

Dry Weight: Sine Qua Non of Adequate Dialysis

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Attainment of dry weight remains a major clinical problem and challenge in current-day dialysis therapies. The vicious cycle of fluid overload and inadequate intradialytic fluid removal with hypotensive episodes, and subsequent poor clinical outcomes, is reinforced by excessive salt accumulation orally as well as during dialysis. Negligence in recognizing the importance of fluid status in dialysis prescriptions with shortened times has contributed to the prevalence of overhydration. The treatment of this problem is exacerbated by the lack of adequate methods to diagnose and manage it. The recent findings of improved fluid status and prognosis with salt restriction, individualized dialysate sodium concentrations, and prolonged hemodialysis times when necessary with well-tolerated fluid removal rates show the path to prolonging survival of dialysis populations. The ongoing development of techniques permitting accurate assessment of hydration status, including those based on bioimpedance analysis, will provide an efficient tool in these efforts.

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Dialysis adequacy is perhaps best defined as that dose of dialysis sufficient to maintain the health and quality of life of end-stage renal failure patients. We use measures of urea removal to characterize dialysis adequacy because the clearance of urea and of no other substance correlates with outcome in randomized trials. Other measures such as phosphate removal, middle molecule clearance, or fluid removal are clearly important to dialysis adequacy, particularly when an adequate Kt/V urea is prescribed. The maintenance of “dry weight,” when patients are euvoletic, is a substantial challenge for both patients and clinicians. Achieving dry weight, credibly a sine qua non of adequate dialysis therapy from the current position of floundering in excess fluid, is likely to be a long journey. Problems with overhydration were well appreciated by the pioneers of dialysis. In the 1960 report of long-term hemodialysis treatment in uremic humans, Scribner et al¹ describe the adverse effects of overhydration and provide basic approaches to this problem. Another early 1963 publication points out the beneficial effect on blood pressure of twice

weekly compared with once-a-week dialysis.² In a 1998 commentary on Scribner’s 1960 classic paper, Ritz states the following: “The genesis of hypertension in the dialyzed patient is certainly multifactorial and complex, but in this very first article Scribner immediately grasped the importance of hypervolemia. It is almost amusing to note that very recently, authors still felt it necessary to point to the importance of hypervolemia in the increasingly confused discussion on hypertension and optimal long-term blood pressure management on dialysis.”³

Overhydration and the Beginnings of Dialysis

In the more than 40 years since Scribner’s publication, many technologic improvements have changed dialysis, including dialyzers with high ultrafiltration properties, machines with controlled ultrafiltration, online blood-volume measurement, automated intermittent blood pressure devices, bicarbonate containing dialysate, blood cooling technology, and potent antihypertensive drugs. Clinicians combine these with comprehensive information concerning the relevant pathophysiology, the ill effects of overhydration, and high interdialytic weight gain. How is it possible then that we are still so ineffective at achieving dry weight?

To answer this question, the major trends in the history of dialysis since the 1960s need

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to be identified. Early dialysis treatments lasted 10 to 12 hours with the plate dialyzer because its ability to clear urea and other small solutes was so limited. With the development of progressively more efficient dialyzers, first coil and then hollow fiber, the need for long treatment times was less evident. Treatment times were often shorter, and the reductions in time were often arbitrary or based on misunderstandings (eg, being satisfied with a lower blood urea nitrogen concentration, even in a malnourished patient). The development of urea kinetic modeling by Gotch⁴ changed the prescription of dialysis to a science because it linked appearance and removal rates of urea (as a surrogate for small-molecular-weight toxins) to an easily measurable dialysis dose. Prescription was based on the elements of dialyzer urea clearance, the volume of distribution of urea, and the time of treatment (Kt/V) with relatively less attention to fluid accumulation and fluid removal requirements. This approach and its relation to outcomes have been extensively validated so that in current practice urea is the only dialytic indicator substance that has predicted outcomes in randomized controlled trials. The description and application of Kt/V urea measurement was followed by reduction in dialysis time, but often this occurred without the essential use of urea kinetic modeling or its approximations, resulting in underdialysis and increased rate of morbid events.^{5,6} The subsequent development of evidence-based clinical practice guidelines, with recommended goals for dialysis session Kt/V urea,^{7,8} often resulted in dialysis prescriptions with shortened dialysis times. This problem still persists to an extent and is particularly harmful when significant access recirculation, poor blood-drawing practices, inadequately calibrated machines, and other complicating factors are ignored.

However, even the prescription of a proven recommended range of dialysis dose as guided by Kt/V urea does not deal directly with the problem of removing excess salt and water. The persistent overhydration that results from short dialysis prescriptions is characterized by hypertension, cardiac hypertrophy, cardiac failure, and increased mortality rates.

Consequences of Overhydration

High salt intake and therefore fluid overload leads to high blood pressure not only because of increased volume but also through induction of increased peripheral resistance,⁹ a mechanism that seems responsible for the long-term hypertensive effect of overhydration in patients with chronic kidney disease. The association between fluid accumulation and high blood pressure has been shown in studies that use bioimpedance analysis for assessment of body fluid compartments. Extracellular volume is lower in normotensive patients than in patients with high blood pressure on maintenance hemodialysis¹⁰ or peritoneal dialysis.¹¹ These observations were confirmed by Fagugli et al¹² who showed in addition that extracellular volume was greater in hemodialysis patients with left ventricular hypertrophy (LVH) than in those without this abnormality. LVH itself is a mortality risk factor for patients with end-stage renal disease,¹³ and extracellular volume is an independent correlate of left ventricular mass (LVM) along with systolic blood pressure and male gender.¹² This finding suggests that chronic hypervolemia leads to LVH not only by contributing to high blood pressure and thus high pressure afterload but also via other pathways. Increased volume preload of the heart plays a main role in eccentric enlargement of the left ventricle. On the other hand, accelerated arterial stiffening as a long-term consequence of augmented mechanical strain in arterial walls may contribute to concentric LVH. Mechanical forces are known to induce changes in gene expression in endothelium, including stimulation of synthesis of growth factors.¹⁴

The causality of the relationship between overhydration and high blood pressure and/or LVH has been shown in interventional prospective studies of short daily hemodialysis. Patients so treated show a decrease in extracellular fluid volume, accompanied by a decrease in blood pressure and LVM.^{15,16} The extent of restoration of euvolemia correlated with the degree of LVH regression.¹⁶

Interdialytic weight gain (IWG) is a related parameter associated with fluid overload and often regarded as its surrogate marker. Positive correlations between IWG and blood

pressure have been shown in several studies,^{17,18} indirectly proving the importance of adequate fluid removal to normalizing the blood pressure. Moreover, Rahman et al¹⁹ showed that IWG was an independent contributor to mean blood pressure in 5,369 prevalent US hemodialysis patients. A few studies did not show a relationship between IWG and 24- to 48-hour or predialytic blood pressure; these studies were performed in small numbers of subjects (10,²⁰ 27,²¹ and 38 patients²²).

On the other hand, IWG has been found to correlate also with nutritional parameters: protein catabolic rate^{18,22} and serum creatinine.^{18,23} This is understandable because higher protein and caloric intake entails larger amounts of food taken in the interdialytic period. Therefore, to use IWG as an estimate of overhydration, adjustment for a patient's nutritional condition must be performed. Studies that did not take this adjustment into account failed to show a negative impact of IWG on survival.^{18,24} In contrast, those trials that met this prerequisite showed higher relative risk of death with excessive IWG in diabetic hemodialysis patients,^{23,25} as well as in a large international hemodialysis population (IWG >5.7% of dry weight).²⁶

Recent findings suggest that overhydration may also play a role in development of a chronic inflammatory state in the course of chronic kidney disease. Vicente-Martinez and co-workers²⁷ showed a positive correlation between serum C-reactive protein (CRP) level and the diameter of inferior vena cava, a marker of hydration, in a group of 20 peritoneal dialysis patients. In another study of peritoneal dialysis patients, Cheng et al²⁸ reported a decrease in CRP level in 18 patients with improved fluid status over 9 months of observation (decreased extracellular volume, as assessed by bioimpedance) and increase in CRP in 10 patients with aggravated fluid overload in the same period. The association between bioimpedance-derived extracellular volume and CRP, even after adjustment for multiple covariates, was recently confirmed by Avila-Diaz et al²⁹ in 183 peritoneal dialysis patients. Finally, Ortega et al³⁰ reported a positive correlation between CRP and N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker of left ventricular distention, in 75 predialysis chronic kidney disease patients,

even after excluding patients with possible cardiogenic hypervolemia because of left ventricular systolic dysfunction. Authors of these studies speculate that bowel wall edema because of high fluid overload may reduce the function of the immune barrier to gut endotoxins and thus stimulate chronic inflammation.

There are 3 major questions that must be answered if overhydration and its widespread prevalence in dialysis populations are to be improved: (1) What are the reasons for accumulation of salt and water? (2) What are the problems in removing this excess fluid load? and (3) How can a dialysis prescription be constructed to calculate the appropriate ultrafiltration total volume and rate?

Salt Accumulation: Causes and Outcomes

Salt is gained during dialysis when the dialysate sodium concentration is higher than the plasma sodium level. It should be noted that although the protein component of plasma reduces the total sodium concentration, this effect is cancelled out by the Gibbs-Donnan equilibrium. This positive sodium balance results in higher interdialytic weight gain and increased blood pressure.^{31,32} A direct relationship exists between the dialysate-plasma sodium concentration gradient and these outcomes.³²⁻³⁴ Keen³⁴ has emphasized that an increase in plasma sodium above an individual sodium set point stimulates thirst and consequent fluid intake until the concentration falls below the set point. Because most commercial dialysate preparations used in the United States have sodium concentrations of 138 mEq/L or higher, most patients will be in positive sodium balance accumulating sodium with each dialysis treatment. The reason dialysate sodium concentrations were designed so high was to protect the plasma volume against changes induced by rapid ultrafiltration by maintaining an osmotic shift of fluid from the interstitial to the plasma compartments. Similar reasoning produced the practice of "sodium modeling" (really a misnomer), a practice of increasing dialysate sodium concentration during dialysis (alternatively named sodium ramping or profiling), which also results in a net increase in sodium load and

plasma concentration. Although short-term benefits may occur, the net increase in interdialytic weight gain increases blood pressure³⁵ and subsequently requires more rapid rates of ultrafiltration with the potential for intradialytic hypotension (IDH) and its consequences. Immediate effects of IDH include limb cramping, dizziness and fainting, symptoms that reduce the quality of life and, more importantly, are potentially harmful, making patients unwilling to accept strict intradialytic fluid removal regimens. The result is never attaining dry weight and thus closing the vicious cycle of overhydration and IDH. Other rare but severe ischemic consequences of IDH include transient visual loss,³⁶ stroke, and myocardial infarction.³⁷ The long-term impact of overhydration-instigated high ultrafiltration rates may entail induction of sympathetic hyperactivity^{38,39} with its deleterious consequences of refractory hypertension⁴⁰ and increased cardiovascular mortality.⁴¹ The Dialysis Outcomes Practice Patterns study of 22,000 hemodialysis patients showed that high ultrafiltration rate (UFR) of greater than 10 mL/h/kg body weight was associated with higher long-term mortality independent of short treatment time and other risk factors.⁴² Also, in the same study, excessive IWG was an independent contributor to high UFR, which emphasizes the following pathophysiological pathway: high IWG leads to overhydration and requires high UFR, resulting in IDH and decreased survival. The patients at greatest risk in this vicious cycle (fluid overload → problems in removing fluid → further fluid overload) are those who begin dialysis with low predialysis blood pressures as the result of severe cardiac failure. The prognosis of these patients is very poor⁴³ because fluid can be removed only very slowly in such patients. Most dialysis units are unable to perform treatments longer than 4 hours. To further aggravate this situation, dialysis patients often have diastolic dysfunction.⁴⁴ In these patients, even a small decrease in filling pressure following dialysis ultrafiltration may result in decreased cardiac output and hypotension. As a result, fluid accumulation progresses inexorably. In addition, autonomic neuropathy complicating uremia and diabetes with inadequate peripheral arteriolar tone reactivity further increases the risk that hypotension occurs when the patient is still fluid overloaded.

While the importance of salt regulating fluid balance has received major emphasis, sodium has also been proposed as a uremic toxin⁴⁵ with specific effects stimulating oxidative stress.⁴⁶ Possibly related to this is the finding that excess sodium may be stored nonosmotically at concentrations of 180 to 190 mEq/L in skin, connective tissue, cartilage, and bone, possibly bound to glucosaminoglycans.⁴⁷ Under various circumstances, this sodium could be intermittently released into the circulation causing hypervolemia and oxidative stress.

Ways To Prevent Overhydration

In contrast to the “vicious cycle” of overhydration and inadequate ultrafiltration, extremely good outcomes have been described in Tassin, France,⁴⁸ by a combination of a low-salt diet (with excellent patient adherence) and longer dialysis times permitting low rates of ultrafiltration. A study by de Paula et al⁴⁹ examined 27 nonhypotensive prone patients dialyzed with lower plasma than dialysate sodium concentration at baseline. Patients were then dialyzed with individualized sodium dialysate concentration, matching the plasma sodium. They showed improved control of blood pressure and decreased interdialytic weight gains with no deterioration of intradialytic hemodynamic stability, a finding confirming Keen’s earlier concept.³⁴ Ozkahya et al⁵⁰ and Gunal et al⁵¹ reported a decrease in LVM along with blood pressure normalization after sodium intake restriction and strict volume control by ultrafiltration both in hemodialysis and peritoneal dialysis patients. Their recent finding of improved survival with this approach⁵² corroborates the benefits of the prevention of salt and fluid overload in dialysis patients. It should be stressed that although salt restriction has not been uniformly beneficial in populations without chronic kidney disease,⁵³ its effects in dialysis-treated patients who accumulate sodium in the course of kidney insufficiency and dialysis will be far more favorable.

Defining Dry Weight

If overhydration increases morbidity and mortality in dialysis patients, it is vital to

define a state of normal hydration or “dry weight” for them. For individuals with normal kidney function, the dry-weight state covers a range of hydration as affected by salt intake (and consequent fluid intake), habit, social drinking of nonalcoholic and alcoholic drinks, water-containing foods, and the concomitant water of metabolism derived from those foods and, on the other side, variable degrees of fluid and salt loss associated with work or exercise. The range of diurnal and day-to-day variation in weight is largely attributable to these factors. We can hardly then expect patients not to have an analogous range in extracellular fluid-volume variation. The challenge is to define dry weight with reasonable precision so that over time the removal of an adequate fluid volume is set for each hemodialysis procedure, and dry weight is reached at its completion. Defining that weight in a dialysis patient has been a major problem. When the jugular venous pressure is clearly raised or peripheral edema is present (in the absence of local factors), the diagnosis of overhydration is obvious and progressive management can be applied. In contrast, overhydration of 2 to 3 L cannot be detected in most patients. The majority of patients receive antihypertensive drugs, have echocardiographic abnormalities, and some have severe cardiac dysfunction, which obscure the clinical picture.

Dry-Weight Estimation

The approach to identification of dry weight has included the measurement of inferior vena cava diameter an hour or more after the end of dialysis to permit equilibration of fluid volumes, serum, or plasma concentrations of atrial natriuretic peptide (ANP), BNP, proBNP, NT-proBNP, and cyclic guanosine monophosphate (cGMP). These techniques have not proved to be generally useful in individual patients because of impracticability and operator dependence (inferior vena cava diameter) or low specificity and wide normal ranges (biochemical markers).⁵⁴⁻⁵⁶

Bioimpedance techniques have been broadly used because they satisfactorily detect changes in extracellular fluid volume.⁵⁷ Some techniques relate the measured resistance in dial-

ysis patient to ranges of values in the normal population.^{58,59} However, the relatively wide ranges in the general healthy population may make it difficult to be accurate in the estimation of dry weight in an individual patient. These whole-body techniques are being improved to adjust for variations of body composition. Recently, a novel approach to dry-weight assessment has been investigated, the continuous monitoring of extracellular resistance in the leg during dialysis using multiple frequency bioimpedance analysis. The legs were chosen because ambulating patients accumulate fluid there more than in the trunk or the arms. During dialysis, excess extracellular fluid is removed continuously by ultrafiltration, and the progress of this removal can be followed continuously by multiple frequency bioimpedance. Ultrafiltration, preferably in small steps reducing the target weight by 200 to 300 g each session, can be monitored carefully until no further fluid is available.⁶⁰ In theory, any attempt to continue ultrafiltration further will result in hypotension because only the plasma volume will be able to contribute the ultrafiltrate. In practice, dry weight need not be precise; it is quite adequate to be close to dry weight. Technical problems (eg, venous pressures, either systemic or local) can influence continued removal of fluid. These new techniques are under further investigation.⁶¹⁻⁶³

In conclusion, salt and water accumulation remain a major problem for dialysis patients. It is important to define ways to minimize intra- and interdialytic salt and water accumulation to prevent excessive cardiovascular morbidity and mortality. Scribner et al's 47 year-old understanding of the importance of the fluid balance has gained importance over the many years since 1960: “The combination of dietary sodium restriction and ultrafiltration during dialysis permits regulation of extracellular volume.”¹ Physicians must define effective ways to evaluate volume frequently and to change the target weight prescription as needed. In the patient without significant heart disease, a gradual reduction in the target weight permits gradual decrease in the fluid overload. New techniques should make it easier to determine when patients have reached the point in which there is little more extra-

cellular fluid volume to lose (ie, they are at their optimal hydration state), with minimized risk of intradialytic hypotensive episodes. Dry weight is the sine qua non of adequate dialysis, and patient outcomes should be better once these principles can be achieved.

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