Volume excess and cardiac remodeling have been shown in epidemiologic studies to have an association with cardiovascular and all-cause mortality in chronic hemodialysis patients (1–5). However, excessive ultrafiltration and volume depletion can lead to frequent episodes of malaise, weakness, increase risk of falls, episodes of intradialytic hypotension, and brain hypoperfusion, with subsequent white matter degeneration (6). In addition, gastrointestinal ischemia leading to endotoxin exposure is also a plausible clinical consequence of overaggressive ultrafiltration (7). Therefore, the clinical challenge is how best to avoid underaggressive ultrafiltration, which could cause cardiac dysfunction and dyspnea, and overaggressive ultrafiltration with its attendant symptoms of fatigue and exercise intolerance, both of which negatively affect quality of life and are equally important from a patient point of view.

What is an optimal dry weight? The concept of dry weight is as old as dialysis itself and has been defined various ways (1). An ideal dry weight should be the posthemodialysis weight that results in the (1) shortest postdialysis recovery time; (2) least intradialytic hypotension; (3) longest patient survival; (4) fewest cardiovascular and cerebrovascular events and hospitalizations; (5) fewest hypovolemia-related access thromboses; and (6) fewest postdialysis falls (8). In 2009, Sinha and Agarwal proposed a definition that combines subjective and objective measurements. According to this definition, dry weight is defined as the lowest tolerated postdialysis weight achieved via gradual change in postdialysis weight at which there are minimal signs or symptoms of hypovolemia or hypervolemia.

Observational studies support the practice of probing dry weight. Flythe and colleagues reviewed clinical outcomes from a cohort of 14,000 hemodialysis patients (10). The analysis compared outcomes in high- versus low-weight gainers (interdialytic weight gains >3 kg versus ≤3 kg) and for longer versus shorter treatment times (<240 versus ≥240 minutes) while adjusting for important confounders. This analysis demonstrated a 32% increased mortality risk in patients prescribed <240 minutes (compared with those prescribed ≥240 minutes) and a 29% increased mortality risk associated with higher compared with lower interdialytic weight gains.

To study the effect of volume status on mortality, Wizeman et al. (1,11) followed 269 prevalent hemodialysis patients for several years. They measured hydration state using a body composition analyzer. If there was ≥15% excess of extracellular water (2.5-L volume excess), they classified such patients as volume overloaded. In a multivariate-adjusted analysis, investigators found that excess hydration was associated with high mortality. The hazard ratio of mortality with excess fluid volume was 2.1 times greater ($P=0.003$) than those without excess fluid volume. A total of 25% of the patients had excess extracellular fluid (ECF) volume. Although the study did not examine reduction in ECF volume with subsequent outcomes, it is quite likely to assume that improvement in ECF volume would be associated with improved survival outcomes if such studies were performed in the future.

There are potential hazards related to probing dry weight, including (1) increased risk of clotted angioaccess, (2) increased rate of attrition in residual renal function, and (3) complications related to intradialytic hypotension. Intradialytic hypotension, in addition to requiring more nursing interventions, can be complicated by cerebral hypoperfusion, seizures, myocardial dysfunction, and mesenteric ischemia.

In this issue of CJSN, Flythe et al. (12) report on the clinical effect of missing target weights (i.e., above and below the prescribed target weight) and clinical outcomes. The authors hypothesized *a priori* that postdialysis weights, above and below the target weight, would be associated with all-cause mortality and that greater frequencies of target weight misses would be related to increased risk of death. Data were obtained from a national cohort of 12,417 prevalent hemodialysis patients undergoing dialysis between 2005 and 2008 in one of 1263 dialysis clinics affiliated with a single dialysis organization located across the United States. A threshold of 2 kg above and below target weight was chosen to minimize bias from scale error, and the coprimary end points were all-cause and cardiovascular mortality. Most of the hemodialysis patients were at their target weight at baseline of the observation period (n=8527; 79.2%), and only 6.4% (n=682) and 14.4% (n=1549) of the cohort were below and above their target weight, respectively. The mean±SD interdialytic weight gain as a percentage of body weight was 2.7±1.5 and 3.9±1.5 kg in the below and above target weight groups, respectively. As expected, participants with postdialysis weight >2 kg above target weight were younger, men, had a higher prevalence of heart failure, and on average had been on dialysis...
therapy for a longer period of time. The median follow-up time was 2.1 years, and there were 2,954 deaths, of which 38% were cardiovascular deaths. Above target weight misses in at least 30% of treatments were associated with a 28% and 26% increase risk in all-cause and cardiovascular mortality when compared with those who achieved their target weight. Similarly, those participants that were below their target weight in at least 30% of the treatments were also associated with a 22% and 56% increase in the hazard of total and cardiovascular death when compared with the control group. Similar results were observed for both clinical outcomes when the target weight was missed in at least 40% of treatments. Of interest, the authors report a statistical significant increase in the hazard even when participants were above or below their target weight by only 1.0 kg. Of note, in participants with below target weight misses, the association with mortality was present in those with a base weight ≥ 60 kg but not in those with a weight < 60 kg (P value for interaction = 0.01). In further analyses, the investigators observed that above target misses were more strongly associated with intradialytic hypotension (systolic BP < 90 mmHg) and large interdialytic weight gains (> 3.5% body wt). Both above and below target weight misses were associated with greater rapid ultrafiltration (> 13 ml/h per kg); however, the magnitude of the risk was higher in those participants with below target weight misses.

Thrice-weekly hemodialysis treatment is currently offered to > 600,000 Americans with CKD stage 5 to remove uremic toxins and restore electrolyte balance (13). Concurrent fluid removal via ultrafiltration, however, is also performed during virtually each hemodialysis treatment. This intermittent ultrafiltration leads to nonphysiologic fluctuations in body fluid. Hence, it is common for patients to gain weight as a result of fluid retention between two consecutive hemodialysis sessions, usually 2–3 days apart. Adherence to fluid restrictions represents one of the most difficult aspects of the hemodialysis treatment regimen (14,15). Intermittent fluid retention may imitate intermittent episodes of acute decompensated heart failure, leading to fluctuations in compensatory mechanisms, including catecholamine release to increase sympathetic activity (16) and changes in the renin-angiotensin-aldosterone system and antiuretic hormone, which alone or together may increase the risk of cardiovascular events and death (17–19). Therefore, the results presented in this epidemiologic cohort study strengthen the relationship between above target weight misses and clinical outcomes.

Less well studied is the presented association between below target weight misses and outcomes. In this analysis, below target weight misses were strongly associated with a high ultrafiltration rate, defined as > 13 ml/h per kg. Retrospective analyses show strong associations between an ultrafiltration rate > 10 ml/h per kg and cardiovascular mortality, with patients with an ultrafiltration rate of < 10 ml/h per kg having the lowest risk of cardiovascular and overall mortality (20,21). Perhaps most compelling are recent data showing less dialysis-induced myocardial stunning in more frequent hemodialysis regimens with a lower ultrafiltration rate compared with conventional hemodialysis treatments with higher rates of ultrafiltration (22). An alternate hypothesis that explains this association is that weights below estimated dry weights are a marker of poor general health. Although the authors had information on serum albumin and performed effect modification analyses with baseline participant weights, other biochemical measures of nutritional status, including normalized protein catabolic rate, serum transferrin, and creatinine, were lacking. Of interest, the participants with below target weight misses had lower average serum phosphorus when compared with those participants on target or with above target weight misses, suggesting a less adequate nutritional status.

Clinicians certainly realize the importance of interventions to minimize interdialytic weight gains and errors in estimating target weights. The available tools to assess fluid status in hemodialysis patients are limited to the underused art of physical examination and a BP cuff, and caregivers often rely on development of hypotension to determine dry weight. However, multiple factors can cause hypotension during a treatment, including BP medications and rapid ultrafiltration rate. If incorrectly interpreted, hypotension can lead to an overestimate of actual estimated dry weight and subsequent inadequate volume removal. Monitoring of relative plasma volume with the Crit-Line device is becoming more common and has recently been validated (23). Bioimpedance spectroscopy has not been approved in the United States, but accumulating data suggest it may be a useful tool in the future (24). Hence, this study reinforces the importance of obtaining an accurate dry weight because misses below and above the target might be harmful to patients on dialysis.

Just like plants, some dialysis patients will need more water, and some will need less. Therefore, judgment, observation, and further research will be required to prevent over-watering or desiccation with their associated complications.

Disclosures

None.

References

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See related article, “Associations of Posthemodialysis Weights above and below Target Weight with All-Cause and Cardiovascular Mortality,” on pages 808–816.