.

The study objective was to derive an equation, using multivariable regression analysis, of modifiable variables that affect IDWG.

5.2 Materials and Methods

Study Population

All patients in the home hemodialysis program of the Southwestern Ontario Regional Renal Program, from February 11, 1998 to December 1, 2012, were included, using a retrospective observational design.

Dialysis Modality

Modality was defined by the duration of dialysis and its frequency. SHD implied a minimum of 5 weekly treatments with treatment times of 1.5-4.0 hours. Intermittent conventional hemodialysis (ICHD) meant a maximum of 4 weekly treatments and times between 3-5 hours. FNHD indicated a minimum of 5 weekly treatments of 6.0 hours or more. Dialysate Na+ concentration was always 140 mmol/L. When patients changed dialysis modality during the observation period, only the first dialysis modality was considered.

Blood sample collection

Pre and post dialysis blood samples are taken each month from the arterial blood line using a standard slow blood and stop dialysate method. Locking solution (3 mL 4% citrate) and a small amount of blood (2 mL) are always spent before blood is collected. The samples are centrifuged, stored and refrigerated until delivered to the laboratory. Of interest to this study were pre and post-dialysis plasma Na+ and pre-dialysis albumins, measured using automated and standardized methods. Only outpatient blood tests were used, to assure that the patient was at their baseline health status, so that the plasma Na+ concentration would not be confounded by acute illness.

Na+ concentration measurement

Plasma Na+ concentration was measured using Beckman-Coulter LX20 Pro Chemistry Analyzer with Ion Selective Electrodes prior to, and Roche Modular P Chemistry Analyzer with Ion Selective Electrodes after November 4, 2008. This change was made by the London Health Sciences Center because of a need for higher volume of laboratory testing. Both plasma Na+ concentration methods were regularly calibrated; thus, the measurements were treated as equivalent on data analysis. Dialysate Na+ concentration was determined using online conductivity measurements built into the Fresenius H series hemodialysis machine, which was used for all patients. Blood glucose was not measured simultaneous to Na+ concentration; thus, plasma sodium levels were not corrected for glucose.

Database Creation

Blood test results were available from the hospital electronic patient record (Power Chart by Cerner). IDWG and dialysis treatment times were obtained from dialysis treatment run sheets. The average monthly values were calculated and entered into the database. For this analysis, a single value for each patient data point was used, being the average of the monthly values regardless of hemodialysis vintage. Demographic patient information, including age, sex, weight (kg) and height (cm) at initiation of therapy, diabetic status, and months of renal replacement therapy prior to initiation of home hemodialysis, were recorded by chart review. Residual glomerular filtration rate (ml/min x 1.73 m^2) at baseline[14] was recorded. Our home hemodialysis program does not perform urine collections if the 24 hour urine volume is less than 250 mL, since we have found that this amount only marginally contributes to weekly standard Kt/V. Thus, patients with less than 250 mL urine daily were recorded as having zero renal function. Once obtained, data was de-identified and then entered into the study specific database for analysis.

Interdialytic Weight Gain

IDWG was calculated as the difference between the post-dialysis body weight and the next dialysis session's pre-dialysis body weight. A single IDWG value for each patient was entered into the database, being the average of the monthly values regardless of hemodialysis vintage.

We chose to use interdialytic weight gain as an absolute value (IDWG), rather than as a percentage of body weight (IDWG%BW), for three reasons. Firstly, using all available clinical and demographic variables, the unadjusted correlation coefficient was higher for IDWG than IDWG%BW (R^2 = 37.3% vs 32.2%). Secondly, on home hemodialysis run sheets, patients did not always record body weight simultaneous to IDWG, so there was temporal inaccuracy in IDWG%BW measurements. Thirdly, IDWG%BW was autocorrelated with age, diabetes status and PPNa+, each of which were important to assess in our final model.

Ethics

Because of concerns regarding the use of a standard dialysate of 140 mmol/L Na+ concentration and prompted by the observation of high IDWGs in patients undergoing FNHD, a quality assurance investigation was instituted. All laboratory tests had been taken as per routine care protocols; demographic and dialysis treatment information were available from patient records. Once extracted, all data was de-identified before analysis. No patient had to provide blood samples, answer questionnaires or do anything specific for this study which was conducted in accordance with the Declaration of Helsinki. Thus, informed written consent was not obtained from the current patients.

Statistics

Two time periods were considered. Data prior to December 30, 2011 were used to determine the equation for IDWG, which was internally validated using bootstrapping. External validation used data from a temporally distinct population group, from August 1 to December 10, 2012.

Univariate analyses were used to investigate the relationship of each covariate with the dependent variables. Descriptive statistics and univariable analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 19.0. Multivariable regression models were used to develop predictive models through backwards selection and a comparison of the adjusted Akaike Information Criterion (AIC) of nested models.[15] Starting with a saturated model (containing all potential covariates) each independent variable starting with the largest p-value, was sequentially removed provided it did not meet the chosen liberal cut-off point for statistical significance i.e. a p-value > 0.10. With each variable removed, the nested model was then compared to the previous model based on the corrected AIC value. The model with the smallest AIC was chosen to be the best model. If the corrected AIC value of the nested model was within 1% of the previous model, we considered the models equivalent and choose the more parsimonious model (fewer covariates). The corrected AIC is calculated[16] as:

$$\text{corrected } AIC = 2k - 2\ln(Likelihood) + \frac{2k(k+1)}{n-k-1},$$

k = number of parameters
n = number of observations and
$\ln(Likelihood)$ = log-likelihood of the model

Corrected AIC was chosen due to the small sample size. Model fit was evaluated using F-statistic, R^2 and adjusted R^2 values.

To establish which factors influenced the dependent variable IDWG, independent variables included PPNa+, dialysis time and frequency, patient age, sex, albumin, diabetes status, and residual renal function. Patient albumin was included in the model because of concerns regarding the Gibbs-Donnan effect.[17] Model building was performed to build our first equation, and the F-statistic, R^2 and adjusted R^2 values were calculated for resulting model.

To derive an equation defining IDWG, we used multivariable regression analysis. PPNa+ cannot be used as an independent variable since the post-dialysis plasma Na+ has to be known. We thus investigated the correlation of PPNa+ to diffusive balance of Na+, represented by the product of DPNa+ and dialysis time, using Pearson's correlation coefficient. A multivariable linear model was then developed leading to Equation 5.2. The F-statistic, R^2 and adjusted R^2 values were calculated.

The final predictive model was validated using internal bootstrapping for both model selection and predictive qualities.[18] Multivariable data analysis and bootstrap validations were conducted using the statistical software R version 2.14.1.[19] Bootstrap validation was conducted by randomly sampling N=86 observations with replacement, to create the validation sample. Estimates of the residual standard error, mean square predictive error and mean residual value were calculated by fitting the bootstrap data to the final predictive model. For each bootstrap sample, we developed new linear models and estimated the regression coefficients and model properties. This process was repeated for 1000 bootstrap samples and the average values of all estimates calculated. To evaluate the predictive properties of the final equation, the data from each of the 1000 bootstrap samples were fit using the predictive model.

For external validation, we applied equation 5.2 to our current home hemodialysis patients and compared predicted with actual IDWGs. The variables required for the predicted were obtained from charts, electronic patient records and dialysis run sheets; data between August and December 2012 with at least 2 pre-dialysis blood sample results were taken, averaged and used in the equation 5.2. Actual IDWGs for each dialysis session in that same period were obtained from run sheets and averaged. Patients who were in the internal validation were excluded, leaving 24 new patients for the external validation. The distribution of dialysis modalities (8 SHD, 8 ICHD, 4 FNHD, 4 INHD) spanned all hemodialysis modalities. Predicted and actual IDWGs were compared by linear regression and Bland-Altman analyses.[20]

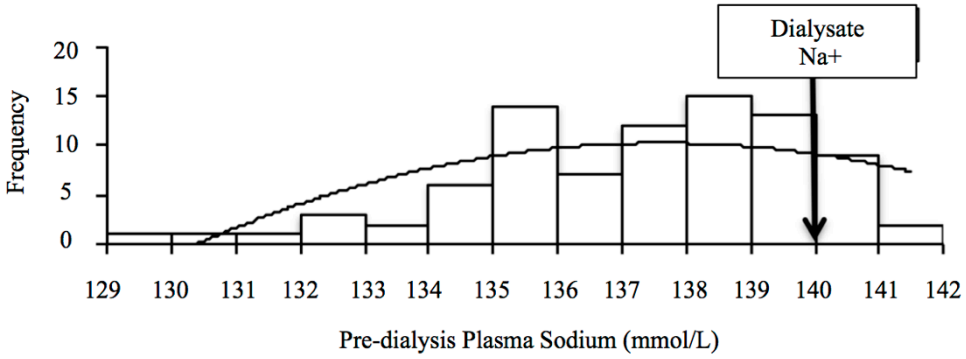

Figure 5.1: Distribution of Pre-Hemodialysis Plasma Sodium Concentrations

5.3 Results

A total of 2868 matched pre and post-dialysis plasma Na+ values were available, giving 86 sets of time-averaged patient pre and post-dialysis Na+ values (Figures 5.1 and 5.2), from SHD (n=32), ICHD (n=17) and FNHD (n=37) patients. The majority (87.2%, 75/86) of the pre-dialysis plasma Na+ values were below the dialysate Na+ of 140 mmol/L, while 16.3% (14/86) were below 135 mmol/L. Both pre-dialysis and post-

dialysis plasma Na+ spanned at least the entire normal range (Table 5.1), with median values of 137.73 mmol/L and 137.37 mmol/L, respectively.

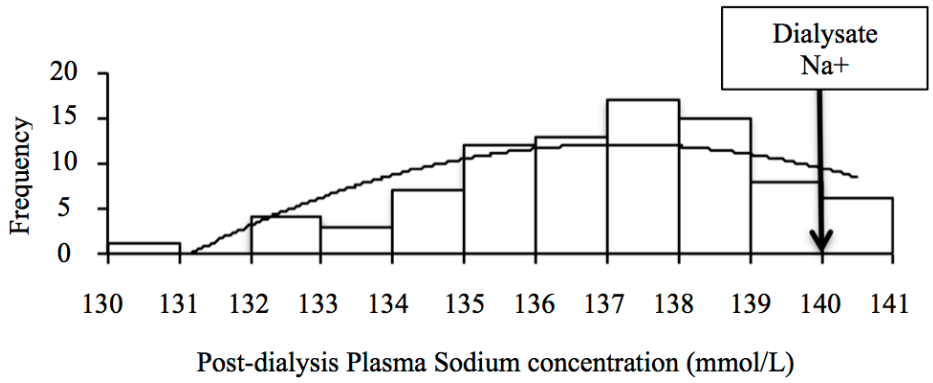

Figure 5.2: Distribution of Post-dialysis Plasma Sodium Concentrations

The mean, median, and standard deviation of all independent variables were calculated (Table 5.1), and the range spanned the range for most factors.

Factor	Mean	Range	Standard Deviation	Median
Number of patients	86	N/A	N/A	N/A
Pre-dialysis Plasma Na+ (mmol/L)	137.27	129.68 to 142.00	2.52	137.73
Post-dialysis Plasma Na+ (mmol/L)	137.03	130.24 to 140.63	2.42	137.37
PPNa+ (mmol/L)	-0.24	-5.21 to 5.00	1.93	-0.45
DPNa+ (mmol/L)	2.73	-2.00 to 10.32	2.52	2.27
Age (years)	46.35	24 to 75	11.7	45
Sex (% female)	43.02	N/A	N/A	N/A
Diabetes Status (% diabetic)	23.26	N/A	N/A	N/A
Albumin (g/L)	38.18	28.42 to 46.75	3.77	38.7
Residual Renal function (mL/min/1.73m^2)	0.77	0.00 to 6.93	1.53	0
Dialysis Time (minutes)	270.08	90 to 497	124.89	225
Dialysis Frequency (sessions/week)	5.01	3.00 to 6.56	0.99	5.24
Interdialytic Weight Gain (Liters): ALL (n=86)	2.56	0.51 to 5.59	0.99	2.40
Short Hours Daily (n=32)	2.35	1.04 to 5.59	0.88	2.24
Intermittent Conventional (n=17)	2.69	0.51 to 4.39	1.20	3.16
Frequent Nocturnal (n=37)	2.70	0.66 to 4.82	0.97	2.53

DPNa+ = dialysate minus Pre-dialysis plasma sodium concentration; PPNa+ = Post-minus Pre-dialysis plasma sodium concentration

Table 5.1: Demographic and Clinical Factors of Patients in Multivariate Regression Model

Independent variable	Coefficient	R^2	p value
PPNa+ (mmol/L)	**0.1694**	**20.36**	**<0.001**
Albumin (g/L)	**-0.0434**	**9.35**	**0.02**
DPNa+ (mmol/L)	0.0063	6.66	0.15
Diabetes status	0.2957	3.38	0.054
Dialysis frequency (per week)	**-0.1719**	**1.74**	**0.02**
Sex (0 if male, 1 if female)	**-0.3021**	**1.28**	**0.03**
Residual renal function ($mL/min/1.73m^2$)	-0.008	0.66	0.44
Age (years)	-0.0171	0.00	0.01

DPNa+ = dialysate minus Pre-dialysis plasma sodium concentration; PPNa+ = Post-minus Pre-dialysis plasma sodium concentration

Table 5.2: Univariate Regression Analysis of Interdialytic Weight Gain in Home Hemodialysis

Using univariable regression analysis for IDWG, the unadjusted *p*-values and correlation coefficients for independent factors were calculated (Table 5.2). PPNa+ (R^2=20.36%, p<0.001), albumin (R^2=9.35%, p=0.020), dialysis frequency (R^2=1.74%, p=0.019) and female sex R^2=1.28%, p=0.029) were significantly (p-value > 0.05, R^2>1%) correlated to IDWG. Univariable regression analysis confirmed that PPNa+ was better than DPNa+ at predicting IDWG (R^2 = 20.36% versus 6.66%, p<0.001 versus 0.152).

Equation 5.1 was calculated using multivariable regression analysis, and the same independent variables, to predict IDWG. Since DPNa+ was less effective at predicting PPNa+, only PPNa+ was used in our regression model for equation 5.1.

Equation 5.1: IDWG = 5.0694 + 0.17889(PPNa) – 0.1542(frequency) – 0.0145(Age) – 0.2316(if female) – 0.0457(Albumin) +0.001354 (Dialysis Time)

Where IDWG = interdialytic weight gain, in liters
PPNa+ = (plasma post-dialysis Na+)–(plasma pre-dialysis Na+),in mmol/L
Frequency = dialysis frequency, in sessions per week
Albumin = average patient albumin, in g/L

Dialysis time = Dialysis session time, in minutes

F-statistic = 7.309 on 6 and 79 degrees of freedom (p-value < 0.001),

R^2 = 35.69% (adjusted R^2 = 30.81%)

Standard errors, p-values and 95% confidence intervals for the regression coefficient estimates are presented in Table 5.3.

Since the post-dialysis plasma Na+ cannot be determined prior to dialysis, we correlated PPNa+ to the diffusive Na+ balance, represented by the product of DPNa+ and dialysis time (minutes). The Pearson correlation coefficient between PPNa+ and this product is 0.4054, suggesting a moderate correlation. In a simple linear regression model between PPNa+ and the product of (DPNa+) and dialysis time, there was an F-statistic of 16.53 on 1 and 84 degrees of freedom, corresponding to a model p-value of <0.001.

Given the product of DPNa+ and dialysis time was well correlated to PPNa+, a second equation was developed by fitting a multivariable linear regression model to IDWG. This second model included all independent variables from equation 5.1, except PPNa+, which was replaced by the covariate of (DPNa+) times dialysis time. Thus, equation 5.2 included factors that were all known prior to the dialysis session.

Equation 5.2: IDWG = 5.8178 + 0.00023215 (DPNa+)(Dialysis time) – 0.0107(Age) - 0.1558(frequency) – 0.2977(if female) – 0.0654(Albumin)

Where IDWG = Interdialytic weight gain, in Liters

DPNa+ = (Dialysate Na+) – (Pre-dialysis plasma Na+)

Dialysis time = Dialysis session time, in minutes

Frequency = dialysis frequency, in sessions per week

Age = years old, of patient

Albumin = average patient albumin, in g/L

F-statistic = 4.1940 on 5 and 80 degrees of freedom (p-value = 0.002),

R^2 = 20.77% (adjusted R^2 = 15.82%)

Standard errors, p-values and 95% confidence intervals for the regression coefficient estimates are presented in Table 5.3. The parameter estimates obtained through the bootstrap sample were all normally distributed. The average (min, max) of

the residuals was 0.0055 (-0.2207, 0.2449); the average deviation of the bootstrap samples from the predictive value is close to 0. The average bootstrap residual median was -0.0091, suggesting that the residuals may have been slightly skewed. The Root Mean Squared Error (RMSE) for equation 5.2 was 0.7208; this describes the discrepancy of observations and the estimated model. The bootstrap samples' average Root Mean Squared Predictive Error was 0.7218; the predictive power is slightly reduced when fitting Equation 5.2 to the bootstrap samples. The unadjusted R^2 value for the bootstrap samples was 20.13%, close to the unadjusted R^2 value (20.77%) in Equation 5.2.

	EQUATION ONE			EQUATION TWO		
Independent variable	**Coefficient**	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**
(Intercept)	**5.0694**	**0.9947**	**< 0.001**	**5.818**	**1.068**	**< 0.001**
Age (years)	**-0.0145**	**0.0068**	**0.4**	-0.0107	0.0075	0.16
Sex (0 = male, 1 = female)	-0.2316	0.1523	0.13	-0.2978	0.1664	0.08
Albumin (g/L)	**-0.0457**	**0.0196**	**0.02**	**-0.0654**	**0.0211**	**0.003**
Dialysis Frequency (per week)	**-0.1542**	**0.0762**	**0.047**	-0.1558	0.0842	0.07
Dialysis Time (min)	**0.0014**	**0.0006**	**0.02**			
PPNa (mmol/L)	**0.1789**	**0.0389**	**< 0.001**			
DPNa, mmol/L) x (Dialysis Time, min)				**0.0002322**	**0.0001**	**0.018**

DPNa+ = dialysate minus Pre-dialysis plasma sodium concentration; PPNa+ = Post-minus Pre-dialysis plasma sodium concentration

Table 5.3: Multivariable Regression Analysis to Predict Interdialytic Weight Gain by Equations 1 and 2

The average R^2 value (min, max) for the 1000 created models was 29.62% (4.80%, 65.85%) and an adjusted R^2 of 24.92% (0.10%, 62.79%). The average F-statistic value was 6.6521 on 5 and 80 degrees of freedom (average *p*-value = 0.005). The average occurrence of variable selection is presented in Table 5.4; (DPNa+)(dialysis duration), sex, albumin and dialysis frequency were in over 80% of the bootstrap samples, while age, diabetes status and residual renal function (Kr) were in 74%, 73% and 41%, respectively. The average regression coefficient estimates are also in table 4; the mean parameter estimates are close to those regression coefficients estimated in

Equation 5.2. The absolute bias for all covariates is less than 0.08 (except for the intercept, which shows an absolute bias of 3.3).

The 95% confidence intervals for the bootstrap parameter estimates are also calculated; the confidence intervals for residual renal function and diabetic status include 0, so these variables were not included in the model. The upper limit for age is close to 0, but we chose to leave Age in the model since it improved our predictive ability. The remaining covariates did not include 0 and thus reinforced their inclusion in the model.

VARIABLE	Occurrence	Mean Parameter Estimate	True Estimate	Absolute Bias	Lower 95% Limit	Upper 95% Limit
Intercept	**100%**	**5.6257**	**5.8178**	**0.1921**	**3.2974**	**7.954**
(DPNa, in mmol/L) x (Dialysis Time, in minutes)	**85.10%**	**0.0799**	**0.0002**	**0.0797**	**0.0184**	**0.1414**
Residual renal function (Kr, mL/min)	41.40%	-0.0612	x	NA	-0.2921	0.1697
Age (years)	**73.90%**	**-0.0159**	**-0.0107**	**0.0052**	**-0.0303**	**-0.0015**
Sex (0 if male, 1 if female)	**83.10%**	**-0.3615**	**-0.2978**	**0.0637**	**-0.6466**	**-0.0764**
Diabetes status (0 if no, 1 if yes)	72.60%	0.4145	x	NA	-0.0014	0.8304
Albumin (g/L)	**92.30%**	**-0.0621**	**-0.0654**	**0.0033**	**-0.1049**	**-0.0193**
Dialysis Frequency (per week)	**87.60%**	**-0.205**	**-0.1558**	**0.0492**	**-0.3632**	**-0.0468**

DPNa+ = dialysate minus Pre-dialysis plasma sodium concentration; PPNa+ = Post-minus Pre-dialysis plasma sodium concentration

Table 5.4: Bootstrap Validation of Predictive Equation for Interdialytic Weight Gain (Equation 2)

A calibration plot was completed for the external validation cohort (n=24) (Figure 5.3). There were 37 pre-dialysis plasma Na+ measurements available for the external validation cohort, an average and median of 1.54 and 1.00 for each patient, respectively. The distribution of IDWG for these patients was determined (Table 5.5), and spanned a wide range (0.39 to 3.16 liters), with a mean and median of 1.83 and 1.87 Liters. The x-axis represents predictions of IDWG from equation 5.2, and the y-axis represents the observed IDWG. The solid 45^0 line represents the performance of the ideal predictive equation, with thick dashed 45^0 lines on either side to depict +/- 0.5 Liters. Most (15/24, 62.5%) observations fell within 0.5 L of predicted IDWG, and almost all (22/24, 91.7%) fell within 1.0 L of predicted IDWG. The line of best fit of the grouped observations (thin dashed line) was almost superimposed upon the ideal predictive equation (solid line). The

correlation between predicted and observed IDWG (Figure 5.3) was strong (R^2 = 0.51, 95% CI 0.25 to 0.75, p<0.001).

A Bland-Altman plot was completed (Figure 5.4). The x-axis represents the average of predicted (from Equation 5.2) and observed IDWG. The y-axis represents the observed minus the predicted IDWG. The correlation between difference and average IDWG (Figure 5.4) was strong (R^2 = 0.49, 95% CI 0.18 to 0.74, p<0.001), suggesting that the difference between observed and predicted IDWG increases with increasing magnitude of IDWG.

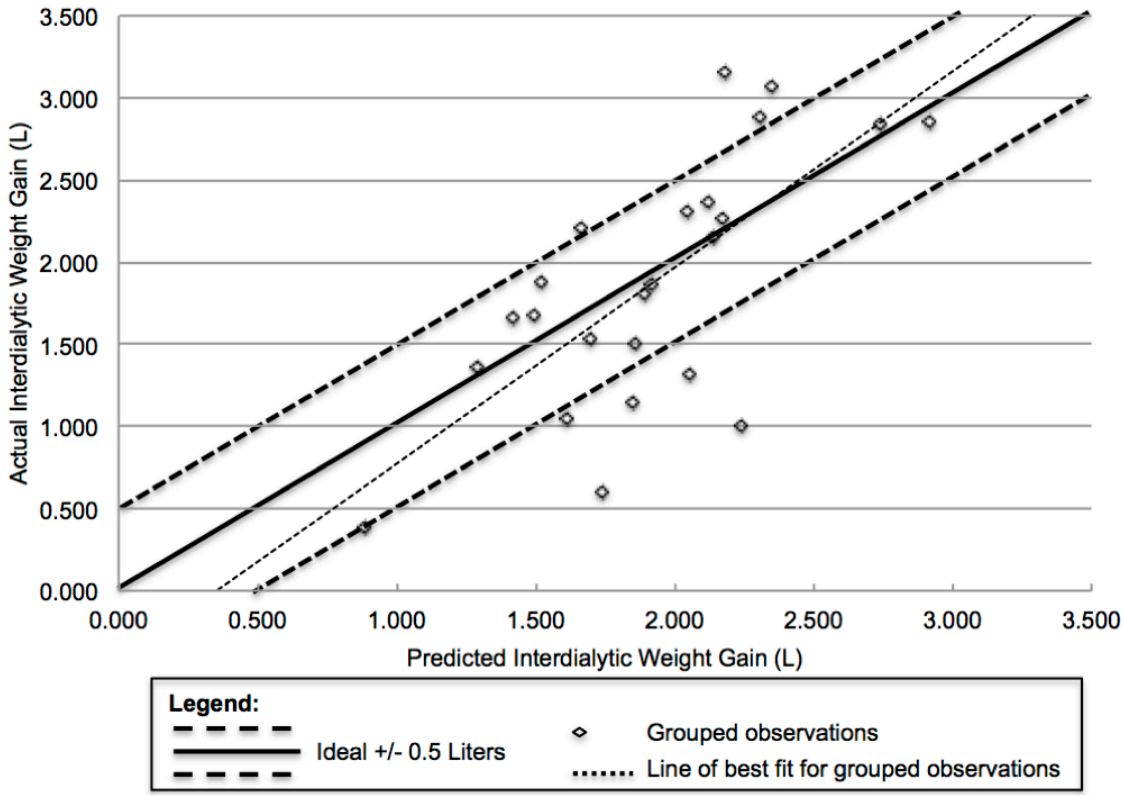

Figure 5.3: Calibration Plot for External Validation Cohort for Equation 5.2

5.4 Discussion

Increased IDWG is associated with hypertension,[1,2,6,8] left ventricular hypertrophy and cardiovascular morbidity and mortality.[3] IDWG is influenced by many factors, but salt balance is one of importance. Dietary salt restriction reduced IDWG, hypertension and

LVH in a Turkish hemodialysis population, while increased salt intake increased IDWG.[21]

Interdialytic Weight Gain (Liters)	Mean	Range	Standard Deviation	Median
All (n=24)	1.83	0.39 to 3.16	0.77	1.87
Short Hours Daily (n=8)	1.27	0.39 to 1.88	0.54	1.44
Intermittent Conventional (n=8)	2.10	1.01 to 3.07	0.73	2.26
Frequent Nocturnal (n=4)	2.07	1.32 to 3.16	0.83	1.90
Intermittent Nocturnal (n=4)	2.42	1.80 to 2.88	0.53	2.50

Table 5.5: Interdialytic Weight Gain in Patients for External Validation

Factors associated with the dialysis treatment may also influence salt balance. The use of a dialysate with a Na+ greater than the pre-dialysis plasma Na+ will lead to diffusive Na+ gain by the patient and therefore the need to increase convective removal by ultrafiltration to restore Na+ balance. Keen and Gotch have shown that the difference between dialysate Na+ and pre-dialysis plasma Na+ positively correlates with IDWG.[22]

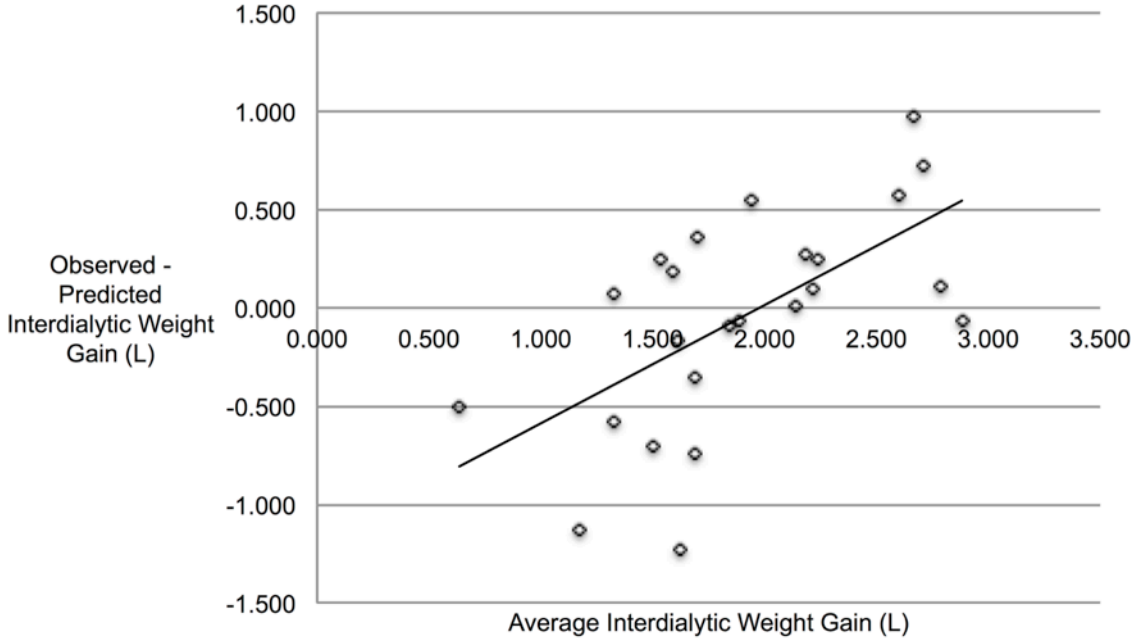

Figure 5.4: Bland-Altman Plot of Observed Minus Predicted Interdialytic Weight Gain Versus Average Interdialytic Weight gain

Several studies have shown that reducing dialysate Na+ concentration will reduce IDWG and improve outcomes.[2-8] The dialysate to patient pre-dialysis Na+ difference is clearly an important factor in this area. Theoretically, the time and frequency of patient exposure to this difference should also influence Na+ balance and IDWG but, to date, this appears to have escaped attention. It may be of relevance that the patients undergoing nightly hemodialysis had significantly higher IDWG than those treated by short hours daily hemodialysis in the London Daily/Nocturnal Hemodialysis study when both were using a dialysate Na+ concentration of 140 mmol/L.[10] Whether reductions in dialysate Na+ concentration are always desirable remains controversial; recent work suggests that reductions in IDWG need to be achieved in context of other potentially adverse outcomes.[23] Prospective controlled trials are certainly indicated.

The reduction of plasma Na+ over the course of dialysis also influences IDWG. We have previously shown that progressive reduction of the end dialysis plasma conductivity (Na+) using a biofeedback control system (DiaControl, Gambro Ab, Sweden) leads to increased ionic mass removal (Na+) by diffusion and significant reductions in IDWG, extracellular water and blood pressure.[24] Whether the dialysate to pre-dialysis plasma Na+ difference, or the pre to post dialysis plasma Na+ change more strongly determines IDWG was uncertain although Hecking and colleagues recently showed that the latter was more predictive of clinical outcomes.[8] The Na+ difference must be the driving force for the plasma Na+ change but other factors will influence that change such as the pre-dialysis plasma Na+ and the duration of the dialysis treatment. It is also possible the plasma albumin via the Gibbs-Donnan effect is of influence.

From the clinical perspective, it is desirable to understand the factors that influence IDWG. There may be factors that can be modified within the dialysis prescription. It is accepted that this cannot be finite and that attention must also be given to psychosocial aspects of salt and water intake. Thus, as part of a Quality Initiative, the records of our home HD patients were examined creating an ideal study because treatment modalities included use of extended times and frequency. Furthermore, pre and post dialysis plasma Na+ levels had been routinely measured.

Knowing the availability of data we chose as possible independent variables that influence IDWG: age, sex, diabetic status, residual renal function, duration and frequency of dialysis treatments, and either DPNa+ or PPNa+. The results of univariable regression analysis showed that PPNa+ was more predictive than DPNa+, supporting the work of Hecking.[8,12] Diabetic status and residual renal function did not appear to predict IDWG based on the univariable and multivariable models (Table 5.2). The remaining independent variables were used in the multivariable analysis in Equation 5.1. This indicated significant associations between IDWG and dialysis frequency, PPNa+, plasma albumin, and age. Female sex was included in this model despite not being statistically significant because it appeared to improve the model.

A moderate correlation of PPNa+ with the product of dialysis duration and DPNa+ was found (Pearson coefficient = 0.4054). Thus, a multivariable linear regression model was developed for Equation 5.2, which determines IDWG as a function of independent variables known before dialysis, eliminating the post-dialysis plasma Na+ value. These are the product of DPNa+ and dialysis duration, plasma albumin, female sex, and dialysis frequency. Patient age was also included in this model despite not being statistically significant, because it generally improved the predictive ability of the model.

An internal bootstrap validation to investigate the predictive properties and model selection was conducted and showed reproducibility of our model selection, suggesting that the predictive model covariates in Equation 5.2 are stable for our data. External validation with a temporally distinct group of new patients showed excellent predictive ability of Equation 5.2. While Bland-Altman plot (Figure 5.4) shows that IDWG is underestimated at high IDWG, almost all (91.7%, 22/24) of observed and predicted IDWG are within 1.0 L, and most (62.5%, 15/25) are within 0.5 L (Figure 5.3). Equation 5.2 does provide clinically important information. The use of a generic dialysate with Na+ content of 140 mmol/L is not desirable for patients undergoing nightly dialysis for 6 to 8 hours per treatment when most (75/86, 87.2%) of the patients have pre-dialysis plasma Na+ levels lower (Figure 5.1). A positive Na+ difference of 5 mmol/L, found in 16.3% (14/86) of our patients, will itself account for 0.42 Liters of IDWG (equation 5.2)

in these circumstances. In most patients, the difference should be zero or even slightly negative. As a result of this quality initiative study, our local practice will change.

The study is limited by the relatively small number of patients studied and the retrospective review of laboratory and dialysis run sheet data (e.g. IDWG). Furthermore, all data points used are aggregates of variable numbers of dialysis and laboratory values obtainable at variable time periods corresponding to patients' attendance at clinics. This may explain why equation 5.1 only provides 30% explanation for IDWG. Post-dialysis weight is not necessarily the dry weight; this likely influences dietary water and salt consumption, neither of which can be easily controlled for.. On the other hand, the study has strengths in that pre and post dialysis plasma Na+ values are available and the fact that a variety of dialysis modalities were used including short hours daily and long nightly.

We have created an equation to predict IDWG on the basis of independent factors readily available before a dialysis session. The modifiable factors include dialysis time and frequency, and dialysate Na+. Patient sex, age and plasma albumin are also correlated to IDWG. Further work is required to establish how improvements in IDWG influence cardiovascular and other clinical outcomes.

5.5 Acknowledgments

The late Paul Heidenheim was instrumental in initiating the database that precipitated this research.

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Chapter 6: Clinical Effects of Personalized Dialysate Sodium in Conventional, Quotidian, and Nocturnal Hemodialysis Patients: A Randomized Crossover Trial.

This manuscript has been submitted for review to *Nephrology Dialysis Transplantation.*

6.1 Introduction

Cardiovascular death is the leading cause of mortality in hemodialysis patients.[1] A chronic state of volume and pressure overload is a major contributor[2-5] leading to hypertension, left ventricular hypertrophy,[6-10] and death.[11,12] Considerable research has evaluated the effect of dialysis frequency and duration on clinical outcomes.[6,13-15] It is well established that longer hemodialysis sessions improve outcomes[13,14,16-19] including mortality.[20-22] How this improvement relates to volume and pressure control remains controversial.

In patients undergoing conventional thrice weekly hemodialysis, pre-dialysis plasma sodium is stable over time,[23,24] and is thus called sodium setpoint (SP). When the dialysate sodium concentration exceeds the SP, diffusion of sodium into the patient occurs, and a number of undesirable clinical outcomes result, including increased interdialytic weight gain (IDWG), blood pressure, and ultrafiltration rate.[25-30] These clinical outcomes are predicted by the magnitude not only of dialysate to pre-dialysis plasma sodium difference (DPNa+), but also by the post to pre-dialysis plasma sodium difference (PPNa+).[30] However, there are no prospective trials evaluating personalized dialysate sodium in patients who dialyze more than thrice weekly, or longer than four hours per session. Quotidian and nocturnal hemodialysis patients are exposed more frequently and longer to a diffusion difference; how this alters clinical outcomes has not been prospectively evaluated.

Three objectives were tested in a randomized crossover study. The first objective was to determine how exposure to a higher DPNa+ altered IDWG, pre- and post-dialysis blood pressure, and ultrafiltration rate, in a study population that included conventional, quotidian and nocturnal hemodialysis patients. The second objective was to determine the effect of dialysis frequency and duration on each of the same clinical outcomes. The third objective was to establish which of PPNa+ or DPNa+ better predicted clinical outcomes.

6.2 Subjects and Methods

Study Population

All patients in the home hemodialysis program of the Southwestern Ontario Regional Renal Program were considered. Patients were excluded if they were under the age of 18, pregnant, or not expected to survive 6 months.

Study Design

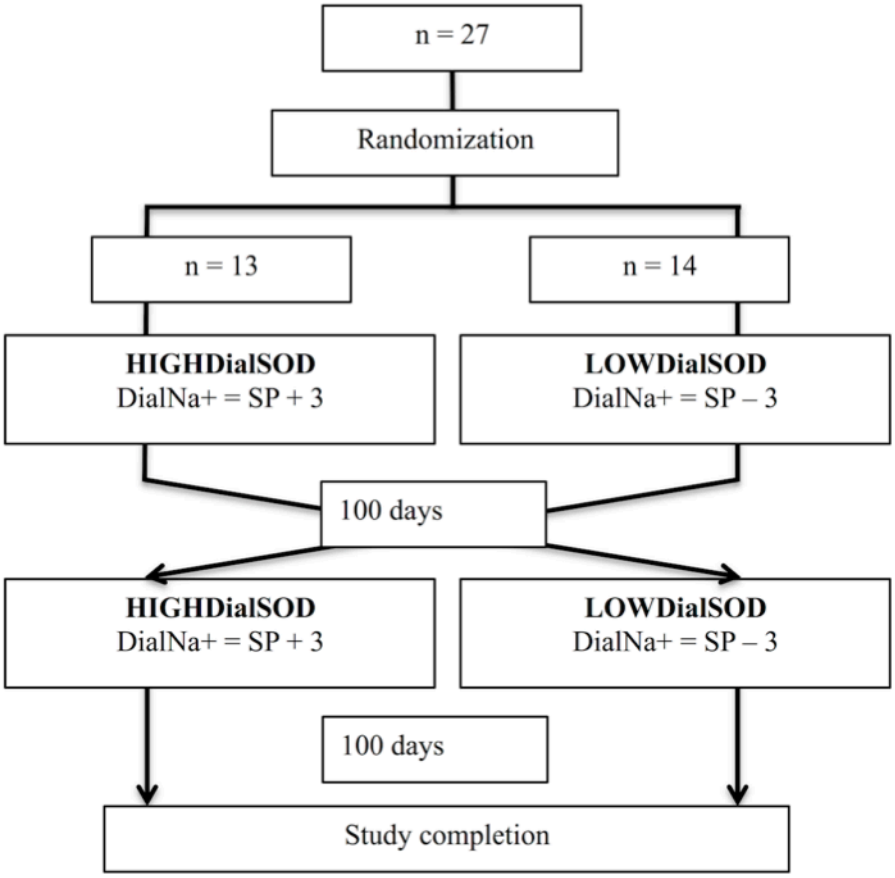
A randomized crossover trial design was used (Figure 6.1). The average of the two most recent monthly pre-dialysis plasma sodium (Pre-Na+) measurements defined the patient's sodium setpoint (SP). Patients were randomized to a dialysate sodium (Dial-Na+) concentration group either 3 mmol/L above (HIGHDialSOD period), or 3 mmol/L below (LOWDialSOD period) their SP (Figure 1). Dialysate sodium concentration range was restricted to between 130 and 150 mmol/L, because of concerns of clinical effects. After 100 days, patients crossed over study periods. Patients were followed for another 100 day period, then the study was completed.

Blood sample collection

Pre-dialysis and post-dialysis blood samples were collected biweekly from the arterial blood line, using a standard slow blood and stop dialysate method. Locking solution (2 mL of 4% citrate) and a small amount of blood (~2 to 5 mL) are spent prior to blood collection. The samples are centrifuged and refrigerated until delivered to the laboratory, within 12 hours of collection. Of interest in this study were pre-dialysis (Pre-Na+) and post-dialysis (Post-Na+) plasma Na+. Only outpatient blood tests were considered, to eliminate the confounding effect of acute illness.

Na+ concentration measurement

Plasma Na+ concentration was measured using Roche Modular P Chemistry Analyzer (Roche Diagnostics, Laval, Quebec, Canada) with ion selective electrodes. Dialysate Na+ concentration was determined using online conductivity measurements in the Fresenius H series hemodialysis machine.



Dial Na+ = dialysate Na+ concentration (mmol/L); SP = Pre-dialysis plasma sodium setpoint (mmol/L); LOWDialSOD = Time period when Dialysate sodium concentration = SP – 3 mmol/L; HIGHDialSOD = Time period when Dialysate sodium concentration = SP + 3 mmol/L

Figure 6.1: Randomized Crossover Study Design

Database creation

Demographic, clinical and hemodialysis data were collected from the electronic patient record (Power Chart by Cerner), home hemodialysis run sheets and the outpatient hemodialysis unit paper chart. Background factors of interest included patient age, sex, diabetes status, height (cm), weight (kg), residual renal function (mL/min x 1.73 m^2) and vintage of hemodialysis (days). Residual renal function was calculated as previously described.[31] Hemodialysis records were used to record target weight (kg) and dialysis frequency (sessions per week) and duration (hours per session) throughout the study.

Outcomes collected included interdialytic weight gain (IDWG), pre- and post-dialysis systolic and diastolic blood pressure, and ultrafiltration volume. IDWG was calculated as the difference between the post-dialysis patient weight and the next dialysis session's pre-dialysis patient weight. Dialysate to pre-dialysis plasma sodium (DPNa+) and post- to pre-dialysis plasma sodium (PPNa+) concentration differences were recorded. We decided *a priori* that a minimum of 3 observations per study period would be required for each outcome, for a patient to be included in the final analysis.

Ethics

Ethics approval was granted by the Western University Health Sciences Research Ethics Board. Informed written consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki.

Statistics

Data were analyzed using the Statistical Package for Social Sciences version 19.0. The mean, median, standard error, and interquartile range were calculated for all background demographic and clinical factors.

Statistics- Objective 1

Each patient's outcomes were averaged for each study period. Patients' outcomes were then averaged for each study period, and compared using paired two-tailed student T-tests, with an α value of 0.05 considered for statistical significance.

Statistics- Objective 2

Pearson correlation coefficients were calculated between each clinical outcome and firstly hemodialysis frequency, then hemodialysis duration. Each patient provided two data points in the analysis, one from each study period. Two-tailed p values with α of 0.05 were used for statistical significance.

Statistics- Objective 3

Pearson correlation coefficients were calculated between each clinical outcome and firstly DPNa+, then PPNa+. Two-tailed p values with α of 0.05 were used for statistical significance.

	HIGHDialSOD Study Period				LOWDialSOD Study Period			
	Mean	Median	Interquartile Range	Standard Deviation	Mean	Median	Interquartile Range	Standard Deviation
Clinical Outcome								
Interdialytic weight gain	46.2	40.0	37.0 - 59.3	21.2	47.0	43.0	34.5 - 60.0	19.4
Pre-dialysis blood pressure	43.4	42.5	35.3 - 57.3	20.8	44.5	41.5	33.3 - 61.8	22.4
Post-dialysis blood pressure	42.4	42.0	34.3 - 55.0	21.8	42.3	40.0	32.5 - 52.8	20.9
Ultrafiltration rate	47.1	42.5	38.3 - 60.3	21.2	48.1	43.5	36.8 - 61.0	19.5
Gradient								
DPNa+	4.15	4.0	3.0 - 5.0	0.97	4.00	4.0	3.3 - 4.8	1.06
PPNa+	3.73	3.5	3.0 - 4.0	1.00	3.27	3.0	3.0 - 4.0	1.15

DPNa+ = dialysate minus Pre-dialysis plasma sodium concentration; PPNa+ = post- minus pre-dialysis plasma sodium concentration; HIGHDialSOD = when Dialysate sodium concentration Setpoint + 3 mmol/L; LOWDialSOD = when Dialysate sodium concentration = Setpoint – 3 mmol/L

Table 6.1: Number of Observations per Clinical Outcome

6.3 Results

A total of 27 patients completed both study periods. All patients had at least 3 observations for each outcome, and were thus included in data analysis. The mean and median observations were greater than 40 for all clinical outcomes in both HIGHDialSOD and LOWDialSOD study periods (Table 6.1). The mean and median observations were at least 3.0 for both DPNa+ and PPNa+ in both study periods.

The study population's background factors included an average age of 54.2 years, with 40.7% female and 33.3% diabetic (Table 6.2). Dialysis frequency averaged 4.4 sessions per week, with a median of 4.0 weekly sessions. Dialysis duration averaged 4.8 hours per session, with a median of 4.0 hours. More than half of study patients had no residual renal function, with a mean of 0.51 and median 0.00 mL/min.

	Mean	Median	Standard Deviation	Interquartile Range
Number Patients	27			
Age (years)	54.2	54.9	11.6	48 – 62
Sex (% female)	40.7			
Diabetes (%)	33.3			
Weight (kg)	82.9	83.1	22.7	69 - 92
Height (cm)	169.9	172.0	12.4	165 - 176
Body mass index (kg/m2)	28.6	27.7	6.6	25 - 32
Dialysis Frequency (sessions per week)	4.4	4.0	1.3	3 -6
Dialysis Duration (hours per session)	4.8	4.0	2.1	3 - 7
Hemodialysis vintage (days)	2539	1654	2720	745 - 3159
Residual renal function (mL/min)	0.51	0.00	1.25	0.00 - 0.00
Systolic blood pressure (mm Hg)	136.6	131.0	23.8	121 - 148
Diastolic blood pressure (mm Hg)	75.6	73.0	12.2	68 - 84
Hemoglobin (g/dL)	113.2	111.0	15.6	106 - 121
Albumin (g/L)	40.8	41.0	3.4	40 - 42

Table 6.2: Background Demographic and Clinical Data

Objective 1

IDWG (2.15 vs. 1.90 kg, p=0.002), IDWG as % target weight (2.78 vs. 2.39%, p=0.002), pre-dialysis systolic (143.3 vs. 138.3 mm Hg, p=0.001), diastolic (78.6 vs. 75.6 mm Hg, p=0.008) and mean arterial pressure (100.2 vs. 96.5 mm Hg, p=0.003) and post-dialysis systolic (135.4 vs. 130.0, p=0.04), diastolic (75.8 vs. 72.4, p=0.006) and mean arterial pressure (95.7 vs. 91.6, p=0.009) were significantly higher in HIGHDialSOD than LOWDialSOD study period (Table 6.3). No change in target weight, or intradialytic change in systolic, diastolic or mean arterial pressure was found.

Objective 2

Hemodialysis frequency was inversely related to IDWG% (R = -0.295, Slope = -0.002, P = 0.034), and positively correlated with post-dialysis diastolic blood pressure (R = 0.366,

slope = 3.464, p=0.008)(Table 6.4). Hemodialysis duration was inversely correlated with ultrafiltration rate (R = -0.593, slope = -0.053, p<0.001) and positively correlated with IDWG (R = 0.562, slope = 0.184, p<0.001) IDWG% (R = 0.507, slope = 0.002, p<0.001) and intradialytic change in diastolic blood pressure (R = 0.280, slope = 1.127, p=0.044).

	HIGHDialSOD STUDY PERIOD	LOWDialSOD STUDY PERIOD	P
Interdialytic weight gain (kg)	2.15	1.90	**0.002**
Interdialytic weight gain (% target weight)	2.78	2.39	**0.002**
Target weight (kg)	82.60	83.58	0.09
Ultrafiltration rate (L/hour)	0.49	0.44	**0.006**
Pre-hemodialysis			
Systolic blood pressure (mm Hg)	143.3	138.3	**0.001**
Diastolic blood pressure (mm Hg)	78.6	75.6	**0.008**
Mean arterial Pressure (mm Hg)	100.2	96.5	**0.003**
Post-hemodialysis			
Systolic blood pressure (mm Hg)	135.4	130.0	**0.04**
Diastolic blood pressure (mm Hg)	75.8	72.4	**0.006**
Mean arterial Pressure (mm Hg)	95.7	91.6	**0.009**
Intradialytic change			
Systolic blood pressure (mm Hg)	-7.9	-8.2	0.90
Diastolic blood pressure (mm Hg)	-3.0	-3.2	0.76
Mean arterial Pressure (mm Hg)	-4.6	-4.9	0.80

HIGHDialSOD = when Dialysate sodium concentration Setpoint + 3 mmol/L; LOWDialSOD = when Dialysate sodium concentration = Setpoint – 3 mmol/L

Table 6.3: Clinical Endpoints for Home Hemodialysis Patients in HIGHDialSOD and LOWDialSOD Study Periods

Objective 3

Increased DPNa+ associated with increased IDWG (R = 0.346, slope = 0.001, p=0.012), pre-dialysis diastolic (R = 0 284, slope = 0.824, p= 0.041) and post-dialysis diastolic (R = 0.325, slope = 1.084, p=0.019) and mean arterial (R = 0.292, slope = 1.030, p=0.036) blood pressure (Table 6.5). Increased PPNa+ associated with increased IDWG (R = 0.306, slope = 0.001, p=0.029) and post-dialysis systolic (R = 0.181, slope = -0.067, p=0.049) blood pressure.

	HEMODIALYSIS FREQUENCY			HEMODIALYSIS DURATION		
CLINICAL OUTCOME	**R**	**SLOPE**	**P**	**R**	**SLOPE**	**P**
Interdialytic weight gain (kg)	-0.228	-0.119	0.097	**0.562**	**0.184**	**<0.001**
Interdialytic weight gain (% target weight)	**-0.295**	**-0.002**	**0.034**	**0.507**	**0.002**	**<0.001**
Ultrafiltration rate (L/hour)	0.143	0.020	0.301	**-0.593**	**-0.053**	**<0.001**
Pre-dialysis blood pressure						
Systolic (mm Hg)	-0.097	-1.460	0.493	0.003	0.028	0.983
Diastolic (mm Hg)	0.204	1.666	0.148	-0.006	-0.032	0.965
Mean arterial pressure (mm Hg)	0.067	0.624	0.636	-0.002	-0.012	0.989
Post-dialysis blood pressure						
Systolic (mm Hg)	0.039	0.571	0.784	0.170	1.546	0.229
Diastolic (mm Hg)	**0.366**	**3.464**	**0.008**	0.179	1.053	0.204
Mean arterial pressure (mm Hg)	0.248	2.500	0.077	0.194	1.217	0.168
Intradialytic change in blood pressure						
Systolic (mm Hg)	0.166	1.960	0.239	0.210	1.534	0.136
Diastolic (mm Hg)	0.262	1.698	0.060	**0.280**	**1.127**	**0.044**
Mean arterial pressure (mm Hg)	0.220	1.767	0.117	0.253	1.258	0.071

Bolded text denotes statistical significance

Table 6.4: Pearson's Correlation of the Clinical Outcome with Hemodialysis Frequency and Duration

6.4 Discussion

In conventional thrice weekly hemodialysis, positive sodium balance is associated with IDWG, hypertension, left ventricular hypertrophy, and cardiovascular morbidity and mortality[5,26-30,32,33] However, the clinical effects of frequent or prolonged exposure to higher dialysate sodium concentrations have not been prospectively evaluated. Our study population included patients on quotidian and nocturnal hemodialysis prescriptions (Table 6.2). There were a high proportion of females (40.7%) and diabetics (33.3%), and a wide spectrum of other demographic factors such as age and body habitus. Furthermore, each patient had multiple measurements of each clinical outcome in each study period. Thus, our study population was representative of a typical hemodialysis population, and the clinical outcomes were rigorously evaluated.

This study confirms that in a patient group with quotidian and nocturnal hemodialysis patients, personalization of Dial-Na+ higher than SP leads to several undesirable clinical outcomes, including IDWG, pre- and post-dialysis systolic, diastolic and mean arterial pressure (Table 6.3). This is consistent with previous trials in thrice weekly conventional hemodialysis patients.[27-30] However, there was no difference in intradialytic change in systolic, diastolic or mean blood pressure between HIGHDialSOD.

	DPNa+			PPNa+		
CLINICAL OUTCOME	**R**	**SLOPE**	**P**	**R**	**SLOPE**	**P**
Interdialytic weight gain (kg)	0.273	0.054	0.050	0.127	0.036	0.374
Interdialytic weight gain (% target weight)	**0.346**	**0.001**	**0.012**	**0.306**	**0.001**	**0.029**
Ultrafiltration rate (L/hour)	0.048	0.003	0.733	-0.072	-0.006	0.616
Pre-dialysis blood pressure						
Systolic (mm Hg)	0.177	1.002	0.209	0.146	1.164	0.306
Diastolic (mm Hg)	**0.284**	**0.824**	**0.041**	-0.054	-0.220	0.707
Mean arterial pressure (mm Hg)	0.264	0.883	0.058	0.051	0.241	0.721
Post-dialysis blood pressure						
Systolic (mm Hg)	0.172	0.921	0.221	**0.181**	**-0.067**	**0.049**
Diastolic (mm Hg)	**0.325**	**1.084**	**0.019**	1.355	-0.312	0.243
Mean arterial pressure (mm Hg)	**0.292**	**1.030**	**0.036**	0.204	0.639	0.731
Intradialytic change in blood pressure						
Systolic (mm Hg)	-0.018	-0.085	0.897	0.037	0.238	0.795
Diastolic (mm Hg)	0.099	0.251	0.483	-0.014	-0.048	0.924
Mean arterial pressure (mm Hg)	0.047	0.147	0.740	0.013	0.055	0.930

Bolded text denotes statistical significance; DPNa+= dialysate minus Pre-dialysis plasma sodium concentration; PPNa+ = post- minus pre-dialysis plasma sodium concentration

Table 6.5: Pearson's Correlation of Clinical Outcomes with DPNa+ and PPNa+ Differences

and LOWDialSOD study periods. Previous trials in thrice weekly conventional hemodialysis patients have demonstrated that low dialysate sodium increases risk for intradialytic hypotension.[34-36] However intradialytic hypotension occurs when increases

in plasma volume from compartments outside plasma occur slower than hemodialysis reduces plasma volume.[35,37] Our study population had longer hemodialysis duration than previous trials (mean 4.8 hours, interquartile range 3 -7 hours, Table 6.2). Since plasma refilling is dependent upon the ultrafiltration rate, longer hemodialysis likely tapered this effect and decreased the dependence of intradialytic blood pressure changes on dialysate sodium concentration.

Whether and how dialysis frequency or duration modifies the clinical outcomes evaluated in this study is of clinical relevance. Our study confirms three important relationships. Firstly, hemodialysis frequency associates with decreased IDWG% (Table 6.4). Consider the common clinical situation of a patient undergoing thrice weekly conventional hemodialysis with persistent volume overload and recurrent intradialytic hypotension. Increased dialysis frequency could improve fluid removal[15,38,39] and a slightly positive DPNa+ difference would protect from intradialytic hypotension.[34,36,40] Our data provide evidence to support increasing hemodialysis frequency to decrease IDWG in such patients. Secondly, hemodialysis duration associates with an increased IDWG and IDWG%. While one might hypothesize that this relates to more prolonged exposure to a DPNa+ difference, the difference was positive in the HIGHDialSOD, but not in the LOWDialSOD study period. Therefore, this could reflect the common practice of avoiding food and drink during hemodialysis; this would disrupt dietary intake for conventional and quotidian, but not nocturnal patients. Thirdly, hemodialysis duration associated with increased intradialytic fall in diastolic blood pressure. Previous research has consistently shown that increased hemodialysis time decreases ultrafiltration rate and risk of intradialytic hypotension,[22,27,34,41] contrary to this study's findings. However, nocturnal hemodialysis patients often sleep during hemodialysis, so post-dialysis blood pressure is measured in the morning in a relaxed state, unlike the shorter hemodialysis sessions in conventional dialysis. Therefore, the intradialytic blood pressure change may relate also to vasomotor tone, rather than ultrafiltration rates.

DPNa+ was superior to PPNa+ in predicting IDWG%, pre-dialysis diastolic, post-dialysis diastolic and mean arterial pressure (Table 6.5). These data are in contrast to a number of trials that suggest PPNa+ to be more predictive.[30,42,43] Plasma Na+ approaches

Dial-Na+ throughout hemodialysis, so intradialytic change in plasma Na+ was predicted to be less than 3 mmol/L in our study, since Dial-Na+ was randomized to be 3 mmol/L above (HIGHDialSOD) or below (LOWDialSOD) the SP. Indeed, mean PPNa+ was quite low in our study (LOWDialSOD PPNa+ = -1.08 mmol/L; HIGHDialSOD PPNa+ = 0.57 mmol/L), so PPNa+ was too small to overcome the lack of precision in the plasma Na+ measurement. However, use of the PPNa+ difference has the disadvantage of using Post-Na+ and therefore not being known prior to a hemodialysis session. Knowing that DPNa+ predicts clinical outcomes better than PPNa+ when Dial-Na+ is 3 mmol/L above or below the SP provides useful information, and helps guide selection of dialysate sodium to improve clinical outcomes. Furthermore, it makes measuring Post-Na+ unnecessary so long as Dial-Na+ is within 3 mmol/L of the Pre-Na+.

This study does have limitations. Firstly, we did not record dialysis membrane surface area or blood glucose,[44-47] each of which can impact diffusive sodium balance on hemodialysis. However, use of a randomized crossover design negated these effects, since each patient served as their own control, and since these factors were unlikely to change for any particular patient between study periods. Secondly, our study population was small. Despite this, an abundance of clinical endpoints and numerous pre- and post-dialysis sodium values were available from all patients on multiple dialysis modalities. We were still able to report important outcomes of statistical and clinical significance.

In conclusion, higher personalized dialysate sodium concentrations lead to increased interdialytic weight gain, pre- and post-dialysis blood pressure, and ultrafiltration rates in a patient population that includes conventional, quotidian and nocturnal hemodialysis patients. While hemodialysis frequency associates with decreased IDWG%, the opposite relationship is seen with hemodialysis duration. Furthermore, longer hemodialysis leads to greater falls in diastolic blood pressure, counter to previous research findings. DPNa+ difference is preferable to PPNa+ to predict clinical outcomes so long as the Dial-Na+ is personalized within 3 mmol/L of the SP. Further work is needed to establish the effect of personalizing the dialysate sodium concentrations on long-term cardiovascular outcomes in quotidian and nocturnal hemodialysis patients.

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Chapter 7: Effect of Personalized Dialysate Sodium Prescription on Plasma Sodium Concentration and Sodium Setpoint in Conventional, Quotidian and Nocturnal Hemodialysis.

This chapter has been submitted for review to *Nephrology Dialysis Transplantation.*

7.1 Introduction

Cardiovascular disease is the leading cause of mortality in hemodialysis patients.[1] Chronic volume and pressure overload are major contributing factors, leading to hypertension, left ventricular hypertrophy and death.[2-5] Several strategies to improve these risk factors have demonstrated success, including dietary sodium restriction,[6,7] increasing hemodialysis frequency and duration,[8-13] and volume management guided by bioimpedance.[14,15] Of recent relevant interest to this topic is the dialysate sodium prescription.[16-18]

Pre-dialysis plasma sodium concentration is relatively stable in thrice weekly conventional hemodialysis patients, and is thus termed the "sodium setpoint" (SP).[19-21] When dialysate sodium concentration is less than SP, increased diffusive sodium removal occurs, leading to improvement in interdialytic weight gain, pre- and post-dialysis blood pressure,[16,18,22-24] and perhaps also in cardiovascular outcomes and mortality.[25,26] However, marked reduction in dialysate sodium concentration gives rise to intradialytic symptoms including intradialytic hypotension.[27,28] This may be mediated by intradialytic shifts in plasma sodium concentration.[27]

While effects of personalized dialysate sodium prescription are well described in conventional thrice weekly hemodialysis patients, these outcomes have not been prospectively evaluated in quotidian or nocturnal hemodialysis patients. Whether plasma sodium concentration changes during more frequent or longer hemodialysis sessions is unknown, and whether such changes impact the sodium setpoint has not been prospectively evaluated. Three objectives were tested in a randomized crossover study, in conventional, quotidian and nocturnal home hemodialysis patients. Our first objective was to determine if personalized dialysate sodium prescription modified plasma sodium concentration from the start to the end of a hemodialysis session. Our second objective was to determine if a change in dialysate sodium concentration altered the pre-dialysis sodium setpoint. Our third objective was to determine if dialysis frequency or duration modulated changes in either plasma sodium throughout dialysis or sodium setpoint.

7.2 Materials and Methods

Study Population

All patients in the home hemodialysis program of the Southwestern Ontario Regional Renal Program were considered. Patients were excluded if they were under the age of 18, pregnant, or not expected to survive 6 months.

Study Design

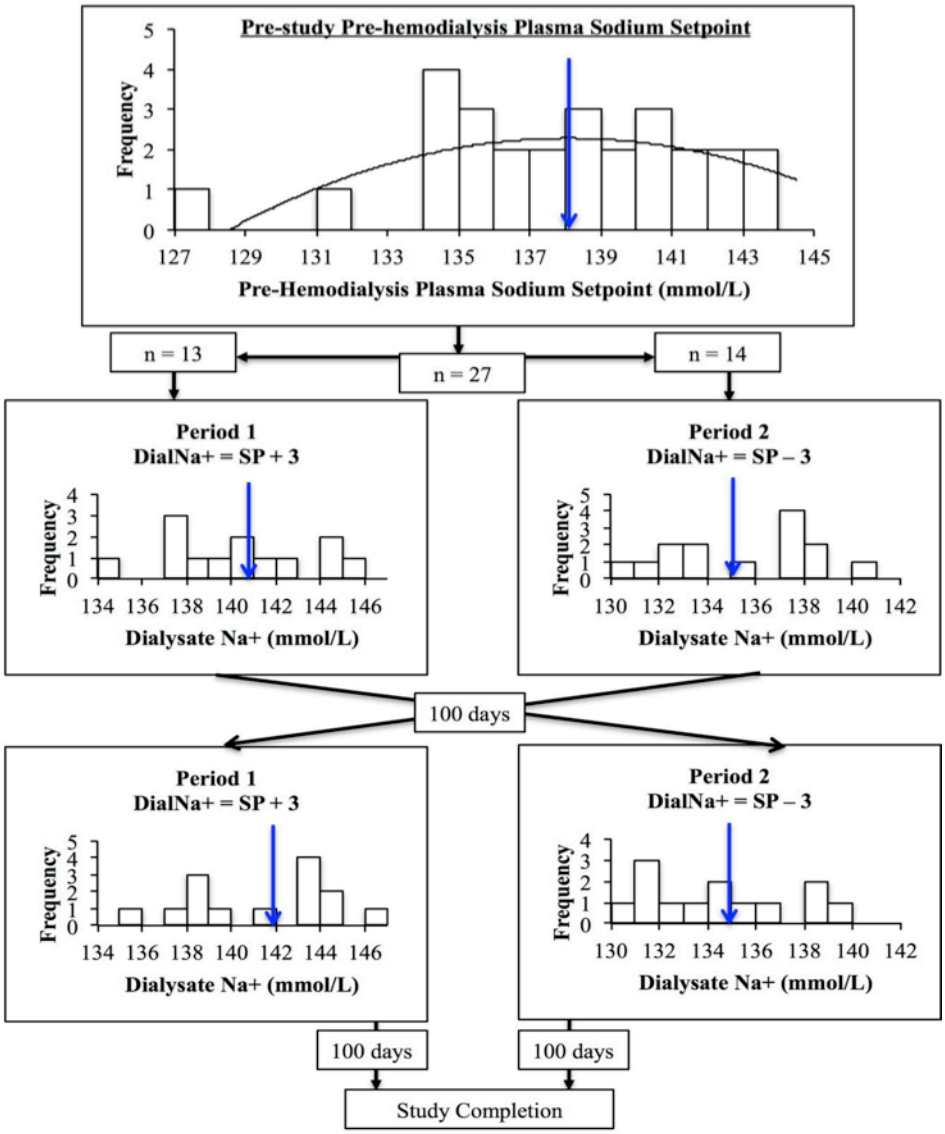
A randomized crossover trial design was used. The average of the two most recent monthly pre-dialysis plasma sodium (Pre-Na+) measurements defined the patient's sodium setpoint (SP). Patients were randomized to a dialysate sodium (Dial-Na+) concentration group either 3 mmol/L above (DialNa+ = SP + 3 = HIGHDialSOD), or 3 mmol/L below (DialNa+ = SP – 3 = LOWDialSOD) their SP (Figure 7.1). Dialysate sodium concentration range was restricted to between 130 and 150 mmol/L, because of concerns of clinical effects. After 100 days, patients crossed over study periods. Patients were followed for another 100 day period, then the study was completed.

Blood sample collection

Pre-dialysis and post-dialysis blood samples were collected biweekly from the arterial blood line, using a standard slow blood and stop dialysate method. Locking solution (2 mL of 4% citrate) and a small amount of blood (~2 to 5 mL) are spent prior to blood collection. The samples are centrifuged and refrigerated until delivered to the laboratory, within 12 hours of collection. Of interest in this study were pre-dialysis (Pre-Na+) and post-dialysis (Post-Na+) plasma Na+. Only outpatient blood tests were considered, to eliminate the confounding effect of acute illness.

Na+ concentration measurement

Plasma Na+ concentration was measured using Roche Modular P Chemistry Analyzer (Roche Diagnostics, Laval, Quebec, Canada) with ion selective electrodes. Dialysate Na+ concentration was determined using online conductivity measurements in the Fresenius H series hemodialysis machine.



SP = Plasma sodium setpoint (mmol/); DialNa+ = dialysate Na+ concentration (mmol/L); Blue arrow denotes mean

Figure 7.1: Prospective Randomized Crossover Study Design

Database creation

Demographic, clinical and hemodialysis data were collected from the electronic patient record (Power Chart by Cerner), home hemodialysis run sheets and the outpatient hemodialysis unit paper chart. Background factors of interest included patient age, sex, diabetes status, height (cm), weight (kg), residual renal function (mL/min x 1.73 m^2) and

vintage of hemodialysis (days). Residual renal function was calculated as previously described.[29] Hemodialysis records were used to record dialysis frequency (sessions per week) and duration (hours per session) throughout the study.

Dialysate to pre-dialysis plasma sodium difference (DPNa+) and post-dialysis (Post-Na+) to pre-dialysis (Pre-Na+) plasma sodium difference (PPNa+) concentration were also recorded. We decided *a priori* that a minimum of 3 observations per DPNa+ and PPNa+ would be required in each of HIGHDialSOD and LOWDialSOD study periods for a patient to be included in the final analysis.

Ethics

Ethics approval was granted by the Western University Health Sciences Research Ethics Board. Informed written consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki.

Statistics

Data were analyzed using the Statistical Package for Social Sciences version 19.0. The mean, median, standard error, and interquartile range were calculated for all background demographic and clinical factors.

Statistics- Objective 1

The average pre- and post-dialysis plasma sodium concentrations were calculated for each patient for each study period. The group average pre- and post-dialysis plasma sodium concentrations were then compared between HIGHDialSOD and LOWDialSOD, using paired two-tailed student t-tests with an α value of 0.05 considered for statistical significance.

Statistics- Objective 2

A change in SP was defined in two ways (Figure 7.2). Firstly, the average Pre-Na+ differed between HIGHDialSOD and LOWDialSOD study periods. Secondly, the slope of Pre-Na+ (M100) over time differed between study periods. Differences were detected

using paired two-tailed student t-tests with an α value of 0.05 considered for statistical significance.

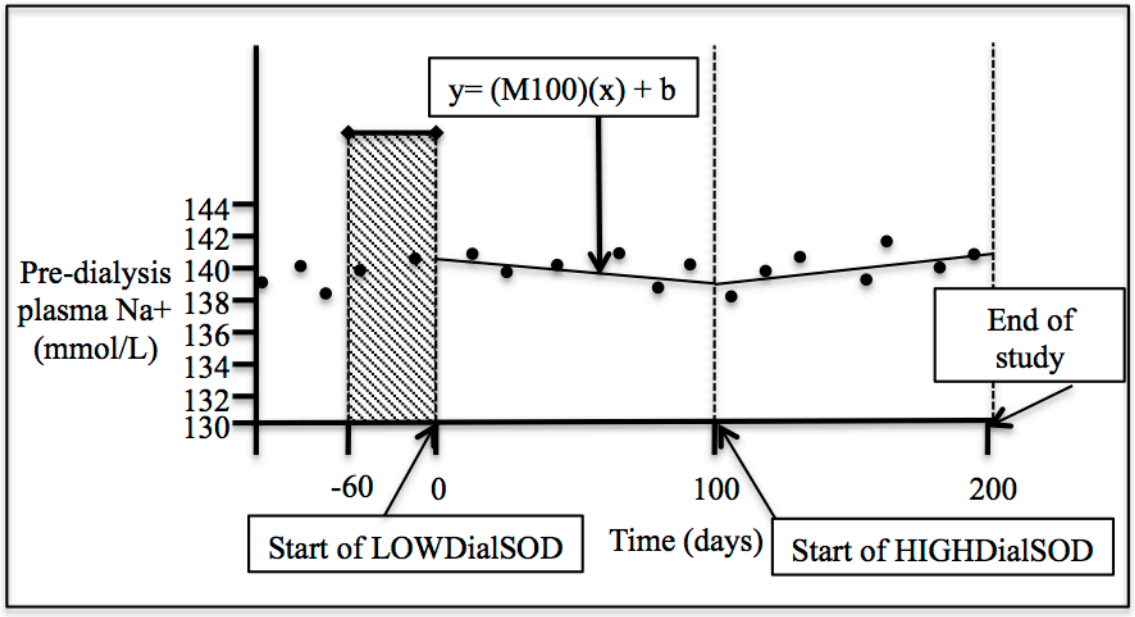


Figure 7.2: Endpoints to Determine Change in Pre-Dialysis Plasma Sodium Setpoint

Statistics- Objective 3

Pearson correlation coefficients were calculated to determine if changes in SP were modulated by hemodialysis frequency or duration. Y axis included either change in pre-Na+ or slope of Pre-Na+ from HIGHDialSOD to LOWDialSOD study periods. X axis included hemodialysis frequency or duration. Slope of correlation was calculated and two-tailed p values were determined with an α value of 0.05 for statistical significance.

7.3 Results

A total of 27 patients completed both study periods. All patients had at least 3 observations for each of DPNa+ and PPNa+, and were thus included in the final analysis. Mean and median SP was 138.1 and 138.5 mmol/L, with an interquartile range of 135.5 to 141.0 mmol/L (Figure 7.1, Table 7.1). The study population was an average age of 54.2 years, with 40.7% female and 33.3% diabetic (Table 7.1). Dialysis frequency

averaged 4.4 sessions per week, with a median of 4.0 weekly sessions. Dialysis duration averaged 4.8 hours per session, with a median of 4.0 hours. More than half of patients had no residual renal function, with a mean of 0.51 and median 0.00 mL/min.

	Mean	Median	Standard Deviation	Interquartile Range
Number Patients	27			
Pre-dialysis plasma sodium setpoint (mmol/L)	138.1	138.5	3.8	135.5 - 141.0
Age (years)	54.2	54.9	11.6	48 - 62
Sex (% female)	40.7			
Diabetes (%)	33.3			
Weight (kg)	82.9	83.1	22.7	69 - 92
Height (cm)	169.9	172.0	12.4	165 - 176
Body mass index (kg/m2)	28.6	27.7	6.6	25 - 32
Dialysis Frequency (sessions per week)	4.4	4.0	1.3	3 -6
Dialysis Duration (hours per session)	4.8	4.0	2.1	3 - 7
Vintage (days)	2539	1654	2720	745 - 3159
Residual renal function (mL/min)	0.51	0.00	1.25	0.00 - 0.00
Systolic Blood Pressure (mm Hg)	136.6	131.0	23.8	121 - 148
Diastolic Blood Pressure (mm Hg)	75.6	73.0	12.2	68 - 84
Hemoglobin (g/dL)	113.2	111.0	15.6	106 - 121
Albumin (g/L)	40.8	41.0	3.4	40 - 42

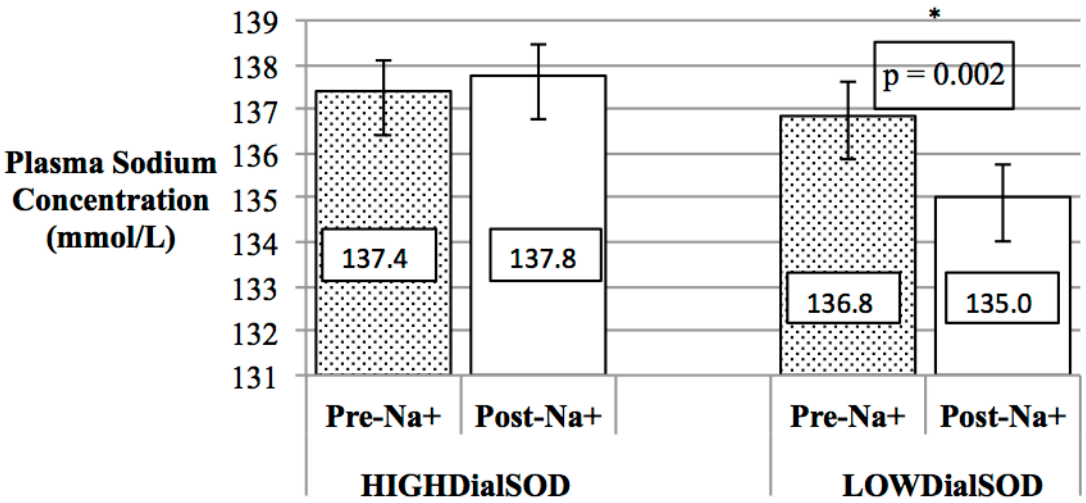
Table 7.1: Background Demographic and Clinical Data

Objective 1

Pre-Na+ and Post-Na+ did not differ in HIGHDialSOD study period (137.4 to 137.8 mmol/L, p=0.45). However, plasma Na+ fell throughout dialysis (136.8 to 135.0 mmol/L, p=0.002) in LOWDialSOD study period (Figure 7.3).

Objective 2

Pre-Na+ sodium setpoint decreased from HIGHDialSOD to LOWDialSOD study period (137.4 to 136.8 mmol/L, p=0.03) (Table 7.2). The slope of Pre-Na+ (M100) also decreased from HIGHDialSOD to LOWDialSOD study periods (0.014 to -0.015 mmol/L/day, p=0.009).



HIGHDialSOD= when Dialysate sodium concentration is 3 mmol/L greater than pre-dialysis plasma sodium "setpoint"; LOWDialSOD=when Dialysate sodium concentration is 3 mmol/L lower than pre-dialysis plasma sodium "setpoint."

Figure 7.3: Pre and Post-Dialysis Plasma Sodium Concentration with High (Period 1) or Low (Period 2) Personalized Dialysate Sodium

Objective 3

The change in Pre-Na+ across study periods was not correlated to hemodialysis frequency (R = 0.264, p=0.193) or duration (R = 0.032, p=0.877) (Table 7.3). Likewise, the change in slope of Pre-Na+ across study periods was not correlated to hemodialysis frequency (R = 0.172, p=0.401) or duration (R=0.067, p=0.745).

7.4 Discussion

Reduction in dialysate sodium concentration can reduce IDWG, blood pressure and negative cardiovascular outcomes.[16,18,23] However, it may also give rise to intradialytic hypotension,[27,28] mediated by intradialytic shifts in plasma sodium concentration.[27] Whether personalized dialysate sodium prescription associates with intradialytic shifts in plasma sodium in quotidian or nocturnal hemodialysis patients is previously unreported.

	Study Period		
Outcome	**HIGHDialSOD**	**LOWDialSOD**	**p**
Pre-dialysis plasma sodium (mmol/L)	**137.4**	**136.8**	**0.03**
Slope of pre-dialysis plasma sodium [(mmol/L)/day]	**0.014**	**-0.015**	**0.009**

HIGHDialSOD = Dialysate sodium concentration 3 mmol/L higher than pre-dialysis sodium setpoint; LOWDialSOD = Dialysate sodium concentration 3 mmol/L lower than pre-dialysis sodium setpoint. **Bolded** text denotes statistically significant changes.

Table 7.2: Difference in Absolute and Slope of Pre-Dialysis Plasma Sodium Setpoint with Two Personalized Dialysate Sodium Concentrations

	Dialysis Frequency			Dialysis Duration		
Outcome	**R**	**Slope**	**P**	**R**	**Slope**	**P**
Pre-dialysis plasma sodium (Pre-Na+)(mmol/L)	0.264	0.464	0.193	0.032	0.036	0.877
Slope pre-dialysis plasma sodium (mmol/L/day)	0.172	0.007	0.401	0.067	0.002	0.745

P = p value; R = Pearson's correlation coefficient

Table 7.3: Effect of Hemodialysis Frequency and Duration on Change Across Study Periods in Absolute and Slope of Pre-Dialysis Sodium Setpoint

This randomized crossover study included patients with a spectrum of dialysis frequency (mean = 4.4, interquartile range = 3 to 6 sessions per week) and duration (mean = 4.8, interquartile range 3-7 hours)(Table 7.1). There was a high number of females (40.7%) and diabetics (33.3%) and a wide spectrum of other demographic and clinical factors such as blood pressure, age and body habitus. Every patient had at least 3 recordings of PPNa+ and DPNa+ during each study period. The sodium setpoint (SP) varied widely in our study population (interquartile range 135.5 to 141.0, Table 1 and Figure 7.1). Thus, our study population was representative of a typical hemodialysis population, and outcomes were evaluated with rigor.

While the HIGHDialSOD plasma sodium did not change over dialysis (137.4 to 137.8 mmol/L, p=0.45), there was a significant decrease from Pre-Na+ to Post-Na+ in the LOWDialSOD study period (136.8 to 135.0 mmol/L, p=0.002)(Figure 7.3). This is consistent with Suckling *et al*'s recent work.[27] While the magnitude of intradialytic plasma sodium change was small in our study, there is still reason for concern. Firstly, intradialytic decrease in plasma sodium is linked to intradialytic hypotension,[27] which independently increases risk of death.[28] Secondly, ignoring patient-specific SP by facility level decreases in dialysate sodium concentrations will lead to significantly negative DPNa+ differences in some patients. Again, this increases the risk of intradialytic hypotension. Ultimately, selection of dialysate sodium should be personalized to the patient to limit adverse outcomes of a very positive DPNa+, while simultaneously avoiding the complications of intradialytic plasma sodium shifts from a negative DPNa+; this can only be done by regularly following the Pre-Na+ and adjusting the Dial-Na+ accordingly.

While Pre-N+ is stable as a "setpoint" in thrice weekly conventional hemodialysis patients,[19-21] this has not been prospectively evaluated in quotidian or nocturnal hemodialysis patients. A retrospective study by our research group found that conversion from thrice weekly conventional to quotidian hemodialysis associated with a reduction in SP, when DPNa+ was neutral or negative.[30] We confirm a change in SP prospectively in this study, as mean pre-Na+ (137.4 vs. 136.8 mmol/L, p=0.03) and slope of pre-Na+ (0.014 vs. -0.015 mmol/L/day, p=0.009)(Table 2) differ between HIGHDialSOD and LOWDialSOD study periods. While the magnitude of the change in pre-Na+ is small, this is both statistically and clinically important. Firstly, decreases in sodium setpoint are independently associated with increased mortality.[31,32] Secondly, hemodialysis units that use facility wide dialysate sodium prescriptions will lead many patients to having highly negative DPNa+ and thus more exaggerated decreases in SP. Thirdly, in units that personalize dialysate sodium by following Pre-Na+, repeated decreases in Dial-Na+ to maintain a negative DPNa+ could cause repeated and undesirable decreases in SP. Finally, this raises the possibility that hemodialysis prescription might be modified to increase SP in vulnerable patients. More research will be required to determine the

pathophysiologic mechanism of a change in SP in these patients, and to determine the impact on cardiovascular outcomes.

There are limitations to this study. Firstly, we did not measure blood glucose, lipids or paraprotein levels, each of which can impact plasma sodium measurement.[33-35] However, use of a randomized crossover study design negated these effects, since each patient served as their own control, and since these factors were unlikely to change for any particular patient between study periods. Secondly, our study population was small. However, our patients are highly compliant, having participated in multiple previous research trials.[12,13] This enabled the recording of numerous pre- and post-dialysis sodium values from all patients on multiple hemodialysis modalities. We were thus able to report statistically and clinically significant outcomes.

In conventional, quotidian and nocturnal hemodialysis patients, the personalization of Dial-Na+ to lower than the SP decreases plasma sodium throughout hemodialysis. Furthermore, Dial-Na+ can modify the Pre-Na+ "setpoint." Further research is needed to determine the effect on cardiovascular morbidity and mortality.

7.5 Acknowledgments

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Chapter 8: General Discussion and Conclusions

8.0 General Discussion and Conclusions

The most common cause of death in patients with end stage kidney disease is cardiovascular (Figure 1.1).[1] A major contributor is the chronic state of volume and pressure overload,[2-8] which leads to left ventricular hypertrophy[9-17] and death.[18,19] Of critical importance is the total sodium balance during a hemodialysis session,[8,20-24] which is determined by the sum of diffusion and osmosis.

Diffusive balance during hemodialysis reflects the effects of several factors (Equation 1.4). Many factors are not modifiable, such as dialyzer hollow fiber radius (Chapter 1.1.1.1 and 1.1.1.2), length (Chapter 1.1.1.1 and 1.1.1.3) or thickness (Chapter 1.1.1.4). Likewise, several factors must be maintained within a narrow range, such as dialysate temperature (Chapter 1.1.1), patient hematocrit and albumin (Chapter 1.1.1.8). On the other hand, the hemodialysis frequency and duration can be modified, as can the difference between dialysate and pre-hemodialysis plasma sodium concentrations (DPNa+). In Chapter 4, using retrospective data, we confirm that the post- to pre-dialysis plasma sodium difference (PPNa+) is superior to DPNa+ to predict clinical outcomes such as interdialytic weight gain, blood pressure, and the change in blood pressure during a hemodialysis session.[25] However, the opposite was found using prospective data (Chapter 6). This could be because the magnitude of the DPNa+ and PPNa+ difference was much smaller as the study design involved personalization of the dialysate sodium within 3 mmol/L from the pre-hemodialysis plasma sodium concentration, or "setpoint." This is an important observation for three reasons. Firstly, there is no clinical advantage to current practice of performing pre- and post-hemodialysis plasma sodium concentrations, so long as the dialysate sodium concentration is within 3 mmol/L of the setpoint. Secondly, the dialysate sodium concentration can be chosen before a dialysis session, making it modifiable, unlike the post-dialysis plasma sodium concentration. Finally, it confirms that the selection of dialysate sodium concentration greater than the setpoint leads to undesirable increases in interdialytic weight gain and blood pressure.

Selection of dialysate sodium concentration within 3 mmol/L of the setpoint requires knowing it will remain stable over time. Previous trials confirm setpoint stability in thrice weekly conventional hemodialysis.[26-28] However, the setpoint is not stable in a patient population of quotidian, conventional and nocturnal hemodialysis patients, retrospectively in Chapter 3,[29] nor prospectively in Chapter 7. Use of a Dial-Na+ of 140 mmol/L led to decrease in setpoint in patients with pre-hemodialysis plasma sodium concentration greater than or equal to 140 mmol/L (Chapter 3). Furthermore, personalization of dialysate sodium concentration 3mmol/L less than the SP leads to a decrease in setpoint (Chapter 7). Given that low pre-hemodialysis plasma sodium concentration independently predicts mortality,[30] this is an important observation. This gives pause to the practice of increasing diffusive sodium loss by using a dialysate sodium concentration lower than the pre-hemodialysis plasma sodium concentration. Further research is required to determine if intentional increases in setpoint are possible or beneficial for cardiovascular and all-cause morbidity and mortality.

The factors that determine interdialytic weight gain are important to delineate, so that they may be modified prior to a hemodialysis session. In Chapter 5, those variables were determined to be dialysis time, frequency and dialysate sodium.[31] Furthermore, several unmodifiable factors were important, including patient sex, age and serum albumin. Ultimately, an equation was created that was validated internally using bootstrapping and externally using a temporally distinct patient subset. Our research group is currently prospectively validating this equation, with a dataset that includes patients with a variety of dialysate sodium concentrations, dialysis durations and frequencies, and residual renal functions. We hope to finish this work by June, 2015.

As plasma water is removed from a patient, plasma hematocrit increases during hemodialysis, causing an increase in blood viscosity (Section 1.1.1.8). As interdialytic weight gain increases, the requirement for fluid removal during hemodialysis also increases, and thus also blood viscosity. Since increases in blood viscosity lead to decreased diffusive sodium loss (Equation 1.5), one might hypothesize that the increased mortality from higher interdialytic weight gain occurs partially due to decreased solute clearance towards the end of hemodialysis, when blood viscosity reaches its maximum.

As our equation is validated in more populations, we will need to establish the effect of blood viscosity on solute clearance and mortality. This hypothesis evidently needs further evaluation.

While hemodialysis equipment modification was not the focus of this thesis, it is noteworthy that the design of materials already considers Poiseuille's Law (Equation 1.7). Specifically, it is desirable not to have increased pressure drop across the hollow fiber of the dialysis membrane; this prevents backfiltration of the dialysate, which is undesirable (Section 1.1.1.2 and 1.1.1.3). Even a small (10%) increase in hollow fiber radius causes a large (46%) decrease in blood flow resistance. So long as the blood flow is constant, this leads to a significant increase in the pressure drop over a hollow fiber, which again leads to backfiltration of dialysate (Equation 1.8). Similarly, a long hollow fiber would increase pressure drop (Equation 1.7), but would also increase surface area for diffusion (Equation 1.6). It is thus inevitable that advances in hemodialysis technology will play a key role in optimizing safe diffusive and osmotic sodium removal in the years to come. In light of these future trials designed to improve hemodialysis technology, our work will play a key role in assuring their safe and effective design. Specifically, it will be essential to monitor the pre-dialysis plasma sodium setpoint to assure stability. Use of the DPNa+ and PPNa+ concentration differences under particular circumstances that have been defined by our studies will also be important. Finally, focusing on factors that are modifiable for patients' interdialytic weight gain will improve the yield of such studies.

Hemodialysis prescription continues to be an essential consideration in improving cardiovascular mortality in patients with end stage kidney disease. Future research will need to combine dialysis prescription with monitoring measurements such as bioimpedance. While low dialysate sodium improves clinical outcomes such as interdialytic weight gain and blood pressure, it is associated with decrease in setpoint in patients on frequent or longer hemodialysis treatments. It is thus proposed that sodium balance-neutral or slightly positive is a preferable choice, ensuring quality dialysis with minimal sodium gain-related complications. Only with careful monitoring of pre-dialysis

setpoint and personalized selection of dialysis frequency, duration and dialysate sodium concentration can outcomes be optimized.

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5. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int.* Mar 2003;63(3):793-808.

6. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Greenland S, Kopple JD. Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: the 58th annual fall conference and scientific sessions. *Hypertension.* Apr 2005;45(4):811-817.

7. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, et al. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation.* Feb 10 2009;119(5):671-679.

8. Kimmel PL, Varela MP, Peterson RA, et al. Interdialytic weight gain and survival in hemodialysis patients: effects of duration of ESRD and diabetes mellitus. *Kidney Int.* Mar 2000;57(3):1141-1151.

9. Agarwal R, Bouldin JM, Light RP, Garg A. Probing dry-weight improves left ventricular mass index. *Am J Nephrol.* 2011;33(4):373-380.

10. Chan CT, Greene T, Chertow GM, et al. Determinants of left ventricular mass in patients on hemodialysis: Frequent Hemodialysis Network (FHN) Trials. *Circ Cardiovasc Imaging.* Mar 2012;5(2):251-261.

11. Foley RN, Curtis BM, Randell EW, Parfrey PS. Left ventricular hypertrophy in new hemodialysis patients without symptomatic cardiac disease. *Clin J Am Soc Nephrol.* May 2010;5(5):805-813.

12. Io H, Matsumoto M, Okumura K, et al. Predictive factors associated with left ventricular hypertrophy at baseline and in the follow-up period in non-diabetic hemodialysis patients. *Semin Dial.* May-Jun 2011;24(3):349-354.

13. Khangura J, Culleton BF, Manns BJ, et al. Association between routine and standardized blood pressure measurements and left ventricular hypertrophy among patients on hemodialysis. *BMC Nephrol.* 2010;11:13.

14. Koc Y, Unsal A, Kayabasi H, et al. Impact of volume status on blood pressure and left ventricle structure in patients undergoing chronic hemodialysis. *Ren Fail.* 2011;33(4):377-381.

15. Patel RK, Oliver S, Mark PB, et al. Determinants of left ventricular mass and hypertrophy in hemodialysis patients assessed by cardiac magnetic resonance imaging. *Clin J Am Soc Nephrol.* Sep 2009;4(9):1477-1483.

16. Wald R, Goldstein MB, Wald RM, et al. Correlates of left ventricular mass in chronic hemodialysis recipients. *Int J Cardiovasc Imaging.* Feb 2014;30(2):349-356.

17. Seibert E, Muller SG, Fries P, et al. Calf bioimpedance spectroscopy for determination of dry weight in hemodialysis patients: effects on hypertension and left ventricular hypertrophy. *Kidney Blood Press Res.* 2013;37(1):58-67.

18. London GM, Pannier B, Guerin AP, et al. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol.* Dec 2001;12(12):2759-2767.

19. Devereux RB, Wachtell K, Gerdts E, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. *Jama.* Nov 17 2004;292(19):2350-2356.

20. Flythe JE, Curhan GC, Brunelli SM. Disentangling the ultrafiltration rate-mortality association: the respective roles of session length and weight gain. *Clin J Am Soc Nephrol.* Jul 2013;8(7):1151-1161.

21. Lopez-Gomez JM, Villaverde M, Jofre R, Rodriguez-Benitez P, Perez-Garcia R. Interdialytic weight gain as a marker of blood pressure, nutrition, and survival in hemodialysis patients. *Kidney Int Suppl.* Jan 2005(93):S63-68.

22. Ozkahya M, Ok E, Toz H, et al. Long-term survival rates in haemodialysis patients treated with strict volume control. *Nephrol Dial Transplant.* Dec 2006;21(12):3506-3513.

23. Sezer S, Ozdemir FN, Arat Z, Perim O, Turan M, Haberal M. The association of interdialytic weight gain with nutritional parameters and mortality risk in hemodialysis patients. *Ren Fail.* Jan 2002;24(1):37-48.

24. Brown TA. Sodium and Water Balance, Fluid Compartments. In: Goljan EF, ed. *Rapid Review Physiology, 2nd Edition*: Elsevier Publishers; 2011.

25. Thomson BK, Huang SH, Leitch RE, et al. Pre to post-dialysis plasma sodium change better predicts clinical outcomes than dialysate to plasma sodium gradient in quotidian hemodialysis. *Hemodial Int.* Oct 2013;17(4):548-556.

26. Peixoto AJ, Gowda N, Parikh CR, Santos SF. Long-term stability of serum sodium in hemodialysis patients. *Blood Purif.* 2010;29(3):264-267.

27. Keen ML, Gotch FA. The association of the sodium "setpoint" to interdialytic weight gain and blood pressure in hemodialysis patients. *Int J Artif Organs.* Nov 2007;30(11):971-979.

28. Basile C, Libutti P, Lisi P, et al. Sodium setpoint and gradient in bicarbonate hemodialysis. *J Nephrol.* Nov-Dec 2013;26(6):1136-1142.

29. Thomson BK, Huang SH, Chan CT, House AA, Lindsay RM. Plasma sodium setpoint: is it constant or changed by hemodialysis prescription? *Asaio J.* Sep-Oct 2013;59(5):497-504.

30. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int.* Sep 2004;66(3):1212-1220.

31. Thomson BK, Dixon SN, Huang SH, et al. Modifiable variables affecting interdialytic weight gain include dialysis time, frequency, and dialysate sodium. *Hemodial Int.* Oct 2013;17(4):576-585.

Chapter 9: Curriculum Vitae

BENJAMIN K.A. THOMSON
B.Sc (Hon), M.Sc., MB, BCh, BAO, FRCPC
Last update: October 24, 2014

FACULTY APPOINTMENTS

Adjunct Professor, Western University (Department of Internal Medicine)
(July 2012-present)
1. Attending Physician, Inpatient Clinical Teaching Unit (CTU) 10 weeks/annum
2. Initiator and Physician of Refugee Internal Medicine outpatient clinic,
London Intercommunity Health Clinic *(February 2014-present)*

Adjunct Professor, Western University (Department of Nephrology**)**
(*July 2012-present)*
1. Attending Physician, Nephrology Inpatient service, 4 to 6 weeks per annum
2. Nephrology and Chronic Kidney Disease outpatient clinic, one to two times weekly

MEDICAL EDUCATOR

(30 hrs/yr) **Schulich School of Medicine,** Mentor
(August, 2014-present)
Mentor in "Professional Portfolio program" for first year medical students

(12 hrs/yr) **Schulich School of Medicine**, Medical student educator
(*January 2012-present)*
Lead small group session for 10 medical students in genitourinary medicine

(91 hrs/yr) **Schulich School of Medicine**, Curriculum Committee member
(*July 2013-present)*
Course Advisor, "Physicians as Leaders": Curriculum development, lecture presenter, recruiter of guest speakers

(150 hrs/yr) **Book Primary Author,** Critical References Nephrology
(*July 2013)*
Summarized the importance of the most essential trials for 62 clinical nephrology topics, to be updated annually.

(122 hrs/yr) **General Internal Medicine teaching** (PGY-4)
(*July 2012-present)*
1. Initiated and led internal medicine preparation course
2. Designed comprehensive examination preparation sessions for all PGY-4
3. Presented more senior medicine resident (SMR) rounds than any physician in London Health Science Center; my format now used as template for SMR rounds
4. Ultrasound procedure course (Mar-May 2014); central line and lumbar puncture expert
5. Presenter of Nephrology Emergencies Summer Series for internal medicine residents.

(150 hrs) **Chief Nephrology Fellow**
(*July 2011-July 2012)*
1. Initiated and created 2 year academic half-day nephrology curriculum
2. Renal Physiology Course: Initiator, Designer, Creator.
3. Initiated and created nephrology academic half-day evaluation system
4. Created, and chief editor of UWO Nephrology Quarterly Newsletter

University of Calgary **Internal Medicine Residency** (PGY-1 to PGY-3)
(*July, 2007-June,2010)*
Taught as part of "Master Teacher" program, to first year residents and medical students, rated "excellent" overall (2nd highest rating out of 6)

National University of Ireland: Biochemistry Lecturer
(*Sept 2005-June 2006)*
1. Initiated evaluation process for lecturers
2. Evaluated to be 2nd best lecturer in department of 15 lecturers.

PERSONAL EDUCATION

Western University: Nephrology Research Fellowship	*July 2012-present*
Clinical Investigator Program**:** Western University	*July 2012 – June 2014*
Western University**:** M.Sc. student, D. Medical Biophysics	*Jan, 2013 – Present*
Western University: Nephrology Clinical Fellowship (FRCPC	*July 2010-June 2012*
University of Calgary**:** Internal Medicine Residency (FRCPC)	*July 2007-June 2010*
National University of Ireland (Cork): Medical School	*Sept, 2002-May, 2007*
McGill University: M.Sc., Anatomy and Cell Biology	*Sept, 1999- July, 2001*
University of Waterloo: B.Sc. (Hon), Biology and Business	*Sept, 1994-Apr, 1999*

ADDITIONAL WORK EXPERIENCE

Electrocardiograph technician *Sept, 2005-May, 2006*
South Infirmary Victoria University Hospital, Cork Ireland

Lab Manager, *July, 2001 – August, 2002*
University of Alberta, Department of Medicine, Division of Nutrition

AWARDS and DISTINCTIONS

→ Top Clinical Teaching Unit Attending Physician. (Nominated and Finalist 2012, 2013 and 2014)

→ Western University Department of Medicine Faculty Award for Commitment and Excellence in Teaching. (Winner in 2014)

→ Western University Clinical Investigator Program. (Winner July 2012 – present)

→ Program of Experimental Medicine, Western University. (Grant awardee)

→ Canadian Association of Nephrology, Trainee Research Award. (National Finalist April, 2013)

→ Kristin Sivertz National Resident Leadership Award (National Finalist June, 2012)

→ Chief Nephrology Fellow (July 2011-June 2012)

→ AMGEN Young Investigators Award (Finalist, February 2011)

→ Canadian Society of Internal Medicine annual Research Award (National Finalist, 2010)

→ University of Calgary Internal Medicine research day (top clinical research project in 2010, top research project honorable mention 2009, top quality assurance and quality improvement research project in 2008 and 2009).

→ University of Calgary CANMEDS "model of Professionalism" (for all residents in Calgary, 2009)

→ University of Calgary Internal Medicine, "Most likely to cover call" award (2009)

→ Top Senior Resident, Rockyview General Hospital, Calgary. (July 2008 to June 2009)

→ Dean's List, National University of Ireland (2003, 2004, 2005, 2006 and 2007)

→ University Scholar, National University of Ireland (2004 and 2006)

→ McGill Anatomy and Cell Biology student scholarship (Sept 1999 to June 2001)

→ Ireland Power-Lifting National Champion (2004, 2005)

→ World Championships Powerlifting Competitor (Second place overall, November 2005)

→ European Championships Powerlifting (First Place, November 2005)

→ University of Waterloo Federation of Students Leadership Award (September 1998)

→ University of Waterloo Circle of Volunteerism Award (April 1999)

PUBLISHED WORKS:

Books:

Thomson BK, Acedillo RR. Critical References Nephrology- First Edition. CreateSpace 2013. Available for review and purchase at: www.amazon.com (search "best evidence nephrology").

Invited Oral Presentations:

1. Thomson BK, Dixon S, Huang SH, Leitch R, Heidenheim AP, Suri R, Chan C, Lindsay RM. Modifiable variables affecting interdialytic weight gain include dialysis time, frequency and dialysate sodium. Canadian Society of Nephrology for April, 2013 (Montreal, Canada).

2. Identification and Management of common nephrological emergencies. Invited by: Palestinian Health Authority for Feb 2-24, 2013.

3. Thomson BK, MacRae JM, Barnieh L, Zhang J, MacKay E, Manning MA, Hemmelgarn BR. Evaluation of an electronic warfarin nomogram for anticoagulation of hemodialysis patients. AMGEN Young Investigators Forum, National Finalist Presentation, 2011 (Montreal, Canada).

4. Thomson BK, MacRae JM, Barnieh L, Zhang J, MacKay E, Manning MA, Hemmelgarn BR. Evaluation of an electronic warfarin nomogram for anticoagulation of hemodialysis patients. Canadian Society of Internal Medicine, National Finalist Presentation, 2010 (Vancouver, Canada).

Peer-Reviewed Journal Articles:

Submitted, under review

1. Thomson BK, Li L, Leitch RE, Spanner ED, Kamphuis S, Lindsay RM. Clinical effects of personalized dialysate sodium in conventional, quotidian and nocturnal hemodialysis patients: A randomized crossover trial. Submitted and under review to: Nephrology Dialysis Transplantation.

2. Thomson BK, Li L, Leitch RE, Spanner ED, Kamphuis S, Lindsay RM. Effect of Personalized Dialysate Sodium Prescription on Plasma Sodium Concentration and Sodium Setpoint in Conventional, Quotidian and Nocturnal Hemodialysis. Submitted and under review to: Nephrology Dialysis Transplantation.

In Press

1. Thomson BK, Nolin TD, Velenosi TJ, Feere DA, Knauer MJ, Asher LJ, House AA, Urquhart BL. Effect of Chronic Kidney Disease and Dialysis Modality on Exposure to Drugs Cleared by Non-Renal Mechanisms. Accepted for publication in: *American Journal of Kidney Diseases: Contribution = 30%*

2. Thomson BK, Clark WF, Hladunewich M, Joseph G, Patel A, Blake PG, Eastabrook G, Matsui D, Sharma A, House A. Maternal, Pregnancy and Fetal Outcomes in *de novo*

Anti-glomerular Basement Membrane Antibody Disease in Pregnancy: A Systematic Review. Accepted for publication in: *Clinical Kidney Journal: Contribution = 80%.*

3. Thomson BK, Huang SH, Lindsay RM. The Choice of Dialysate Sodium is Influences by Hemodialysis Frequency and Duration: What should it be and for what modality? Accepted for publication in: *Seminars in Dialysis: Contribution = 80%.*

4. Huang SH, Filler G, Thomson BK, Blake PG, Lindsay RM. Elevated Blood Lead Levels in Home Hemodialysis Patients: Are They Toxic or Acceptable? Accepted for publication in: *Blood Purification: Contribution = 10%.*

5. Huang SH, Laporte S, Thomson BK, Shah S, Filler G, Lindsay RM. What is Single Needle Cannulation Hemodialysis: Is it Adequate?" Accepted for publication in: *Blood Purification*: *Contribution = 5%*

In circulation

6. Juma S, Thomson BK, Lok CE, Clase CM, Blake PG, Moist L. Warfarin use in hemodialysis patients with atrial fibrillation: decisions based on uncertainty. BMC-Nephrology 2013; 14: 174 *Contribution :50%.*

7. Thomson BK, Huang SH, Chan CT, Urquhart B, Skanes A, Lindsay RM. Nocturnal home hemodialysis associates with improvement of electrocardiographic features linked to sudden cardiac death. ASAIO J 2014; 60(1): 99-105. *Contribution: 85%.*

8. Marek C, Thomson BK, Shoker A, Luke P, Moser M. The prognostic value of time needed on dialysis (TND) in patients with delayed graft function. Nephrol Dial Transplant 2014; 29(1), 203-208. *Contribution: 40%.*

9. Thomson BK, Moser M, Marek C, Bloch M, Weernink C, Shoker A, Luke PP. Peritoneal Dialysis versus Hemodialysis in Patients with Delayed Graft Function. Clin Transplant 2013; 27(6): E709-14. *Contribution: 80%.*

10. Thomson BK, Momciu B, Huang SH, Chan CT, Urquhart B, Skanes A, Krahn A, Klein G, Lindsay RM. ECG Machine QTc intervals are inaccurate in hemodialysis patients. Nephron Clin Pract 2013; 124(1-2): 113-118. *Contribution: 85%.*

11. Thomson BK, Huang SH, Leitch RE, Dixon S, Heidenheim P, Suri RS, Chan CT, Lindsay RM. Pre to post-dialysis plasma sodium change better predicts clinical outcomes than dialysate to plasma sodium gradient in quotidian hemodialysis. Hemodial Int 2013 April 3 (Epub ahead of print). *Contribution: 85%.*

12. Thomson BK, Dixon SN, Huang SH, Leitch RE, Suri RS, Chan CT, Lindsay RM. Modifiable variables affecting interdialytic weight gain include dialysis time, frequency and dialysate sodium. Hemodial Int 2013 Jun 18 (Epub ahead of print). *Contribution: 75%.*

13. Thomson BK, Huang SH, Chan CT, House AA, Lindsay RM. Plasma Sodium Setpoint: Is it Constant or Changed by Hemodialysis Prescription? ASAIO J 2013 Jul 26 (Epub ahead of print). *Contribution: 85%.*

14. Thomson BK, Momciu B, Huang SH, Chan CT, Urquhart BL, Skanes AC, Krahn AD, Klein GJ, Lindsay RM. Frequent Nocturnal Hemodialysis Associates with Improvement of Prolonged QTc Intervals. Nephron Clin Pract 2013 Jul 11: 123 (1-2) 74-82. *Contribution: 80%.*

15. Clase CM, Holden RM, Sood MM, Rigatto C, Moist LM, Thomson BK, Mann JF, Zimmerman DL. Should patients with advanced chronic kidney disease and atrial fibrillation receive chronic anticoagulation? Nephrol Dial Transplant. 2012;27(10):3719-24. *Contribution: 10%.*

16. Thomson BK, Zhang J, MacRae J, MacKay E, Manning M, Hemmelgarn B**.** Evaluation of an electronic warfarin nomogram for anticoagulation of hemodialysis patients. BMC Nephrol. 2011. 12: 46. *Contribution: 75%.*

17. Thiesen A, Tappenden KA, McBurney MI, Clandinin MT, Keelan M, Thomson BK, Drozdowski LA, Wild G, Thomson ABR. Dietary lipids alter the effect of steroids on the transport of Fructose Following intestinal resection in rats. Dig Dis Sci. 2008. 53: 2126-39. *Contribution: 15%.*

18. Park EJ, Suh M, Thomson BK, Ma DWL, Ramanujam K, Thomson ABR, Clandinin MT. Dietary Ganglioside inhibits acute inflammatory signals in intestinal mucosa and blood induced by systemic inflammation of *Escherichia coli* lipopolysaccharide. Shock 2007; 28(1), 112-117. *Contribution: 15%.*

19. Park EJ, Suh M, Thomson BK, Thomson ABR, Ramanujam KS, Clandinin MT. Dietary ganglioside decreases cholesterol content, caveolin expression and inflammatory mediators in rat intestinal microdomains. Glycobiology 2005; 15 (10), 935-942. *Contribution: 25%.*

20. Thomson AB, Drozdowski L, Iordache C, Thomson BK, Vermeire S, Clandinin MT, Wild G. Small bowel review: Diseases of the small intestine. Dig Dis Sci. 2003 Aug;48(8):1582-99. *Contribution: 15%.*

21. Thomson AB, Drozdowski L, Iordache C, Thomson BK, Vermeire S, Clandinin MT, Wild G. Small bowel review: Normal physiology, part 2. Dig Dis Sci. 2003 Aug;48(8):1565-81. *Contribution: 15%.*

22. Thomson AB, Drozdowski L, Iordache C, Thomson BK, Vermeire S, Clandinin MT, Wild G. Small bowel review: Normal physiology, part 1. Dig Dis Sci. 2003 Aug;48(8):1546-64. *Contribution: 15%.*

23. Thiesen AL, Tappenden KA, McBurney MI, Clandinin MT, Keelan M, Thomson BK, Wild GE, Thomson AB; Cell and Molecular Biology Collaborative Network in Gastrointestinal Physiology. Dietary lipids alter the effect of steroids on transport of glucose after intestinal resection: Part II. Signalling of the response. J Pediatr Surg. 2003 Apr;38(4):575-8. *Contribution: 15%.*

24. Thiesen AL, Tappenden KA, McBurney MI, Clandinin MT, Keelan M, Thomson BK, Wild GE, Thomson AB. Dietary lipids alter the effect of steroids on the transport of glucose after intestinal resection: Part I. Phenotypic changes and expression of transporters. J Pediatr Surg. 2003 Feb;38(2):150-60. *Contribution: 15%.*

25. Thiesen A, Wild GE, Tappenden KA, Drozdowski L, Keelan M, Thomson BK, McBurney MI, Clandinin MT, Thomson AB. The locally acting glucocorticosteroid budesonide enhances intestinal sugar uptake following intestinal resection in rats. Gut. 2003 Feb;52(2):252-9. *Contribution: 15%.*

26. Thiesen A, Wild GE, Tappenden KA, Agellon LB, Drozdowski L, Keelan M, Thomson BK, McBurney MI, Clandinin MT, Thomson AB. Intestinal resection- and steroid-associated alterations in gene expression were not accompanied by changes in lipid uptake. Digestion. 2002;66(2):112-20. *Contribution: 15%.*

27. Thiesen A, Tappenden KA, McBurney MI, Clandinin MT, Keelan M, Thomson BK, Agellon L, Wild G, Thomson AB. Dietary lipids alter the effect of steroids on the uptake of lipids following intestinal resection in rats. Dig Dis Sci. 2002 Aug;47(8):1686-96. *Contribution: 15%.*

Poster Presentations

American Society of Nephrology, November, 2013 (Atlanta, United States)

1. Urquhart BL, Thomson BK, Nolin, TD, Velenosi TJ, Feere DA, Knauer MJ, Asher LJ and House AA. Midazolam and Fexofenadine Pharmacokinetics are Altered in Patients with Chronic Kidney Disease (abstract 2409). *Contribution: 30%.*
2. Thomson BK, Momciu B, Huang SH, Chan CT, Urquhart BL, Skanes AC, Krahn AD, Klein GJ, Lindsay RM. Frequent Nocturnal Hemodialysis Associates with Improvement of Prolonged QTc Intervals (abstract 4966). *Contribution: 80%.*
3. Thomson BK, Huang SH, Leitch RE, Lindsay RM. Effect of Personalize Dialysate Sodium on Clinical Outcomes and Sodium Setpoint Stability, in Patients on Nocturnal and Frequent Hemodialysis Modalities (abstract 4996). Contribution: 80%.

Canadian Society of Nephrology, April, 2013 (Montreal, Canada)

4. Thomson BK, Huang SH, Leitch RE, Dixon S, Heidenheim P, Suri RS, Chan CT, Lindsay RM. Pre to post-dialysis sodium Gradient more predictive than Dialysate to Pre-dialysis sodium Gradient for Clinical Outcomes in Quotidian Hemodialysis. *Contribution: 85%.*

5. Thomson BK, Huang SH, Chan C, House A, Lindsay RM. Plasma Sodium Setpoint; Is it constant or Changed by Hemodialysis Prescription? *Contribution: 85%.*
6. Thomson BK, Huang SH, Chan CT, Skanes AC, Krahn AD, Klein GJ, Lindsay RM. Dialysis Frequency and Duration: Effect on Electrocardiographic QTc intervals. *Contribution: 85%.*

Canadian Association of Transplantation, March 13, 2013 (Banff, Canada)

7. Marek C, Thomson BK, Bloch M, Shoker A, Luke P, Moser M. The prognostic value of "Time Needed on Dialysis" in patients with Delayed Graft Function (DGF). *Contribution: 40%.*
8. Thomson BK, Moser M, Marek C, Bloch M, Weernink C, Shoker A, Luke P. Peritoneal Dialysis versus Hemodialysis in Patients with Delayed Graft Function. *Contribution: 80%*

American Society of Nephrology, 2012 (San Diego, United States of America)

9. Thomson BK, Dixon S, Huang SH, Leitch R, Heidenheim AP, Suri R, Chan C, Lindsay RM. Modifiable variables affecting interdialytic weight gain include dialysis time, frequency and dialysate sodium. *Contribution: 75%.*

Canadian Society of Nephrology, 2012 (St. Johns, Canada)

10. Juma S, Thomson BK, Lok CE, Clase CM, Blake PG, Moist L. Canadian Society of Nephrology Survey confirms clinical equipoise for using warfarin in hemodialysis patients with atrial fibrillation. *Contribution: 50%.*

American Society of Nephrology, 2011 (Philadelphia, United States of America)

11. Juma S, Thomson BK, Lok CE, Clase CM, Blake PG, Moist L. Canadian Society of Nephrology Survey confirms clinical equipoise for using warfarin in hemodialysis patients with atrial fibrillation. *Contribution: 50%.*

American Society of Nephrology, 2010

12. Thomson BK, MacRae JM, Barnieh L, Zhang J, MacKay E, Manning MA, Hemmelgarn BR. Evaluation of an electronic warfarin nomogram for anticoagulation of hemodialysis patients. *Contribution: 75%.*

Canadian Society of Nephrology, 2010

13. Thomson BK, MacRae JM, Barnieh L, Zhang J, MacKay E, Manning MA, Hemmelgarn BR. Evaluation of an electronic warfarin nomogram for anticoagulation of hemodialysis patients. *Contribution: 75%.*